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Association Between Long-term Ambient $PM_{2.5}$ Exposure and Cardiovascular Outcomes Among US Hemodialysis Patients

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Abstract

Rationale & Objective: Ambient $PM_{2.5}$ (particulate matter with a diameter of 2.5 microns) is a ubiquitous air pollutant with established adverse cardiovascular (CV) effects. However, quantitative estimates of the association between $PM_{2.5}$ exposure and CV outcomes in the setting of kidney disease are limited. This study assessed the association of long-term $PM_{2.5}$ exposure with CV events and cardiovascular disease (CVD)–specific mortality among patients receiving maintenance in-center hemodialysis (HD).

Study Design: Retrospective cohort study.

Settings & Participants: 314,079 adult kidney failure patients initiating HD between 2011 and 2016 identified from the US Renal Data System.

Exposure: Estimated daily ZIP code–level $PM_{2.5}$ concentrations were used to calculate each participant's annual average $PM_{2.5}$ exposure based on the dialysis clinics visited during the 365 days before the outcome.

Outcome: CV event and CVD-specific mortality were ascertained based on ICD-9/ICD-10 diagnostic codes and recorded cause of death from Centers for Medicare & Medicaid Services form 2746.

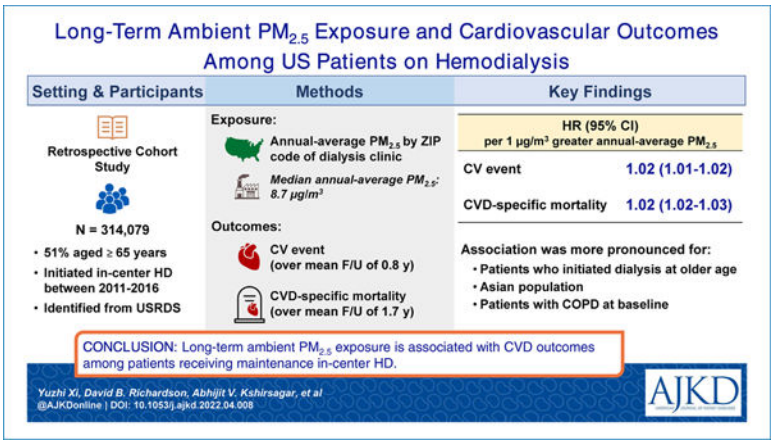
Analytical Approach: Discrete time hazards models were used to estimate hazards ratios per 1 $\mu g/m^3$ greater annual average $PM_{2.5}$, adjusting for temperature, humidity, day of the week, season, age at baseline, race, employment status, and geographic region. Effect measure modification was assessed for age, sex, race, and baseline comorbidities.

Results: Each 1 $\mu g/m^3$ greater annual average $PM_{2.5}$ was associated with a greater rate of CV events (HR, 1.02 [95% CI, 1.01–1.02]) and CVD-specific mortality (HR, 1.02 [95% CI, 1.02–1.03]). The association was more pronounced for people who initiated dialysis at an older age, had chronic obstructive pulmonary disease (COPD) at baseline, or were Asian. Evidence of effect modification was also observed across strata of race, and other baseline comorbidities.

Limitations: Potential exposure misclassification and unmeasured confounding.

Conclusions: Long-term ambient $PM_{2.5}$ exposure was associated with CVD outcomes among patients receiving maintenance in-center HD. Stronger associations between long-term $PM_{2.5}$ exposure and adverse effects were observed among patients who were of advanced age, had COPD, or were Asian.

Graphical Abstract



PLAIN-LANGUAGE SUMMARY

Long-term exposure to air pollution, also called $PM_{2.5}$, has been linked to adverse cardiovascular outcomes. However, little is known about the association of $PM_{2.5}$ and outcomes among patients receiving dialysis, who are individuals with high cardiovascular disease burdens. We conducted an epidemiological study to assess the association between the annual $PM_{2.5}$ exposure and cardiovascular events and death among patients receiving regular outpatient hemodialysis in the United States between 2011 and 2016. We found a higher risk of heart attacks, strokes, and related events in patients exposed to higher levels of air pollution. Stronger associations between air pollution and adverse health events were observed among patients who were older at the start of dialysis, had chronic obstructive pulmonary disease, or were Asian. These findings bolster the evidence base linking air pollution and adverse health outcomes and may inform policy makers and clinicians.

Particulate matter, 1 of the 6 National Ambient Air Quality Standards (NAAQS) criteria pollutants, has been linked to adverse health outcomes.[1] The latest Integrated Scientific Assessment for Particulate Matter concluded that evidence supports a causal relationship between long-term exposure to particulate matter with a diameter of 2.5 microns ($PM_{2.5}$) and cardiovascular disease (CVD).[1] Due to their fine size, inhaled $PM_{2.5}$ particles can travel deep in the lungs and enter the circulatory system.[2] Toxicology studies in animals and controlled exposure in human volunteers have demonstrated inflammation (local and systemic) and autonomic nervous system activation, and epidemiologic studies have demonstrated associations between $PM_{2.5}$ exposure and CVD, other morbidities, and mortality in the general population.[3–6] However, the effects of long-term $PM_{2.5}$ exposure among people who may be differentially susceptible to $PM_{2.5}$-associated health effects remains understudied.[1]

Identifying specific populations who are particularly susceptible to the adverse health effects of pollution is a key step in reducing the public health burden of $PM_{2.5}$ exposure. In the United States, individuals with kidney failure treated by maintenance in-center hemodialysis (HD) treatment are a large and growing, potentially susceptible population among whom the association of long-term $PM_{2.5}$ on cardiovascular (CV) outcomes is unknown.[7] Patients receiving maintenance HD are medically fragile and have high burdens of CVD. The relative

risk of death due to CV events in HD patients is 20 times higher than that of the general population.[8] HD patients also experience high mortality rates; the annual mortality rate was 16% in 2021 among US HD patients.[7] Recent data suggest that short-term $PM_{2.5}$ exposure is associated with adverse CV outcomes in HD patients,[9–11] but less is known about the association of long-term $PM_{2.5}$ exposure and CV outcomes in this vulnerable population. To further evaluate the potential CV effect of long-term $PM_{2.5}$ exposure among HD patients, we conducted a retrospective open cohort study to investigate the association between long-term $PM_{2.5}$ exposure and CV event and CVD-specific mortality among patients receiving in-center HD in the contiguous United States.

Methods

Study Setting and Study Population

We identified a retrospective cohort of maintenance HD patients from the US Renal Data System (USRDS), a claims-based national registry of patients with kidney failure that includes nearly all dialysis patients in the United States.[7] We extracted baseline demographics, dialysis treatment, and comorbid medical characteristics for patients who initiated in-center HD treatment between January 1, 2011, and December 31, 2016, in the contiguous United States who had Medicare as their primary payer. Participants were followed from the fourth month of dialysis initiation (ie, time of Medicare coverage stability) until first diagnosis of CVD, change of kidney failure treatment modality (eg, peritoneal dialysis, kidney transplant), loss of Medicare coverage, death, or end of study follow-up (December 31, 2016). We excluded patients who were younger than 18 years old at dialysis initiation, initiated dialysis before January 1, 2011, did not have Medicare as primary payer, or did not survive the first 3 months of dialysis.

Exposure Assessment and Meteorological Data

ZIP code–level daily $PM_{2.5}$ concentrations were estimated with a previously described prediction model.[12–14] In brief, this model estimates daily $PM_{2.5}$ on a 1 km grid for the entire contiguous United States by incorporating satellite aerosol optical depth measurements, chemical transport model simulations, meteorology, land use, and other factors. Gridded $PM_{2.5}$ estimates were then converted to population-weighted ZIP-level estimates using 2010 census tract population values. Long-term exposure was defined as the annual average of daily $PM_{2.5}$ levels across the year before a particular day, which was calculated by averaging the daily $PM_{2.5}$ concentrations across a 365-day period for each patient taking potential ZIP code–level change of location into account. Annual average of daily $PM_{2.5}$ has been used widely to define long-term PM exposure in previous studies and as regulatory standard.[15,16]

Daily temperature and relative humidity data were obtained from the US National Oceanic and Atmospheric Administration (NOAA). Specifically, daily temperature and relative humidity from weather station measurements were interpolated to census tract centroids and then averaged over tracts to ZIP codes.

Outcome Assessment

Follow-up to ascertain CV events and CVD-related deaths through December 21, 2016, was based on USRDS records. The outcomes of interest were CV events and CVD-specific mortality. The primary cause of death recorded in ESRD Death Notification Form (Centers for Medicare & Medicaid Services form 2746) was used to classify mortality into CVD-specific mortalities. We defined CV events as the first CVD-related emergency department (ED) visit, hospitalization, or mortality, whichever occurred first since the beginning of follow-up (recurrent CV events were not accounted for). *International Classification of Disease, 9th and 10th Revision* (ICD-9 and ICD-10) codes were used to identify cause-specific ED visits and hospitalization. In brief, any ED visit and hospitalization with a code indicating cerebrovascular, ischemic heart disease, hypertensive disease, heart failure, cardiac arrest, and related events were classified as CVD-related ED and hospital admission events. The cause of death codes and ICD codes used are summarized in Table S1.

Data Linkage

We linked $PM_{2.5}$ exposure to person-day records and meteorology variables based on date and ZIP code of the (last) dialysis clinic visited. More specifically, each person-day was linked to a 1 year average $PM_{2.5}$ at the ZIP code of the dialysis clinic. To define exposure before dialysis initiation, we used annual average linked to the ZIP code of first available clinic. For each participant-day of follow-up, daily records of $PM_{2.5}$ exposure were assigned based on the ZIP code of the dialysis clinic visited during that period of time. Patients typically visited a dialysis clinic every 2 or 3 days. For a date between claim-filing periods, with no information on clinic visits, the ZIP code of the last clinic visited was assigned (1.3% of the person-days in the mortality analysis had a ZIP code that was different from the previous person-day of the same individual).

Statistical Analysis

We used discrete time hazards models to assess the association between ZIP code–level long-term $PM_{2.5}$ exposure and CV events and CVD-specific mortality.[17] The discrete time hazard is the probability of a case event at discrete time interval t, conditional on remaining event-free up to time $t - 1$. This approach, which has been widely used in occupational and environmental cohort studies,[17–20] is similar to a Poisson regression approach applied to a person-period data structure, which allows controlling for individual-level factors.[17] We created 1 record per day for each participant in this study. Hazard ratios (HRs) per 1-$\mu g/m^3$ greater $PM_{2.5}$, together with corresponding 95% confidence intervals were estimated. The detailed model specification can be found in Item S1. For potential effect measure modifiers (age, sex, race, and baseline comorbidities; Table S2), we tested for the presence of heterogeneity of effect across different strata using the likelihood ratio test. Subsequently, we performed stratified analyses, reporting the effect estimates for each strata separately.

Sensitivity Analysis

To assess for potential variation of effect by duration of long-term $PM_{2.5}$ exposure and using analogous methods to the primary analyses, we examined the 6-month and 2-year averages of daily $PM_{2.5}$ in addition to the annual average. We also considered 2 other outcomes: an

alternative specification of CV events that excluded hypertension-related diagnosis codes and, separately, all-cause mortality. Finally, we tested whether the observed associations for all 3 outcomes differ at levels above the NAAQS annual concentration threshold of 12 $\mu g/m^3$.

The study protocol was reviewed and exempted by the institutional review board of the University of North Carolina on November 16, 2020 (Study 20–1469). Individual-level informed consent was not obtained as the health data were already collected at the time of study start.

Results

The final cohort included a total of 314,079 HD patients (Fig S1) with 193,121,928 person-days of follow-up in the mortality analyses (mean follow-up, 1.7 years) and 94,385,773 person-days in the CV event analysis (mean follow-up: 0.8 year). Between 2011 and 2016, there were 35,857 CVD-related mortalities (43.4% out of total all-cause mortality), and 208,113 patients experienced at least 1 CV event. Table 1 displays the study population characteristics. More than half of the participants were older than 65 years of age at the initiation of HD. Approximately 44% of the study participants were female, and 52% were White. At HD initiation, more than half of the cohort had diabetes, about 60% had CVD, and 10% had chronic obstructive pulmonary disease (COPD).

The distribution of long-term ambient $PM_{2.5}$ concentrations varied across different ZIP areas (Fig S2). The median annual average ambient $PM_{2.5}$ for the mortality analysis was 8.7 (IQR, 2.2) $\mu g/m^3$ (Table 2). For CV event analysis, the annual average $PM_{2.5}$ exposure distribution was nearly identical to that of the mortality analysis, with a median of 8.8 (IQR, 2.3) $\mu g/m^3$. The distributions of meteorology variables are presented in Table S3.

Overall, greater long-term ambient $PM_{2.5}$ was associated with greater hazards of CV events and CVD-specific mortality (Figs 1–3; Table S4). The associations were slightly higher when longer time windows were used to define the exposure, but the 95% confidence intervals were overlapping; therefore, the long-term associations were robust against different long-term exposure definitions assessed (Fig 1). The annual average $PM_{2.5}$ was reported as the primary exposure of interest for the robustness of association regardless of average time window. The hazard ratios (HR) associated with 1 $\mu g/m^3$ greater annual average $PM_{2.5}$ for CV events and CVD-specific mortality were 1.02 (95% CI, 1.01–1.02) and 1.02 (95% CI, 1.02–1.03), respectively (Fig 1). We did not observe evidence for differential association estimates at concentrations above the NAAQS (12 $\mu g/m^3$) for all 3 outcomes. Findings were consistent in analyses considering the alternative specification of CV events and all-cause mortality (Table S4, Table S5).

For CV events, the association was relatively higher among HD patients who started dialysis in the oldest age group (≥75 years), those who were White, and followed by those who were Asian and those with COPD at dialysis initiation (Fig 2). For every 1 $\mu g/m^3$ greater annual average $PM_{2.5}$, an HR of 1.02 (95% CI, 1.02–1.03) was observed among HD patients who initiated dialysis at the age of 75 or older (Fig 2). For HD patients who reported to

have COPD at dialysis initiation, an HR of 1.02 (95% CI, 1.02–1.03) was estimated (Fig 2). Among different race ethnicity groups, the HR estimate was highest for White (HR, 1.02 [95% CI, 1.02–1.02]) followed by Asian (HR, 1.01 [95% CI, 1.00–1.03]) individuals. The likelihood ratio test for homogeneity also suggested the associations on CV event were not similar across different levels of dialysis initiating age, sex, race ethnicity, and baseline COPD status (Fig 2).

For CVD-specific mortality, HD patients who started dialysis in the oldest age group, were Asian, and did not have diabetes or had COPD at dialysis initiation experienced a relatively higher $PM_{2.5}$-related association compared with other groups (Fig 3). The highest HR (1.06 [95% CI, 1.03–1.10] per every 1 $\mu g/m^3$ greater annual average $PM_{2.5}$) was observed among HD patients who were Asian (Fig 3). For HD patients who were 75 or older at dialysis initiation, the HR was 1.04 (95% CI, 1.03–1.05) (Fig 3). For HD patients who reported having COPD at dialysis initiation, an HR of 1.03 (95% CI, 1.01–1.04) was estimated (Fig 2). The likelihood ratio test for homogeneity also suggested the association on CVD-specific mortality is not similar across different levels of dialysis-initiating age, race, baseline diabetes status, and baseline COPD status (Fig 3).

Discussion

We estimated the associations of long-term $PM_{2.5}$ exposure with CV events and CVD-specific mortality among US HD patients between 2011 and 2016. Long-term $PM_{2.5}$ exposure was associated with higher hazards for both studied outcomes in this vulnerable population. The hazard of a CV event was greater by 2% for every 1 $\mu g/m^3$ greater annual average $PM_{2.5}$; the same value was obtained for the association with CVD-specific mortality. We also observed relatively higher $PM_{2.5}$ hazards among HD patients who initiated dialysis at an older age, who had COPD at dialysis initiation, and who were Asian.

Epidemiological studies have linked long-term $PM_{2.5}$ exposure to CV outcomes. Currently, there are 3 hypotheses regarding the mechanisms of PM exposure's biological effect.[21] The first 2 hypotheses posit that $PM_{2.5}$ inhalation activates systemic inflammation in the lung and other target tissues via direct entry into the circulation.[22–25] The third hypothesis posits that inhaled particulate matter activates sensory receptors in the lung, leading to imbalance of the autonomic nervous system and subsequent increases in catecholamines.[22–25] Both elevated catecholamines and systemic inflammation can contribute to the development of atherosclerosis, thrombosis, endothelial dysfunction, alteration in heart rate, vasoconstriction, and elevated blood pressure—preclinical precursors to CV outcomes such as the ones observed in this analysis.[22–25]

Our findings add to the emerging evidence regarding the association between $PM_{2.5}$ exposure and outcomes among HD patients and are consistent with previous results in this population. Wyatt et al[9] reported a 0.9% (95% CI, 0.4%−1.8%) increase in hospital admission risk for CV causes was associated with same-day $PM_{2.5}$ exposure in the United States. A recent study by Feng et al[26] observed mortality risk elevation with long-term $PM_{2.5}$ exposure. For CVD mortality, they reported a similar HR (1.38 [95% CI, 1.21–1.58] per 10 $\mu g/m^3$ greater annual average $PM_{2.5}$ above 12 $\mu g/m^3$).[26] Another recent study among

patients with kidney failure in Hong Kong also observed an association between $PM_{2.5}$ exposure and mortality.[27] These findings, bolstered by the results of our study, support the conclusion that long-term exposure to particulate matter, even when at relatively low levels, is associated with higher risks of CVD and mortality among HD patients.

However, it was unexpected that the association size observed for CV events was lower than that of CVD-specific mortality (1.6% vs 2.2% greater HRs, albeit with overlapping confidence intervals) because it is logical that individuals would develop an incident CV event before their death. This could be due to the use of different diagnosis coding algorithms used to define CVD-specific mortality versus CV event, a high CVD prevalence within this cohort, or the plausible impact of long-term $PM_{2.5}$ exposure on CVD case fatality rates.

Our findings also suggest larger magnitudes of association between long-term $PM_{2.5}$ exposure and health outcomes among patients who initiated dialysis treatment at an older age, had COPD at dialysis initiation, were not diabetic at dialysis initiation, and were Asian. The observed age-related effect modification may be explained by the higher prevalence of pre-existing conditions and higher baseline mortality risk in the older age group. Feng et al[26] also observed a higher long-term $PM_{2.5}$ exposure effect on all-cause mortality among older dialysis initiators.

The $PM_{2.5}$-outcome association was also larger among patients with COPD (vs without). This finding is not surprising because COPD contributes to compromised respiratory function and underlying pulmonary inflammation, potentially increasing susceptibility to air pollution.[28,29] Yet previous studies have yielded inconsistent results in this regard, and more population-specific studies are needed.[28–32]

We also found higher hazards for CVD-specific mortality among patients without diabetes at dialysis initiation. This differential association by baseline diabetes status on mortality could be potentially explained by the fact that more patients with diabetes (50.4% vs 46.5%) initiated dialysis at a younger age (before 65) (Table S6). To our knowledge, no study has assessed the long-term $PM_{2.5}$ effect by baseline diabetes status among dialysis patients. Studies among the general population yield mixed or nonsignificant results.[1,33–35]

Finally, we observed a higher $PM_{2.5}$ association on CVD-specific mortality among Asians. This difference could be potentially explained by differences in age distribution by race (Table S6) and exposure levels.[36] Studies in the general or other populations have also reported mixed results on race stratification for PM effects.[1] Thus, it is not conclusive to determine if and how race and ethnicity modifies the long-term PM effect among dialysis patients.

This study had several strengths. First, the USRDS database is highly representative of US HD patients, with a nearly complete inclusion of those who initiated in-center HD between 2011 and 2016. Second, linkage of the $PM_{2.5}$ concentrations using the dialysis treatment date and ZIP code of the dialysis clinic visited enabled the best exposure classification we can achieve with the available data. It has been reported that patients in the USRDS cohort who received maintenance in-center dialysis travel a median distance of 5.7 miles

from their homes to dialysis clinics.[37,38] In our study population, more than half of the included patients had at least 1 ZIP code–level change of location during follow-up. Thus, it is necessary to take location changes into account for exposure linkage to avoid potential exposure misclassification. Third, the ZIP code–level daily $PM_{2.5}$ concentrations were estimated with a sophisticated model of high spatial and temporal resolution with proven accuracy.[12,39] Last, the use of discrete time hazards models allowed for controlling for individual-level time invariant factors together with time-varying factors to better estimate the health risk associated with fluctuation in ambient $PM_{2.5}$.

This study also had some limitations. First, exposure misclassification is often a concern in environmental exposure studies because the individual-level exposure measurement is not available. Instead, the assumption is made that the average exposure is similar across patients within the same ZIP code area and that the degree of exposure misclassification does not vary simultaneously with daily variation in ZIP code–level exposure and health risk. Furthermore, $PM_{2.5}$ is generally considered and regulated as a regional pollutant, and the modeled exposure is currently considered the best available exposure surface.[39,40]

Second, in this analysis socioeconomic status (SES) was classified based on employment status at dialysis initiation. For our dataset, it was the only available proxy of SES, yet it could lead to inaccurate classification of SES. Future study should identify additional sources of information and/or collect information for individual SES classification (eg, income, education) to better understand its potential confounding or modification effect.

Third, there are other potential effect measure modifiers that were not able to be assessed in this analysis. For example, the information of urbanicity is lacking, which should be collected and assessed in future studies. Also, future study should assess geographic region–specific effects. Furthermore, the composite definition of CV events, which included hypertension, although consistent with environmental literature definitions, may have limitations in regard to clinical interpretation. Reassuringly, the analyses considering an alternative CV event definition excluding hypertension yielded consistent findings. Finally, for all observational studies there is the possibility of unmeasured confounding, and in the presence of unmeasured confounding, our estimates should not be interpreted as causal.

In conclusion, in this large retrospective open cohort study, we found evidence of associations between long-term ambient $PM_{2.5}$ exposure and CVD outcomes among patients receiving maintenance in-center HD. The annual average ZIP code–level $PM_{2.5}$ for the majority of the included person-days in this analysis (75th percentile: 9.8 $\mu g/m^3$) was below the current NAAQS regulatory standard of 12 $\mu g/m^3$. However, the PM concentration in many highly populated urban areas still exceeds the NAAQS standard, and extreme events like wildfires also lead to high-level exposures despite the fact that the national level ambient $PM_{2.5}$ concentration has decreased 39% between 2000 and 2018.[41] Our findings suggest that exposure mitigation on the individual level could be beneficial to at-risk individuals. Future studies should be conducted to study the potential health impact of additional air pollutants (ozone, NO_x, etc) among such vulnerable populations.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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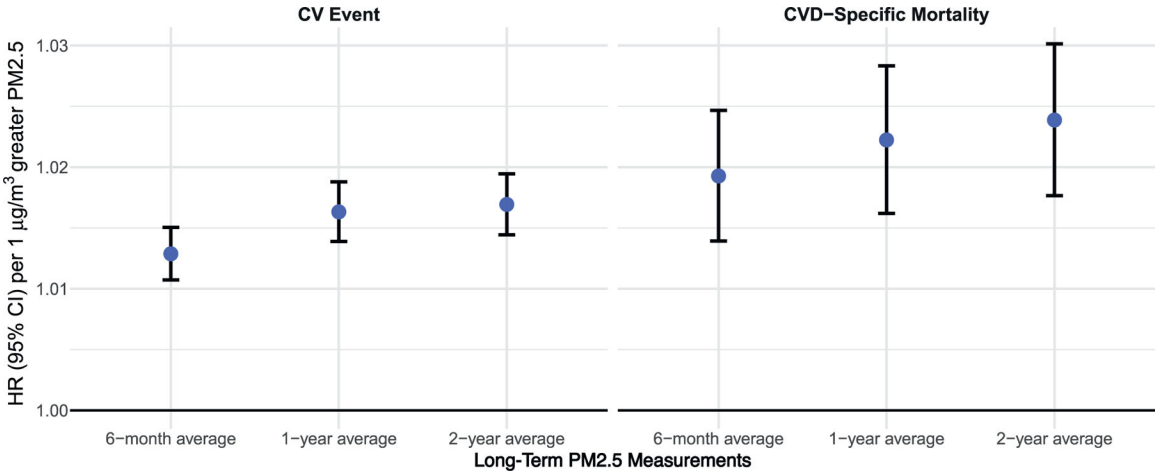

Figure 1.

Association of long-term ambient $PM_{2.5}$ exposures on CV event and CVD-specific mortality among HD patients, 2011–2016. All effect estimates reported here (given as HR and 95% CI) were obtained from models that adjusted for time since dialysis initiation, temperature, relative humidity, day of the week (DOW), season, age at dialysis initiation, race ethnicity, employment status at dialysis initiation, and geographic region (Northeast, Midwest, South, and West) at dialysis initiation. Abbreviations: CV, cardiovascular; CVD, cardiovascular disease; $PM_{2.5}$, particulate matter with a diameter of 2.5 microns.

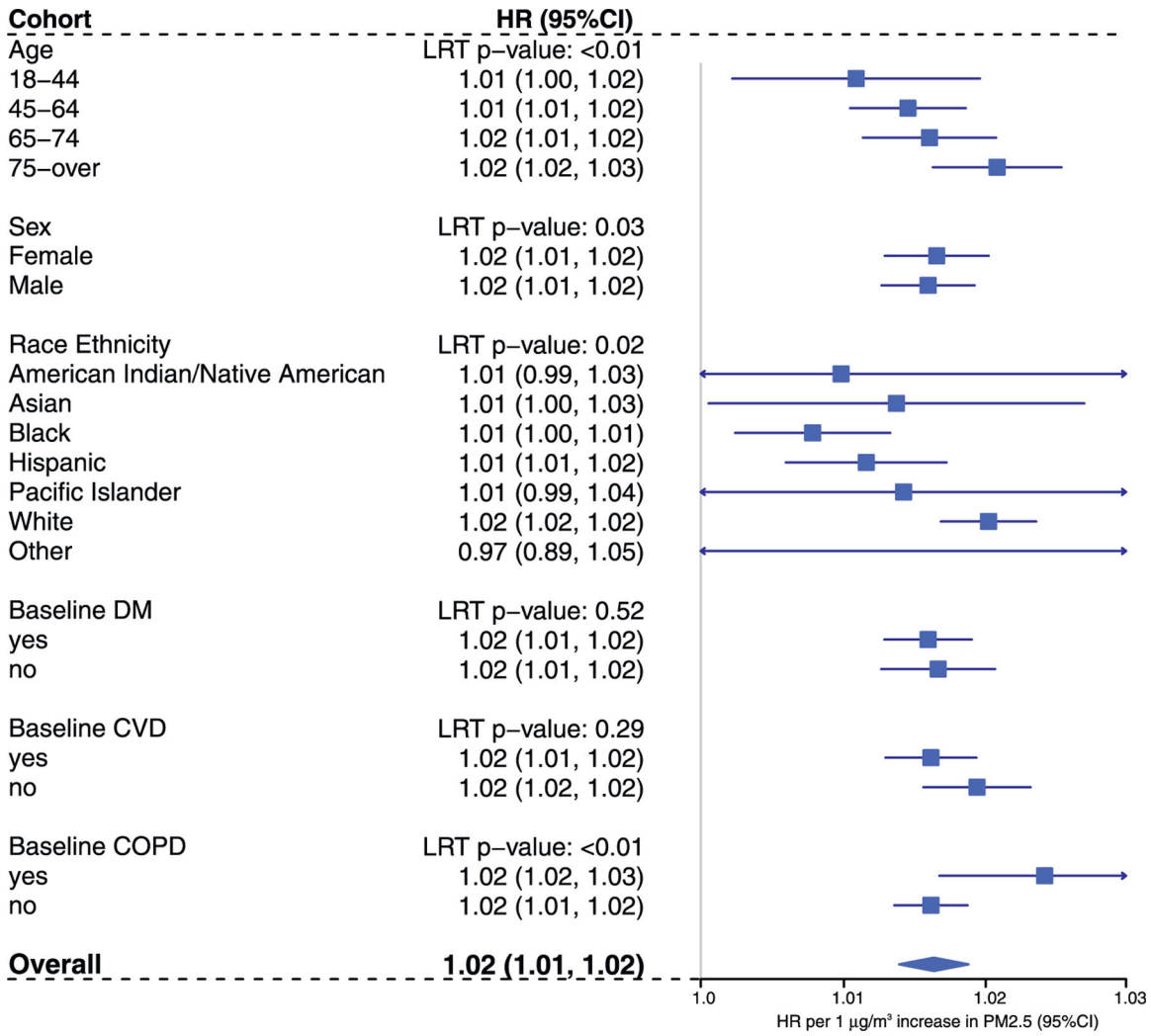

Figure 2.

CV event stratification analysis by age at dialysis initiation, sex, race, vascular access type, and comorbidity status at dialysis initiation. Estimates (HRs per 1 µg/m_3 greater $PM_{2.5}$) of association between annual average $PM_{2.5}$ exposure and first CV event since dialysis initiation among HD patients, 2011–2016. Effect estimates reported for age at dialysis initiation groups were adjusted for temperature, relative humidity, DOW, season, race ethnicity, employment status, and geographic region. Effect estimates reported for race ethnicity groups were adjusted for temperature, relative humidity, DOW, season, age at dialysis initiation, employment status, and geographic region. The rest estimates were obtained from models that adjusted for temperature, relative humidity, DOW, season, age at dialysis initiation, race ethnicity, employment status, and geographic region. Abbreviations: COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cardiovascular disease; DM, diabetes mellitus; DOW, day of the week; HR, hazard ratio; LRT, likelihood ratio test; $PM_{2.5}$, particulate matter with a diameter of 2.5 microns.

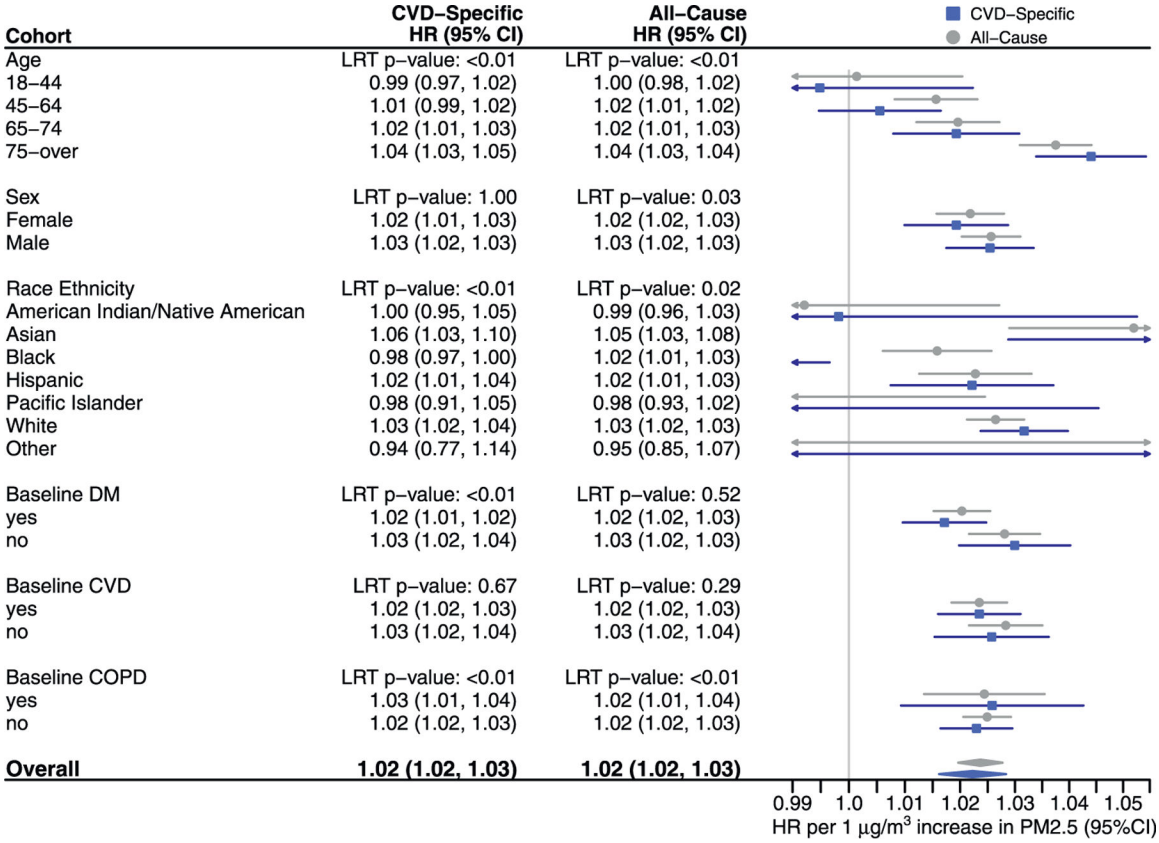

Figure 3.

CVD-specific and all-cause mortality stratification analysis by age at dialysis initiation, sex, race, vascular access type, and comorbidity status at dialysis initiation. Estimates (HRs per 1 µg/m3 greater $PM_{2.5}$) of association between annual average $PM_{2.5}$ exposure and CVD-specific and all-cause mortality among HD patients, 2011–2016. Effect estimates reported for age at dialysis initiation groups were adjusted for temperature, relative humidity, DOW, season, race ethnicity, employment status, and geographic region. Effect estimates reported for race ethnicity groups were adjusted for temperature, relative humidity, DOW, season, age at dialysis initiation, employment status, and geographic region. The rest estimates were obtained from models that adjusted for temperature, relative humidity, DOW, season, age at dialysis initiation, race ethnicity, employment status, and geographic region. Abbreviations: COPD, chronic obstructive pulmonary disease; CVD, cardiovascular disease; DM, diabetes mellitus; DOW, day of the week; HD, hemodialysis; HR, hazard ratio; LRT, likelihood ratio test; $PM_{2.5}$, particulate matter with a diameter of 2.5 microns.

Table 1.

Study Population Baseline Characteristics Overall and by Outcomes of Interest

Characteristics	Total	CVD-Specific Mortality	CV Event
No. of patients	314,079	35,857	208,113
Person-days	193,121,928	193,121,928	94,385,773
Age at HD initiation, y	63.6 ± 14.6	69.4 ± 13.2	65.4 ± 14.0
Age at HD initiation			
18–44 y	34,191 (10.9%)	1,808 (5.0%)	17,019 (8.2%)
45–64 y	119,140 (37.9%)	10,759 (30.0%)	74,068 (35.6%)
65–74 y	81,741 (26.0%)	10,280 (28.7%)	57,125 (27.5%)
75 y and older	79,007 (25.2%)	13,010 (36.3%)	59,901 (28.8%)
Follow-up time, y	1.7 ± 1.4	1.5 ± 1.2	0.7 ± 0.8
Follow-up time			
<1 y	132,344 (42.1%)	16,505 (46.0%)	163,151 (78.4%)
1–2 y	73,099 (23.3%)	9,116 (25.4%)	29,250 (14.1%)
2–3 y	48,238 (15.4%)	5,491 (15.3%)	10,277 (4.9%)
3–4 y	31,401 (10.2%)	3,106 (8.7%)	3,867 (1.9%)
>4 y	28,997 (9.2%)	1,639 (4.6%)	1,568 (0.8%)
BMI, kg/m2	29.9 ± 8.1	29.3 ± 8.0	29.8 ± 8.2
Female sex	131,209 (43.9%)	15,244 (42.5%)	93,832 (45.1%)
Race ethnicity			
American Indian/Alaskan Native	3,540 (1.1%)	352 (1.0%)	2,181 (1.0%)
Asian	10,003 (3.2%)	1,032 (2.9%)	6,142 (3.0%)
Black	91,057 (29.0%)	8,835 (24.6%)	59,604 (28.6%)
Hispanic	40,957 (13.0%)	3,911 (10.9%)	25,207 (12.1%)
Pacific Islander	2,037 (0.7%)	190 (0.5%)	1,189 (0.6%)
White	163,338 (52.0%)	21,322 (59.5%)	111,852 (53.7%)
Other	3,147 (1.0%)	215 (0.6%)	1,938 (0.9%)
Reported cause of kidney failure			
Diabetes	152,106 (48.4%)	18,734 (52.3%)	105,544 (50.7%)
Glomerulonephritis	20,846 (6.6%)	1,368 (3.8%)	11,351 (5.5%)
Hypertension	97,204 (31.0%)	11,530 (32.2%)	64,554 (31.0%)
Other	43,923 (14.0%)	4,225 (11.8%)	26,664 (12.8%)
Access type			
AVF	54,008 (18.1%)	4,937 (13.8%)	32,914 (15.8%)
Graft	9,527 (3.2%)	1,070 (3.0%)	6,543 (3.1%)
Catheter	235,042 (78.6%)	28,782 (80.3%)	159,809 (76.8%)
Other	496 (0.2%)	61 (0.2%)	327 (0.2%)
Baseline comorbidities			
CVD	160,760 (53.8%)	24,218 (67.5%)	123,121 (59.2%)

Characteristics	Total	CVD-Specific Mortality	CV Event
COPD	30,417 (10.2%)	5,220 (14.6%)	24,067 (11.6%)
Diabetes mellitus	178,489 (59.7%)	22,728 (63.4%)	128,114 (61.6%)
Geographic region			
Northeast	68,668 (21.9%)	8,831 (24.6%)	47,707 (22.9%)
Midwest	59,243 (19.9%)	6,033 (24.6%)	39,405 (18.9%)
West	40,001 (12.7%)	4,146 (11.6%)	24,398 (11.7%)
South	146,167 (46.5%)	16,847 (47.0%)	96,603 (46.4%)
Baseline employment status			
Employed	30,746 (9.8%)	2,082 (5.8%)	15,655 (7.5%)
Retired	196,525 (62.6%)	26,353 (73.5%)	139,909 (67.2%)
Unemployed	76,338 (24.3%)	6,793 (10.9%)	47,033 (22.6%)
Other	10,470 (3.3%)	629 (1.8%)	5,516 (2.7%)

Values for continuous variables given as mean ± SD. Abbreviations: AVF, arteriovenous fistula; BMI, body mass index; COPD, chronic obstructive pulmonary disease; CV, cardiovascular; CVD, cardiovascular disease; HD, hemodialysis.

Table 2.

ZIP Code–Level Long-term $PM_{2.5}$ Concentrations in Mortality and CV Event Analyses

	Mean ± SD	Range	Median (Q1-Q3)
Mortality Analysis (n = 193,121,928 Person-Days)			
Annual average $PM_{2.5}$, μg/m3	8.7 ± 1.8	0.9–21.3	8.7 (7.6–9.8)
6-month average $PM_{2.5}$, μg/m3	8.6 ± 2.0	0.8–31.6	8.5 (7.4–9.8)
2-year average $PM_{2.5}$, μg/m3	8.9 ± 1.8	1.3–20.4	9.0 (7.9–10.0)
CV Event Analysis (n = 94,385,773 Person-Days)			
Annual average	8.7 ± 1.9	0.9–21.3	8.8 (7.6–9.9)
6-month average	8.6 ± 2.1	0.8–31.6	8.6 (7.4–9.8)
2-year average	9.0 ± 1.8	1.3–20.4	9.0 (7.9–10.0)

Abbreviations: CV, cardiovascular; $PM_{2.5}$, particulate matter with a diameter of 2.5 microns; Q, quartile.