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Combined effects of air pollution and extreme heat events among ESKD patients within the Northeastern United States

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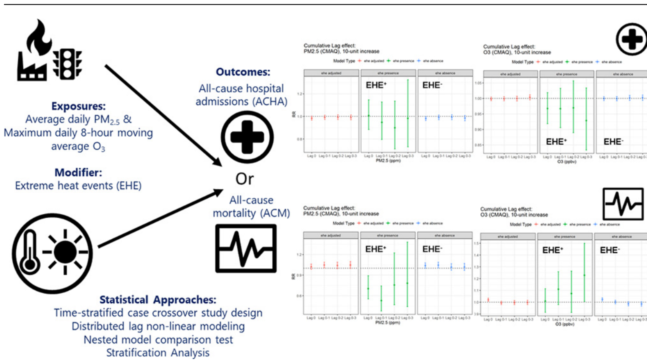
HIGHLIGHTS

- Daily $PM_{2.5}$ and O_3 exposures are associated with increased mortality risk as independent effects.
- Mortality risks due to ozone exposures are considerably increased during extreme heat events.
- Combined effects observed between air pollutants and extreme heat events with mortality.
- Mostly null associations between air pollutants and hospital admissions.

GRAPHICAL ABSTRACT



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ABSTRACT

Background: Increasing number of studies have linked air pollution exposure with renal function decline and disease. However, there is a lack of data on its impact among end-stage kidney disease (ESKD) patients and its potential modifying effect from extreme heat events (EHE).
Methods: Fresenius Kidney Care records from 28 selected northeastern US counties were used to pool daily all-cause mortality (ACM) and all-cause hospital admissions (ACHA) counts. County-level daily ambient $PM_{2.5}$ and ozone (O_3) were estimated using a high-resolution spatiotemporal coupled climate-air quality model and matched to ESKD patients based on ZIP codes of treatment sites. We used time-stratified case-crossover analyses to characterize acute exposures using individual and cumulative lag exposures for up to 3 days (Lag 0–3) by using a distributed lag nonlinear model framework. We used a nested model comparison hypothesis test to evaluate for interaction effects between air pollutants and EHE and stratification analyses to estimate effect measures modified by EHE days.
Results: From 2001 to 2016, the sample population consisted of 43,338 ESKD patients. We recorded 5217 deaths and 78,433 hospital admissions. A 10-unit increase in $PM_{2.5}$ concentration was associated with a 5% increase in ACM (rate ratio [$RR_{Lag0–3}$]: 1.05, 95% CI: 1.00–1.10) and same-day O_3 (RR_{Lag0}: 1.02, 95% CI: 1.01–1.03) after adjusting for extreme heat exposures. Mortality models suggest evidence of interaction and effect measure modification, though not always simultaneously. ACM risk increased up to 8% when daily ozone concentrations exceeded National Ambient

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Interaction
Effect modification

Air Quality Standards established by the United States, but the increases in risk were considerably higher during EHE days across lag periods.
Conclusion: Our findings suggest interdependent effects of EHE and air pollution among ESKD patients for all-cause mortality risks. National level assessments are needed to consider the ESKD population as a sensitive population and inform treatment protocols during extreme heat and degraded pollution episodes.

1. Introduction

The prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESKD), which represents the most advanced stage of CKD, are increasing across the globe (Bikbov et al., 2020; United States Renal Data System, 2020). The ESKD population is considered to be particularly vulnerable to environmental risk factors (Chan et al., 2014; Remigio et al., 2019; Xi et al., 2020). While previous studies have shown that exposure to air pollutants such as $PM_{2.5}$ (particulate matter with less than 2.5 μm in aerodynamic diameter) and ground-level ozone (O_3) can increase the risk of all-cause mortality, hospital admissions, and emergency room visits within the general population (Heft-Neal et al., 2018; Peng et al., 2013; Shang et al., 2013; Wellenius et al., 2006), its impact on ESKD patients remains largely under-studied. Physiologically, exposure to $PM_{2.5}$ is associated with vascular changes that can lead to vasoconstriction and increased blood pressure (Bowe et al., 2018; Chuang et al., 2005; Jeong et al., 2020). This response can decrease renal blood flow and, ultimately, reduce estimated glomerular flow (eGFR) and increase urinary albumin-creatine ratios (Wu et al., 2020). Inflammatory mediators induced by airborne particulate matter and other contaminants in the lungs can impact the circulatory system, resulting in systemic inflammation, oxidative stress, and damage to distal organs that include the kidneys. (Bowe et al., 2019; Huang et al., 2020; Mills et al., 2011; Nemmar et al., 2016; Pope et al., 2016). These responses can ultimately result in adverse vascular injuries that can compromise renal function (e.g., eGFR or fluid imbalance), contribute to renal tubular necrosis, and, consequently, acute kidney injuries (Nemmar et al., 2010; Wang et al., 2020a). Such mechanisms, in addition to preexisting comorbidities and lifestyle risk factors, are linked to the development of chronic kidney disease (CKD) and end-stage renal disease (ESKD)- the most severe stage of CKD (Wong et al., 2017). The United States Renal Data System (USRDS) has reported that the national prevalence of CKD risk factors and ESKD is rising (United States Renal Data System, 2020).

An increasing number of studies have linked exposure to air pollution with elevated CKD incidence and CKD progression to ESKD (Blum et al., 2020; Bowe et al., 2017; Bowe et al., 2018; Chan et al., 2018; Wu et al., 2020). In the US, the association between air pollution and renal-related mortality was first observed within a mining population in the Appalachian region (Hendryx, 2009). Among US veterans (Bowe et al., 2017; Mehta et al., 2016), increases in particulate matter, nitrogen dioxide, and carbon monoxide, as individual exposures, were associated with eGFR decline- a precursor to developing CKD and ESKD progression. Another study from Taiwan reported a 6% increased risk of developing chronic kidney disease per 10 $\mu g/m^3$ increase in $PM_{2.5}$ (Chan et al., 2018).

There is a lack of data regarding how specific air pollutants can impact patients living with ESKD, with the only study investigating the association between wildfire-related $PM_{2.5}$ levels and all-cause mortality among ESKD patients (Xi et al., 2020). Likewise, very few studies have investigated how temperature (Remigio et al., 2022) and extreme heat events (Remigio et al., 2019) could increase the risk of hospitalization and mortality among ESKD patients. There is a lack of data regarding the combined effects of acute air pollution and extreme heat among ESKD patients. Addressing this knowledge gap is important for two reasons – i) frequency, duration, and intensity of extreme heat events are increasing and will continue to do so due to a warming climate (Crimmins et al., 2016; US Global Change Research Program, 2016), ii) extreme heat events can increase tropospheric ozone production (Hou and Wu, 2016), and contribute to more frequent wildfires that can degrade regional air quality (Peng et al., 2013; Peterson et al., 2014; Reid et al., 2019; Tao et al., 2020). To address this, we investigated the combined role of short-term air pollution ($PM_{2.5}$ and O_3) exposure and extreme heat on all-cause mortality risks (ACM) and all-cause hospital admissions (ACHA) among ESKD patients undergoing hemodialysis at FKC facilities located within the Northeast United States.

2. Methods

2.1. Study population and outcome measures

We created a cohort of ESKD patients undergoing hemodialysis treatments at FKC clinics in selected northeastern US counties between 2001 and 2016 ($N = 48{,}338$). These patients were treated at 104 clinics scattered across 28 counties between Maine and the District of Columbia (Fig. 1). ZIP codes from the FKC clinics served as a proxy for linking recorded outcomes with county-specific air pollution and EHE exposures. Counties were identified and enumerated using Federal Information Process Standards (FIPS) codes. Patients with less than 20 recorded treatments were excluded from the study. We subset ACM and ACHA events during warmer months (May to September: MJJAS) as two unique outcomes for our analyses.

2.2. Exposure assessment

The main exposures of interest are county-level daily average $PM_{2.5}$ concentration, daily 8-h average O_3 concentrations, and extreme heat events (EHE). We obtained air quality data using model outputs from coupled Climate-Weather Research and Foresting and Community Multiscale Air Quality (CWRF-CMAQ) simulations (He et al., 2020; Tao et al., 2020). Briefly, local weather-air quality conditions were simulated through the state-of-the art regional climate dynamic downscaling and atmospheric chemical transport modeling. Detailed information on the modeling system can be found elsewhere (He et al., 2020, Tao et al., 2020). The CWRF-CMAQ model simulated hourly concentrations of O_3 and $PM_{2.5}$ at a 30 × 30 km grid over the Contiguous United States (CONUS). We calculated daily mean $PM_{2.5}$ and daily maximum 8-hour average (MDA8) O_3 concentrations for the selected counties with FKC clinics using all the grids contained within each county boundary. County-specific and regional summary statistics for studied air pollutants are shown in supplementary materials (**Tables S1-S3**). Averaging times for modeled $PM_{2.5}$ and O_3 estimates are based on USEPA National Ambient Air Quality Standards (NAAQS) (United States Environmental Protection Agency, 2020). Additionally, we dichotomized continuous air pollution measures using NAAQS as thresholds (1 = NAAQS exceedance, 0 = no exceedance): 70 parts per billion by volume [ppbv] for MDA8 O_3 and 35 $\mu g/m^3$ for daily $PM_{2.5}$ (United States Environmental Protection Agency, 2020).

To identify EHEs, we used calendar day-specific 95th percentile temperature thresholds derived using 30 years of baseline temperature data (1960–1989) as previously described (Remigio et al., 2019; Romeo Upperman et al., 2015) within Philadelphia. The daily maximum temperature for each day during the study period were compared to their respective calendar day-specific thresholds and then categorized as an 'extreme heat event' if the value exceeded the upper 95th percentile threshold during baseline. County-level EHE data were matched to ESKD patient's clinic ZIP code. EHE is a useful marker for extreme heat events driven by climate change and compatible with event-based health data. Metric development and methodology are described elsewhere (Romeo Upperman et al., 2015).

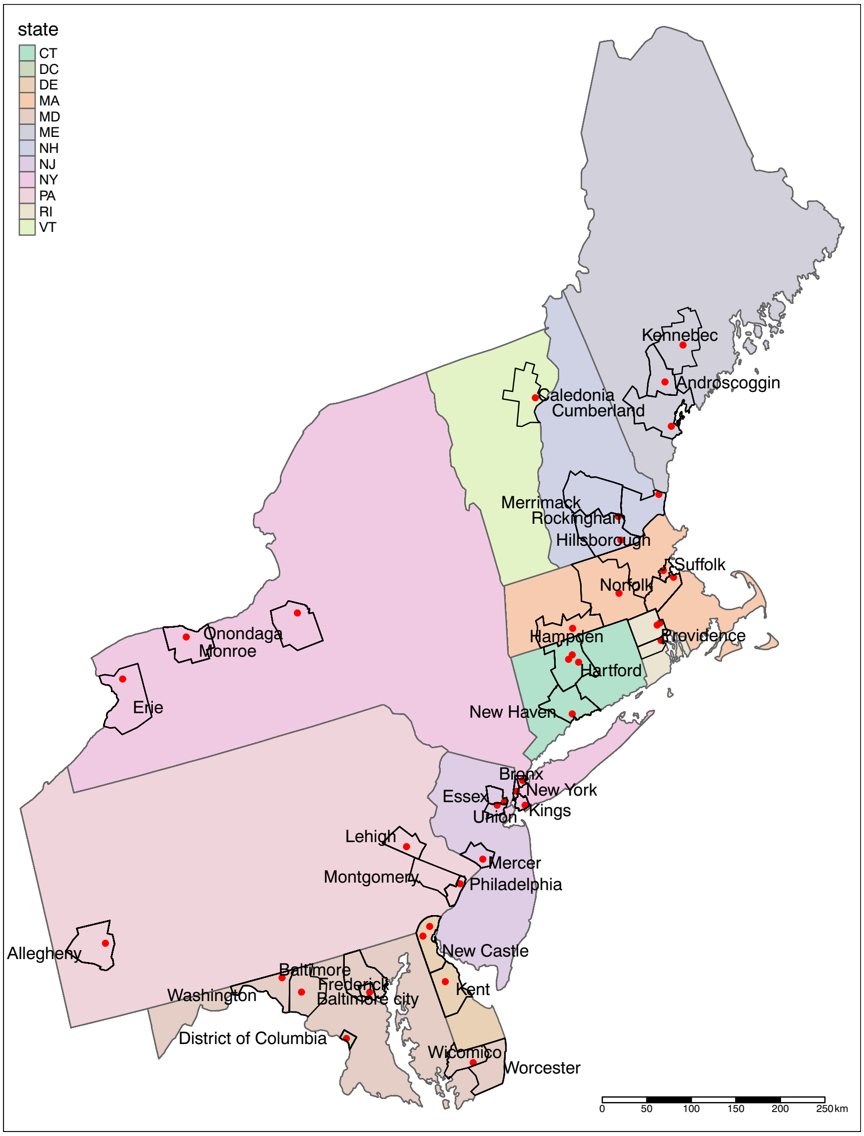

Fig. 1. Map of focused counties within Northeastern study catchment area.

2.3. Statistical analysis

We applied a time-stratified case-crossover design to evaluate the short-term effects of intermittent environmental exposures ($PM_{2.5}$, O_3, and EHE) on event-based daily health endpoints (ACM and ACHA) (Fisher et al., 2017; Lu and Zeger, 2007; Madrigano et al., 2015; Remigio et al., 2019; Soneja et al., 2016; Zhou et al., 2017). Because this study design entails using each case as his/her own control, the methodology has added advantages of eliminating measured and unmeasured time-invariant individual-level confounders, such as age, race, sex, and socioeconomic status (Greenland, 1996; Jaakkola, 2003; Janes et al., 2005) and temporal confounding, such as seasonality and long-term trends, by design (Bateson and Schwartz, 1999; Janes et al., 2005).

We used the conditional Poisson model (CPM) to estimate regional-level air pollutant effects for crude and EHE-adjusted models. The regression model accounts for varying population changes during a study period and accounts for over-dispersion (Armstrong et al., 2014). As part of the self-matching mechanism, strata indicators were included to match the day of the week, month, year, and county. Air pollution exposures occurring on the day of outcome events (Lag 0) and exposures occurring in days prior to outcomes (Lag1, Lag 2, and Lag3) were examined in additional models to capture the delayed effects of acute exposures. Overall cumulative lag effects were estimated for 0–3 lag days for continuous and NAAQS-based predictors. We also incorporated delay effects for EHE up to three days to match temporal consistency with air pollutant exposures. For adjusted models, we matched lag structures from air pollutant parameters to EHE. Natural cubic spline functions were applied to O_3 and $PM_{2.5}$ terms.

All analyses were restricted to MJJAS months to emphasize air quality at higher temperatures and adjusted for EHE. Measures of associations were reported as rate ratios (RRs) using 95% confidence intervals (95% CI). The rate ratios for $PM_{2.5}$ and O_3 as continuous variables were expressed as per 10-$\mu g/m^3$ and 10-ppbv incremental increases. All analyses were conducted using R statistical software version 3.6.1 (R Core Team, 2019). Statistical software for CPR and DLNM is available as R packages through CRAN. The *gnm* and *dlnm* packages are peer-reviewed and frequently updated (Gasparrini, 2011; Turner and Firth, 2020).

2.4. Interaction hypothesis testing and stratification analysis

This study tested for the interaction and effect modification between extreme heat events and air pollution on all-cause hospital admission and all-cause mortality for up to three days after exposure. As an initial analysis to evaluate interaction effects between cumulative lag air pollutants and EHE, we compared distributed nonlinear lag model (DLNM) models without interaction terms (reduced) and with interaction terms (full) using goodness-of-fit tests in non-stratified models. Nested models were compared using *F*-tests. The addition of interaction terms between cross basis terms representing cumulative air pollution exposures over lags of 0–3 days and cumulative EHE exposures over lags of 0–3 days was used mainly to determine model improvement and serve as an indirect model specification test for interaction effects (Li et al., 2015; Ren et al., 2006).

As the second step, we conducted an EHE-stratified analysis using the same health endpoints and cumulative lagged effect to estimate air pollution-related risks due to EHE modification. Prior research on acute air pollution effects has successfully used subgroup analysis (e.g., EHE vs. non-EHE) for effect modification analyses using a DLNM framework (Breitner et al., 2014; Iranpour et al., 2020; Li et al., 2015). This approach can estimate a cumulative net effect along defined lag periods in addition to individual lags (Gasparrini and Armstrong, 2013; Gasparrini et al., 2010). In this work, we adapted the case-crossover analysis and applied DLNM to estimate cumulative lag effects in EHE-stratified models. Similar to adjusted EHE models, lag structure periods for air pollutant exposures were also applied to the EHE variable. For example, for calculating estimates based on cumulative Lag 0–2 exposure for $PM_{2.5}$, individual Lag 0, Lag 1, and Lag 2 EHEs were used for stratification. We specified natural cubic splines and natural B-spline with 2 degrees of freedom per year for air pollutant and lag model fits, respectively. Results from the stratification analysis present variation in air pollution-related effect measures across EHE-strata. Statistical significance for effect modification was conducted using methods described in similarly designed work (Remigio et al., 2019; Zanobetti et al., 2014).

3. Results

Among 48,338 eligible FKC patients in 28 selected counties within the northeastern US region (Fig. 1), there were 5217 deaths and 78,433 hospital visits from 2001 to 2016 during MJJAS months. Sixty percent of the patients reported having diabetes (Table 1). There were near equal proportions of non-Hispanic Black (43.4%) and non-Hispanic White (42.2%). Daily $PM_{2.5}$ and O_3 concentrations were both significantly higher during EHE days compared to non EHE days ($PM_{2.5}^{EHE}$ mean (SD) = 13.08 (5.91) μg/m^3 vs $PM_{2.5}^{non\text{-}EHE}$ = 8.35 (5.53) μg/m^3; and O_3^{EHE} = 75.38 (19.75) ppbv vs $O_3^{non\text{-}EHE}$ = 62.63 (15.84) ppbv (Table 2). There was a total of 218 and 17,694 NAAQS exceedance days for CMAQ-based $PM_{2.5}$ and O_3 estimates during the 15-year period. County-level daily $PM_{2.5}$ and O_3 estimates are shown in **Tables S4-1 and S4-2**. Overall, the Pearson correlation coefficients (*r*) between CWRF-CMAQ derived $PM_{2.5}$ and O_3 concentrations varied across counties and ranged from 0.40 to 0.63 (**Fig. S4-1**). The regional correlation was moderate ($r = 0.54$, $p < 2.2e\text{-}16$) after aggregation (**Fig. S4-2**). During the study period, there were 9.7 EHEs/year/county with a standard deviation (SD) of 6.5 and a regional mean daily maximum temperature of 25.6 °C (SD = 5.3) during the warmer months.

Table 1
Summary statistics for the study population and exposures from 2001 to 2016 from May to September (MJJAS) months.

Characteristics	
Counties, n	28
Clinics, n	104
Patients, n	48,338
Race/Ethnicity, n (%)	
Hispanic	3834 (7.9)
non-Hispanic Black	20,974 (43.4)
non-Hispanic White	20,398 (42.2)
Asian	756 (1.6)
Other/Not Reported	538 (1.1)
Diabetes	
Yes, n (%)	28,772 (59.9)
Sex	
Men, n (%)	27,782 (57.5)

Table 2
Summary for health outcomes and air pollution from 2001 to 2016 stratified by extreme heat events during May to September (MJJAS) months. Significant mean differences between EHE and non-EHE strata are denoted by $p < 0.05$.

		EHE Stratification		
	All	EHE	Non-EHE	p-value
Mortality, n (%)	5217 (10.8)	344 (0.7)	4873 (10.1)	0.198
Hospital admissions, n	78,443	5058	73,375	0.121
Hospital admission rate, #/person, mean (SD)	2.89 (3.1)	1.2 (0.5)	3.2 (3.3)	<0.001
Air pollution exposures				
CMAQ PM2.5 [μg/m3], mean (SD)	8.6 (5.7)	13.1 (5.9)	8.4 (5.5)	<0.001
CMAQ PM2.5 NAAQS Exceedance	218 (0.3)	14 (0.02)	204 (0.2)	0.863
CMAQ O3 [ppbv], mean (SD)	63.4 (16.4)	75.4 (19.8)	62.6 (15.8)	<0.001
CMAQ O3 NAAQS Exceedance	17,694 (23.8)	2094 (2.8)	15,600 (21.0)	<0.001

3.1. Main effect analysis

Associations between short-term $PM_{2.5}$ and O_3exposure and risk of ACM and ACHA are presented in Tables 3 and 4, respectively, first as a 10-unit increase in exposure (Models 1 & 2), then as ambient air standard exceedances for $PM_{2.5}$ or O_3 (Models 3 & 4). Models 2 & 4 display adjusted main effect estimates for air pollutants and EHE. A 10 μg/m^3 increase in $PM_{2.5}$ exposures (Lag 0–3) was associated with a 5% increase in mortality among ESKD patients after adjusting for cumulative EHE exposures ($RR_{Lag0–3}$:1.05, 95% CI: 1.00–1.10). $PM_{2.5}$ NAAQS exceedance was associated with increased ACM risk. However, the risk increases were not statistically significant ($p < 0.05$), irrespective of the lag structure (Table 3). A 10 ppbv increase in ozone exposure was associated with a 2% increase in mortality (RR_{Lag0}:1.02, 95% CI: 1.01–1.03). Likewise, same-day NAAQS ozone exceedances were associated with an 8% increase in mortality (RR_{Lag0}:1.08, 95% CI: 1.04–1.13). EHE appeared not to confound the association between ozone and mortality since the effect estimates for EHE-adjusted models were virtually identical (Table 3). Overall, ACM rates from both pollutants dampened as lag periods increased. In ACHA models (Table 4), we mainly observed null estimates across all model fits for each pollutant except for significant negative associations for cumulative Lag 0–3 in NAAQS-based $PM_{2.5}$ ($RR_{Lag0\text{-}3}$: 0.73, 95% CI: 0.57–0.93).

3.2. Interaction hypothesis testing and stratification analysis

Model comparison test results (F-statistic, degrees of freedom (df), and *p*-value) examining the inclusion of cumulative EHE across respective lags as an interactive term are shown in Tables 5-6. Overall, we observed some instances of significant interaction between extreme heat events and continuous measures of air pollutants for ACM (Lag 0–3 $PM_{2.5}$ & EHE: F = 2.655 p = 0.031; and Lag 0–3 O_3 & EHE: F = 3.915, p = 0.004). Similar interactive effects between O_3 & EHE were also observed for Lag 0–2 and Lag 0–1 exposures (Table 5). Such interactive effects were not observed for ACHA (**Supplemental Table 4**).

We stratified our analysis by EHE to investigate if the associations between air pollution and ACM are different between EHE and non-EHE days. We observed some evidence of effect modification by EHE for ozone exposure. A 10 ppbv increase in ozone exposure across 4-days (Lag 0–3) resulted in 23% increases in risk during EHE days ($RR_{Lag0–3}$:1.23, 95% CI: 1.01–1.50) when compared to non-EHE days ($RR_{Lag0–3}$:0.99, 95% CI: 0.97–1.00). The results for PM exposure were reversed where we observed decreased risk during EHE days (RR_{Lag0}:0.70, 95% CI: 0.55–0.89) and increased risk observed during non-EHE days

Table 3
Rate ratios and 95% confidence intervals for associations between air pollution and all-cause mortality (ACM) across individual lags and cumulative 4-day lag (Lag 0–3). Models 1 & 2 represent continuous exposure (10-unit increment). Models 3&4 represent categorical exposure (NAAQS exceedance: Daily maximum 8-h average of 70 ppbv for Ozone and Daily average of 35 μg/m^3 for $PM_{2.5}$).

		Mortality					
		Model 1 Unadjusted, continuous	Model 2 Adjusted, continuous		Model 3 Unadjusted, NAAQS	Model 4 Adjusted, NAAQS	
Pollutant type	Lag	Air Pollutant	Air Pollutant	EHE	Air Pollutant	Air Pollutant	EHE
$PM_{2.5}$	Lag 0	1.03 (0.99–1.06)	1.02 (0.98–1.06)	1.07 (0.99–1.57)	1.14 (0.85–1.53)	1.14 (0.85–1.53)	1.09 (1.01–1.17)
	Lag 1	1.02 (0.98–1.07)	1.02 (0.98–1.07)	0.95 (0.87–1.04)	1.01 (0.73–1.41)	1.01 (0.72–1.41)	0.96 (0.88–1.04)
	Lag 2	0.99 (0.95–1.03)	0.99 (0.95–1.04)	0.94 (0.85–1.03)	1.04 (0.72–1.51)	1.04 (0.72–1.51)	0.94 (0.86–1.03)
	Lag 3	1.00 (0.96–1.04)	1.01 (0.97–1.05)	0.97 (0.90–1.05)	0.98 (0.70–1.38)	0.98 (0.70–1.38)	0.97 (0.90–1.05)
	Lag 0–3	1.04 (0.99–1.08)	1.05 (1.00–1.10)	0.92 (0.83–1.03)	1.19 (0.74–1.92)	1.18 (0.73–1.92)	0.95 (0.85–1.05)
O_3	Lag 0	1.02 (1.01–1.04)	1.02 (1.01–1.03)	1.09 (1.01–1.18)	1.09 (1.04–1.13)	1.08 (1.04–1.13)	1.07 (0.99–1.16)
	Lag 1	0.97 (0.96–0.99)	0.97 (0.96–0.99)	0.97 (0.88–1.05)	0.97 (0.92–1.01)	0.97 (0.93–1.01)	0.96 (0.88–1.05)
	Lag 2	1.00 (0.99–1.02)	1.00 (0.99–1.02)	0.94 (0.86–1.03)	0.94 (0.98–1.02)	0.98 (0.94–1.03)	0.94 (0.86–1.03)
	Lag 3	1.00 (0.99–1.01)	1.00 (0.99–1.02)	0.97 (0.89–1.05)	1.01 (0.96–1.05)	1.01 (0.97–1.06)	0.97 (0.90–1.05)
	Lag 0–3	1.00 (0.98–1.01)	1.00 (0.98–1.01)	0.96 (0.87–1.07)	1.04 (0.97–1.11)	1.05 (0.98–1.12)	0.95 (0.85–1.05)

(RR_{Lag0}:1.04, 95% CI: 1.00–1.08). Analogous analysis for ACHA showed null results **(Supplemental Table 4)**.

Similarly, we extended the same stratification analysis using a dichotomous classification for NAAQS exceedance (Table 6). All-cause mortality increased when ozone levels exceeded the NAAQS threshold. Notably, the increases in mortality risk associated with ozone NAAQS exceedance were considerably higher during EHE days. For example, same-day mortality risk increased by 22% (RR_{Lag0}:1.22, 95% CI: 1.07–1.40) during extreme heat days, whereas risk increased 9% during non-EHE (RR_{Lag0}:1.09, 95% CI: 1.04–1.14. Evidence of EHE modification between O3-NAAQS exceedance and ACM was observed in Lag 0–2 models (EHE days RR_{Lag0-2}:1.34, 95% CI: 1.09–1.66 vs. non-EHE days RR_{Lag0-2}:1.03, 95% CI: 0.97–1.10). We did not observe such association for ACHA outcomes. Analysis using $PM_{2.5}$ NAAQS exceedances were excluded due to limited data.

4. Discussion

In this regional-scale analysis of an ESKD population undergoing HD treatments in FKC clinics located within 28 northeastern US counties, exposure to $PM_{2.5}$ and O_3 were associated with increased risk of mortality. Findings regarding hospitalizations were mainly null. There were multiple instances of significant interaction between extreme heat events and continuous measures of ozone (Lag 0–1, Lag 0–2, and Lag 0–3) and $PM_{2.5}$ (Lag 0–3) in ACM models. We found examples of qualitative effect

Table 4
Rate ratios and 95% confidence intervals for associations between air pollution and all-cause hospital admission (ACHA) across individual lags and cumulative 4-day lag (Lag 0–3). Models 1 & 2 represent continuous exposure (10-unit increment). Models 3&4 represent categorical exposure (NAAQS exceedance: Daily maximum 8-h average of 70 ppbv for Ozone and Daily average of 35 μg/m^3 for $PM_{2.5}$).

		Hospital admissions					
		Model 1 Unadjusted, continuous	Model 2 Adjusted, continuous		Model 3 Unadjusted, NAAQS	Model 4 Adjusted, NAAQS	
Pollutant type	Lag	Air pollutant	Air pollutant	EHE	air pollutant	Air pollutant	EHE
$PM_{2.5}$	Lag 0	0.99 (0.97–1.01)	0.99 (0.97–1.00)	1.03 (1.00–1.07)	0.96 (0.81–1.13)	0.96 (0.82–1.14)	1.03 (0.99–1.06)
	Lag 1	1.01 (0.99–1.03)	1.01 (0.99–1.03)	1.00 (0.96–1.04)	0.90 (0.75–1.09)	0.90 (0.75–1.08)	1.00 (0.96–1.04)
	Lag 2	1.00 (0.98–1.01)	1.00 (0.98–1.02)	0.99 (0.91–1.03)	0.97 (0.82–1.15)	0.97 (0.82–1.15)	0.95 (0.91–0.99)
	Lag 3	1.00 (0.98–1.02)	1.00 (0.98–1.01)	1.03 (0.99–1.06)	0.86 (0.74–1.01)	0.87 (0.74–1.01)	1.03 (0.99–1.06)
	Lag 0–3	0.99 (0.97–1.01)	0.99 (0.97–1.01)	1.00 (0.96–1.05)	0.73 (0.57–0.93)	0.73 (0.57–0.93)	1.00 (0.96–1.05)
O_3	Lag 0	1.00 (0.99–1.00)	1.00 (0.99–1.00)	1.03 (0.99–1.07)	1.00 (0.98–1.02)	1.00 (0.98–1.02)	1.03 (0.99–1.06)
	Lag 1	1.00 (0.99–1.01)	1.00 (0.99–1.01)	1.00 (0.96–1.04)	1.02 (1.00–1.04)	1.02 (1.00–1.04)	1.00 (0.96–1.04)
	Lag 2	1.00 (0.99–1.01)	1.00 (0.99–1.01)	0.95 (0.91–0.99)	0.99 (0.97–1.01)	0.99 (0.97–1.01)	0.95 (0.91–0.99)
	Lag 3	1.00 (1.00–1.01)	1.00 (1.00–1.01)	1.02 (0.99–1.06)	1.00 (0.98–1.02)	1.00 (0.98–1.02)	1.03 (0.99–1.06)
	Lag 0–3	1.00 (0.99–1.01)	1.00 (0.99–1.01)	0.99 (0.95–1.04)	1.01 (0.98–1.04)	1.01 (0.98–1.04)	1.00 (0.95–1.05)

Table 5
Adjusted main effect, model comparison test outputs for interaction (F-statistic, degrees of freedom (df), *p*-value), and EHE-stratified effects. Results displayed across cumulative Lag 0, Lag 0–1, Lag 0–2, and Lag 0–3 lag structures using $PM_{2.5}$ and O_3 exposures and ACM outcome (per 10 μg/m^3 for $PM_{2.5}$ and 10 ppbv for O_3). Bold values denote significant modification.

Lag Structure	Air Pollutant	RR (95% CI)	Interaction with EHE		EHE Stratification	
			F-test, df	p-value	EHE Days	Non-EHE Days
Lag 0–3	$PM_{2.5}$	1.05 (1.00–1.10)	F(2.655), 4	p = 0.031	0.78 (0.44–1.38)	1.02 (0.97–1.07)
	O_3	1.00 (0.98–1.01)	F(3.915),4	p = 0.004	**1.23 (1.01–1.50)**	**0.99 (0.97–1.00)**
Lag 0–2	$PM_{2.5}$	1.04 (0.99–1.09)	F(2.129), 3	*p* = 0.094	0.76 (0.92–1.22)	1.02 (0.97–1.07)
	O_3	0.99 (0.98–1.01)	F(4.430), 3	p = 0.004	1.07 (0.91–1.26)	0.99 (0.97–1.00)
Lag 0–1	PM2.5	1.05 (1.00–1.09)	F(2.694), 2	*p* = 0.068	**0.53 (0.38–0.74)**	**1.04 (1.00–1.09)**
	O_3	0.99 (0.98–1.01)	F(3.857), 2	*p* = 0.021	1.11 (0.98–1.26)	1.00 (0.99–1.02)
Lag 0	$PM_{2.5}$	1.02 (0.98–1.06)	F(2.261), 1	*p* = 0.133	**0.70 (0.55–0.89)**	**1.04 (1.00–1.08)**
	O_3	1.02 (1.01–1.03)	F(0.610), 1	*p* = 0.435	1.01 (0.91–1.11)	1.02 (1.01–1.04)

modification (Bours, 2021) where cumulative lag structures with significant effect modification (Lag 0–3 O_3, Lag 0–1 $PM_{2.5}$, and Lag 0 $PM_{2.5}$) displayed opposite direction of effects between EHE and non-EHE days within continuous exposure models for ACM. Whereas for O_3-NAAQS exceedance analyses, Lag 0–2 ACM exhibited quantitative effect modification (Bours, 2021) where EHE-stratified effects suggest more substantial effects during EHE-days when compared to non-EHE days. Also, mostly all cumulative ozone exposures yielded increased effect sizes for EHE days compared to non-EHE days in this study.

Our study provided preliminary evidence that extreme heat events can interact with EHE and modify the short-term association between $PM_{2.5}$ and O_3-related mortality. The findings are consistent with prior studies that have confirmed interaction and effect modification by temperature between air pollutants and mortality among the general population (Chen et al., 2018b; Kim et al., 2015; Li et al., 2015; Ren et al., 2006; Stafoggia et al., 2008). By comparison, analyses did not suggest such effect modification for ACHA outcomes and NAAQS-based exposure models. While few studies have shown the independent effect of air pollution on ESKD patients (Wyatt et al., 2020; Xi et al., 2020), this work is one of the first studies to demonstrate the combined effect between EHE and air pollution among ESKD patients. Understanding ESKD sensitivities from heat-air quality exposures is critical, especially when considering projected increases in average regional temperatures and extreme heat frequencies and durations within the near term (Chen et al., 2018a). As an example, increased temperature projections will very likely increase ozone production, and as a result, contribute to deleterious human health effects. Recent work has highlighted the complex relationships between air pollution, greenhouse gases, and climate change as stressors that can, directly and indirectly, impact human health as well as the natural environment (Orru et al., 2017; Sillmann et al., 2021). Though, region-specific efforts in evaluating and anticipating combined health impacts for vulnerable populations such as the ESKD population are scant. Recent environmental and occupational epidemiological work has identified air pollution and heat stress exposures as risk factors for declining renal function and chronic kidney disease. The heat-air quality interdependence within the context of a changing climate and its impact among the ESKD population also remains relatively unknown.

Unhealthy levels of $PM_{2.5}$ and ground-level O_3 are known to impair breathing, trigger asthmatic episodes, and exacerbate respiratory-related illnesses (Lippmann, 1989; Lovasi et al., 2013; Sapkota et al., 2020). In this work, we extend these findings to include mortality risk among ESKD patients. Our findings have clinical implications as exposure to these pollutants can exacerbate shortness of breath and result in unintended complications. This is especially critical since HD patients commonly have to manage respiratory-related symptoms caused by fluid build-up in the lungs between dialysis treatments (Zoccali et al., 2013).

Regionally, our findings do suggest that exceeding regulatory ozone NAAQS may substantially increase mortality risk among ESKD patients. An additional layer of importance is the consideration of ESKD patients as a priority population consisting of individuals with chronic healthcare needs (Agency for Healthcare Research and Quality, 2021; Moy et al., 2005) for developing air quality standards, in addition to older adults, children, and persons with asthma. Atmospheric warming due to ongoing climate change can enhance ground-level ozone production during warmer months (Chen et al., 2018a; He et al., 2016; He et al., 2018; Weaver et al., 2009; Wuebbles et al., 2017). Our results indicate that ESKD patients may face a disproportionate mortality risk during periods of extreme heat and high ozone levels co-occurring as a compound hazard.

Methodologically, we included interaction and effect modification analyses to appreciate the nuanced interdependent effects (VanderWeele, 2009). As expected, we observed some perceived disagreement for evidence of interactive effects and effect modification between stratum-based effect estimates. Li and colleagues have suggested that comparing point estimate differences between EHE strata as a direct approach may create unintended measurement error due to loss of statistical variability when using categorized variables (Li et al., 2015). Also, we may expect differences between interaction and effect modification analyses since our model comparison tests involved the use of a complex interaction term involving two bidimensional variables. The EHE variable represented a complexity that is not suitable for subgroup analyses. A hallmark feature for interpreting interaction analyses is that any observed significant interaction between EHE and air pollutants suggests that both exposures have equal

Table 6
Adjusted main effect, model comparison test outputs for interaction (F-statistic, degrees of freedom (df), *p*-value), and EHE-stratified effects. Results displayed across cumulative Lag 0, Lag 0–1, Lag 0–2, and Lag 0–3 lag structures using NAAQS-O_3 exceedance exposures and ACM & ACHA outcomes (exceeded NAAQS vs. not exceeded NAAQS (ref)). Bold values denote significant modification.

Outcome	Lag structure	RR (95% CI)	Interaction test		EHE stratification	
			F-test, df	p-value	EHE Days	Non-EHE days
Mortality	0–3	1.05 (0.98–1.12)	F(1.614), 4	*p* = 0.168	1.29 (1.00–1.66)	1.04 (0.97–1.11)
	0–2	1.03 (0.97–1.10)	F(0.813),3	*p* = 0.487	1.34 (1.09–1.66)	1.03 (0.97–1.10)
	0–1	1.05 (1.00–1.11)	F(1.107), 2	*p* = 0.330	1.15 (0.97–1.38)	1.05 (1.00–1.11)
	0	1.08 (1.04–1.13)	F(0.223), 1	*p* = 0.636	1.22 (1.07–1.40)	1.09 (1.04–1.14)
Hospital Admissions	0–3	1.01 (0.98–1.04)	F(1.401), 4	*p* = 0.231	0.70 (0.47–1.02)	0.70 (0.47–1.02)
	0–2	1.01 (0.98–1.04)	F(1.680), 3	*p* = 0.221	0.70 (0.50–1.00)	1.00 (0.97–1.03)
	0–1	1.01 (0.99–1.03)	F(1.841), 2	*p* = 0.159	0.85 (0.64–1.11)	1.00 (0.98–1.03)
	0	1.00 (0.98–1.02)	F(1.316), 1	*p* = 0.251	1.00 (0.82–1.21)	0.99 (0.97–1.01)

status. Whereas in effect modification, the effect of air pollution is the primary interest (Bours, 2021).

Unexpectedly, we observed significant EHE modification that resulted in reduced $PM_{2.5}$-related mortality risks during EHE days in Lag 0–1 and Lag 0 models. Protective effects from $PM_{2.5}$ exposures have been recorded in other work (Fisher et al., 2019; Wang et al., 2020b). Wang and colleagues postulated that individuals may reduce outdoor activities during extreme heat days, consequently reducing their exposures to both heat and $PM_{2.5}$ (Wang et al., 2020b). Though, we saw that cumulative ozone exposures had a notable increase in mortality risk during EHE days. Future work could focus on cause-specific analysis to identify clinically meaningful outcomes or competing risks after acute $PM_{2.5}$ exposures during extreme heat exposures. Also, this approach might help provide additional context to understanding delayed effects in some lag structures. Such findings may prove advantageous for identifying mechanistic plausibility associated with combined environmental exposures for ESKD patients as exact mechanisms are unclear.

In this study, we mainly observed negligible or null associations for hospital admissions. A plausible clinical explanation for this population-level response could relate to the higher frequency of clinical visits for HD treatments. Thrice-weekly treatments may promote a survival advantage by stabilizing deleterious health responses after short-term environmental exposures. Similar to identifying meaningful outcomes that might explain the association between air pollutants and morbidities, a cause-specific analysis might also be necessary for hospital admissions. For example, Wyatt and colleagues observed increased cause-specific risk of hospital admissions (Wyatt et al., 2020).

There are several strengths of our study, including the use of temporally-resolved air pollution data. The case-crossover study design diminished concerns related to individual-level confounding. The use of DLNM enabled us to simultaneously estimate risk using both nonlinear and lagged exposure-response functions (Gasparrini et al., 2010). Likewise, the mortality and hospital admission data used in this study are of high quality, obtained from FKC- a major internationally known dialysis service provider. Patient data on mortality and hospital admission events are considered accurate since they are subject to billing requirements and tracking protocols established by Centers for Medicare & Medicaid (CMS) reporting. Our study also has some limitations that include the use of modeled air pollution data. We compared county-level CWRF-CMAQ estimates against stationary USEPA Air Quality System (AQS) observations using the AQS database (US Environmental Protection Agency) which suggest that CWRF-CMAQ observations appear to overestimate O_3 and underestimate $PM_{2.5}$ (**Supplemental Tables 3**, **Supplemental Figs. 2–6**), as reported previously (Girguis et al., 2020; Travis et al., 2016). Another limitation is that we conducted single pollutant models that focused only on $PM_{2.5}$ and O_3. Future studies should incorporate additional air pollutants in multipollutant models. Also, future studies should account for historical lifestyle modifiers that could exacerbate kidney health, such as smoking habits and diet. Likewise, focusing on cause-specific outcomes related to cardiac and vascular systems could enhance clinical specificity for prevention and treatment. Lastly, we did not consider chronic air pollution exposures and the role of social stressors that can also modify and mediate the impact of air pollution within this population (Shmool et al., 2015).

5. Conclusions

Our data suggest that short-term exposure (up to 3 days) to $PM_{2.5}$ and O_3 is associated with increased ACM among ESKD patients. Also, the increases in mortality risk associated with ozone exposure is considerably higher during extreme heat events. Our data has also shown instances of interaction and effect modification between air pollutants and mortality. Further studies are needed to replicate this result. As climate change-driven compound hazards (such as simultaneous exposure to extreme heat and high ozone pollution episodes) continue to increase, advanced warnings for high-risk groups such as ESKD patients and their care providers are needed to enhance adaptation.

CRediT authorship contribution statement

Richard V. Remigio: Conceptualization, Methodology, Investigation, Resources, Formal analysis, Writing – original draft, Visualization, Project administration. **Hao He:** Resources, Data curation, Formal analysis. **Jochen Raimann:** Resources, Data curation. **Peter Kotanko:** Resources, Writing – review & editing. **Frank W. Maddux:** Resources, Writing – review & editing. **Amy Rebecca Sapkota:** Writing – review & editing. **Xin-Zhong Liang:** Resources, Writing – review & editing. **Robin Puett:** Writing – review & editing. **Xin He:** Writing – review & editing. **Amir Sapkota:** Supervision, Conceptualization, Resources, Writing – review & editing.

Declaration of competing interest

Dr. Raimann reported being an employee of the Renal Research Institute (a wholly owned subsidiary of Fresenius Medical Care [FMC]) and owning stock in FMC. Dr. Kotanko reported receiving honoraria from UpToDate, being an employee of the Renal Research Institute, and owning stock in FMC. Dr. Maddux reported owning stock in and being employed by FMC. No other disclosures were reported.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2021.152481.

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