ABSTRACT

Title of Dissertation:	CLIMATE CHANGE RELATED EXTREME EVENTS AND ADVERSE HEALTH OUTCOMES AMONG HEMODIALYSIS PATIENTS
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The increased frequency and intensity of extreme heat events (EHEs) and wildfires due to climate change are posing significant threats to vulnerable communicates including end-stage kidney disease (ESKD) patients. The specific aims of this dissertation are to Aim 1) Examine the association between EHEs exposure and serum concentrations of sodium and potassium among hemodialysis patients in the Western U.S. (2008-2018), Aim 2) Quantify the mortality and hospitalization risk associated with exposure to 2023 Canadian wildfire-related air pollution in the Eastern U.S., and Aim 3) Investigate how EHEs modify the association between wildfire-related air pollution exposure and the risk of mortality and hospitalization among hemodialysis patients in the Western U.S. (2010-2018).

We analyzed health records of patients who receiving hemodialysis treatment at Fresenius Kidney Care clinics. We used the 10°C increase in daily average temperature and daily extreme heat events (EHEs) of each county as the primary exposures. The presence of wildfire smoke plume and wildfire fine particulate matter ($PM_{2.5}$) concentrations for each clinic were measured using satellite-derived smoke polygons (Hazard Mapping System) and ground-based $PM_{2.5}$ monitors (Air Quality System). We estimated mean serum sodium and potassium change per 10 °C increase in daily average ambient temperature using random intercepts linear mixed-effects models. We employed a time-stratified case-crossover analysis with conditional quasi-Poisson model to investigate the risks of mortality and hospitalization associated with exposure to wildfire-related air pollution and EHEs.

In the first study, a 10°C increase in daily average temperature was associated with 0.43 mEq/L (95% Confidence Interval [CI]: 0.47, 0.59) increase in serum sodium during July-August. The serum sodium was 0.15 mEq/L (95% CI: 0.10, 0.20) higher during EHE days compared to non-EHE days. The serum potassium level did not show a significant change. In the second study, during June-July 2023, the presence of wildfire smoke plume was associated with an 18% increase in all-cause mortality risk (Rate Ratio [RR]:1.18; 95% CI: 1.13, 1.24) and a 3% increase in all-cause hospitalization risk (RR:1.03; 95% CI: 1.00, 1.07). A 10-$\mu g/m^3$ increase in wildfire-related $PM_{2.5}$ was associated with a 139% increase in all-cause mortality (RR: 2.39; 95% CI: 1.79, 3.18) and a 33% increase in all-cause hospitalization (RR:1.33; 95% CI: 1.10, 1.62). In the third study, we observed significant interactions between EHEs and wildfire smoke plume for mortality RRs among the hemodialysis patients in the Western U.S. Mortality risk was considerably higher when hemodialysis patients were simultaneously exposed to wildfire smoke plume and EHE compared to wildfire smoke plume alone (RR: 1.52; 95% CI: 1.25, 1.86 vs. RR: 1.15; 95% CI: 1.08, 1.23). We did not observe a significant interaction for all-cause hospitalization.

Our findings underscore the need to revise operational and care protocols to prepare for such potential join exposures to extreme events that are exacerbated by ongoing climate change. Future work should focus on developing early warning systems to enhance resilience against such threats.

CLIMATE CHANGE RELATED EXTREME EVENTS AND ADVERSE HEALTH OUTCOMES AMONG HEMODIALYSIS PATIENTS

by

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Dissertation submitted to the Faculty of the Graduate School of the
University of Maryland, College Park, in partial fulfillment
of the requirements for the degree of
Doctor of Philosophy
2024

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Acknowledgements

Completing this dissertation marks the culmination of a long and challenging journey, and I am deeply grateful to the many individuals who have supported me along the way.

First and foremost, I extend my heartfelt gratitude to my academic advisor, Dr. Amir Sapkota for their unwavering guidance, patience, and encouragement throughout this research endeavor. Their expertise, mentorship, and invaluable insights have been instrumental in shaping this dissertation and my growth as a scholar. Thank you for being my mentor.

I am also indebted to my committee members, Drs. Quynh Nguyen, Xin He, Menglu Liang, Peter Kotanko, and Xin-Zhong Liang, for their constructive feedback, scholarly contributions, and dedication to ensuring the quality and rigor of this work. Their diverse perspectives and expertise have enriched this dissertation and broadened my intellectual horizons.

I extend my sincere appreciation to all the collaborators Drs. Peter Kotanko, Jochen Raimann, Hao He, and Evan Andrew Ellicott who have contributed to this research project. Your collaboration, expertise, and support have been indispensable in advancing our understanding and pushing the boundaries of knowledge in our field.

To my friends – Nicole, Jianyu, Amanda, Richard, Weijun, and Rupa, I am profoundly grateful for your unwavering support and encouragement throughout this journey. Your presence during both the highs and lows of doctoral study has been a constant source of strength and inspiration. Whether it was lending an empathetic ear, offering words of encouragement, or celebrating milestones with me, your friendship has made this journey all the more meaningful. Thank you for your endless support and for being a cherished part of my life.

Lastly, to my parents, brother, and sister: your love and belief in me have been the cornerstone of my academic journey. From the earliest stages of my education to this significant milestone of completing my PhD, your unwavering support has been my guiding light. I am profoundly grateful for the countless ways you have stood by me, cheered me on, and celebrated my successes. Thank you for being my rock and for always believing in me,

This dissertation is a testament to the collective effort, dedication, and support of all those who have been a part of my academic and personal journey. Thank you for believing in me and for being a source of inspiration every step of the way.

Table of Contents

List of Tables

List of Figures

List of Abbreviations

°C	Degree Celsius
°F	Degree Fahrenheit
95% CI	95% Confidence Interval
ACR	Albumin to Creatinine Ratio
ACS	American Community Survey
AOD	Aerosol Optical Depth
AQS	Air Quality System
BMI	Body Mass Index
CKD	Chronic Kidney Disease
CKDu	Chronic Kidney Disease of Unknown Origin
CWRF-CMAQ	Climate-Weather Research and Foresting and Community Multiscale Air Quality
DAG	Directed Acyclic Graph
DLNM	Distributed Lag Non-Linear Model
eGFR	Estimated Glomerular Filtration Rate
CH_4	Methane
CO	Carbon Monoxide
CO_2	Carbon Dioxide
COPD	Chronic Obstructive Pulmonary Disease
D.C.	District of Columbia
df	Degree of Freedom
ECMWF	European Centre for Medium-Range Weather Forecasts
EHE	Extreme Heat Events
EPA	Environmental Protection Agency
ERA5	The Fifth Generation of the European Reanalysis
ESKD	End-Stage Kidney Disease
FKC	Fresenius Kidney Care
GEOS	Goddard Earth Observing System
GFED3	Global Fire Emissions Database
GOES	Geostationary Operational Environmental Satellite
HMS	Hazard Mapping System
IDWG	Inter-Dialytic Weight Gain
Lag 0	Same-day
Lag 1	One-day Lag
Lag 8	Eight-day Lag
mEq/L	Milli Equivalents Per Liter
NAAQS	National Ambient Air Quality Standard
NASA	National Aeronautics and Space Administration
NH	Non-Hispanic
NOAA	National Oceanic and Atmospheric Administration
NO_2	Nitrogen Dioxide
N_2O	Nitrous Oxide
PAHs	Polycyclic Aromatic Hydrocarbons

PM	Particulate Matter
$PM_{2.5}$	Particulate Matter with Aerodynamic Diameter Less than Or Equal to 2.5 Microns
r	Pearson Correlation Coefficient
RR	Rate Ratio
SD	Standard Deviation
SDI	Social Deprivation Index
SES	Socioeconomic Status
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
T_{max}	Maximum Temperature
U.S.	United States
USRDS	United States Renal Data System
VOCs	Volatile Organic Compounds
$\mu g/m^3$	Microgram per cubic meter

Chapter 1: Introduction

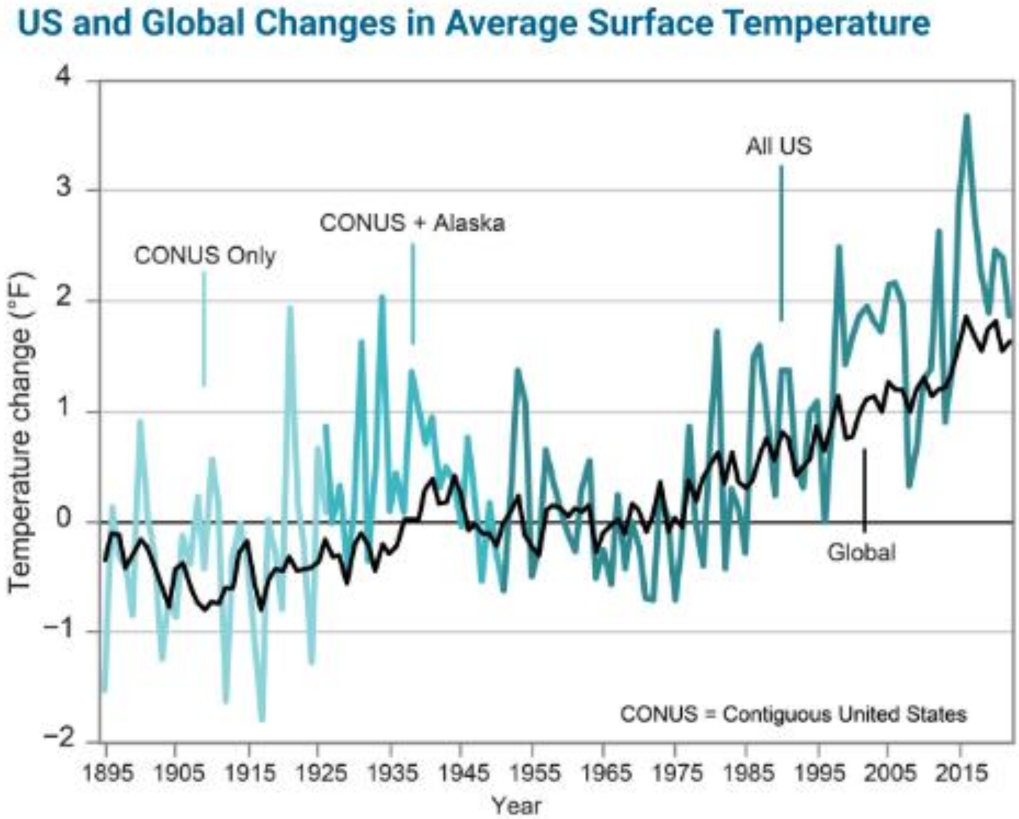
1.1 Climate Change

Climate change refers to long-term alterations in Earth's climate patterns, characterized by shifts in temperature, precipitation, and other climatic variables.[1] Scientific evidence have linked excessive emission of greenhouse gases (e.g., carbon dioxide (CO_2), methane (CH_4), and nitrous oxide (N_2O)) that are emitted from human activities (industrialization, transportation, and agriculture) with the ongoing climate change.[2] The accumulation of greenhouse gases enhances the natural greenhouse effect, leading to heat retention and an increase in the Earth's average surface temperature, a phenomenon commonly known referred to global warming.[3] This increasing trend in global temperature is projected to increase by 1.5°C in the near future (2021-2040), largely due to increased anthropogenic CO_2 emissions.[4] This warming trend has profound impact on the Earth's climate system, disrupting atmospheric circulation patterns, ocean warming and sea level rises, and melting glaciers and ice sheets.[2] Consequently, the impacts of climate change demonstrate in diverse ways across the globe, including more frequent and intense heatwaves, flooding and droughts due to altered precipitation patterns, and an increased frequency of extreme weather events such as hurricanes, cyclones, and wildfires.[5]

Climate change in the U.S. presents a multifaceted challenge with far-reaching impacts across the country. The average surface temperature in the U.S. shows a clear warming trend over the past century, with 2°F (1.12°C) increase in 2023 compared to the average of 1951-1980 (**Figure 1.1**).[6] Such increase in temperature has involved warmer spring temperature, earlier ice breakup in the spring of the rivers in Alaska, reduced snowpack in the Western U.S., and earlier leaf and bloom dates.[7]

Climate change disproportionately affect marginalized communities, encompassing BIPOC (Black, Indigenous, and People of Color), individuals and communities with low socioeconomic status (SES), women, people with disabilities or chronic illnesses, sexual and gender minorities, and children.[6] A recent review study summarized the 89 recent studies (2017-2022) of disparate health impact of climate change on the people of color in the U.S. and suggested that Black, Latinx, Asian, Native American, Pacific Islanders, and children are at higher risk of health impacts associated with extreme cold, heatwave, wildfires, hurricanes, and flooding.[8] Communities of color face disproportionate health risks due to cumulative exposure to environmental hazards such as air pollution and heat, as well as systemic socioeconomic disparities like access to health care, quality housing, and education.[8,9]

Figure 1.1. Annual average surface temperature compared to the 1951-1980 average[6]

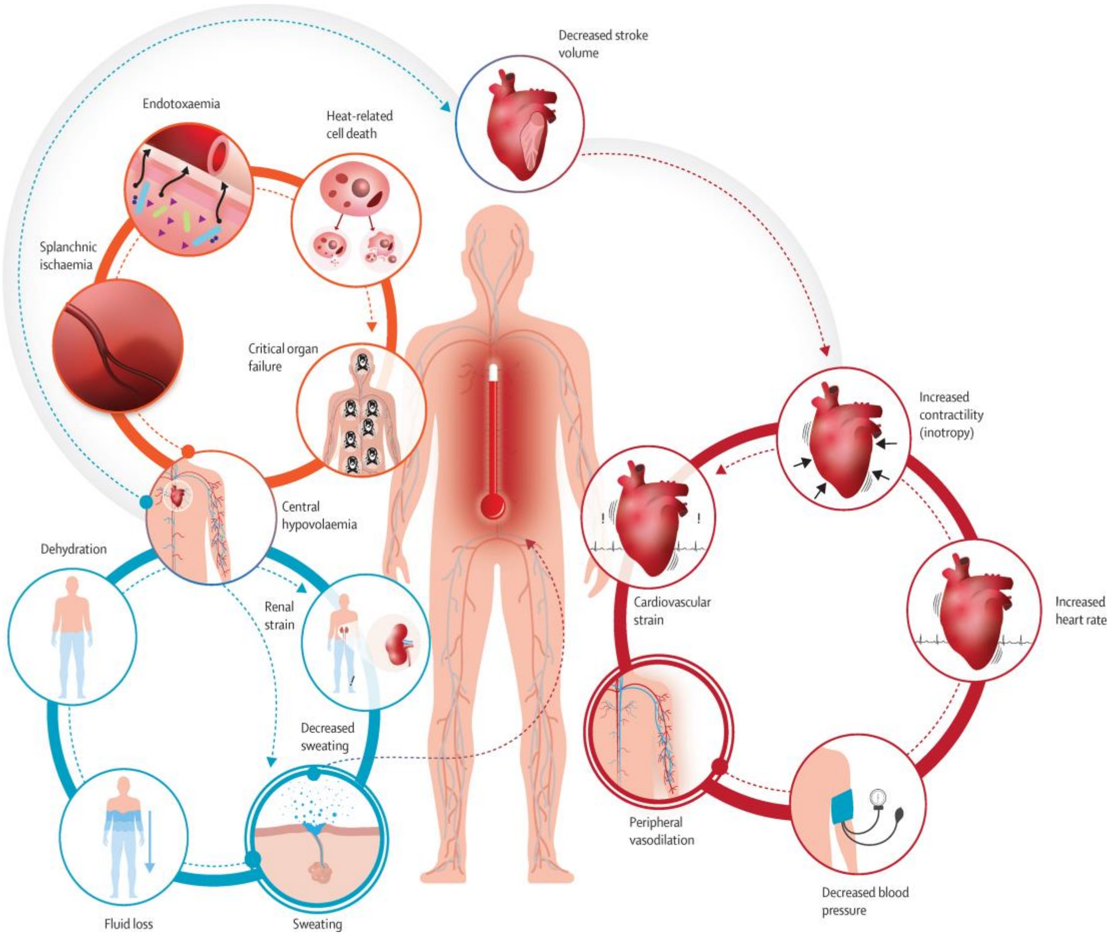


1.2 Climate Change and Extreme Heat Events

As global temperatures rise, the frequency and intensity of Extreme Heat Events (EHEs) are escalating, underscoring the urgent need to understand and mitigate their health impacts.[10] The recent decades have witnessed a multitude of severe extreme heat waves. One of the most notable EHEs in the U.S. is the July 1995 Heat Wave in the Midwest, which resulted in more than 500 deaths in Chicago.[11,12] The main casualties of this heat wave were elderly individuals residing in large cities within the center of the urban heat island.[11] Similarly, the 2003 heatwave in Western Europe demonstrated the substantial hazards of prolonged exposure to high temperatures, contributing to approximately 25,000 excess deaths.[13] Consequently, governments across Europe acknowledged the necessity for early warning systems to mitigate the impact of forthcoming heatwaves.[14] EHEs has represented a critical intersection of climate change and public health, inducing profound impacts on communities worldwide.

The health impact of EHEs encompasses a spectrum of conditions, from mild heat-related illnesses to life-threatening heat strokes.[15] EHE exposure is particularly hazardous for elderly and individuals with pre-existing health conditions[16–18] because heat exposure induces impaired thermoregulation and impaired breathing pattern intended to cope with increase in core temperature (**Figure 1.2**)[19]. This, coupled with systemic inflammation, exacerbates pre-existing cardiovascular, respiratory, and renal diseases.[20]

Figure 1.2. Physiological heat stress responses [21]



EHEs represent the leading cause of weather-related deaths in the U.S.[22], with an average of 702 deaths annually between 2004 and 2018.[23] The frequency and intensity of extreme heat events (EHEs) are expected to increase in the U.S.[6] and that this trend will continue in response to climate change.[4] Consequently, it is essential to understand the multifaceted health impact of EHEs for developing proactive measures to protect public health and enhance resilience in the face of escalating climate challenges.

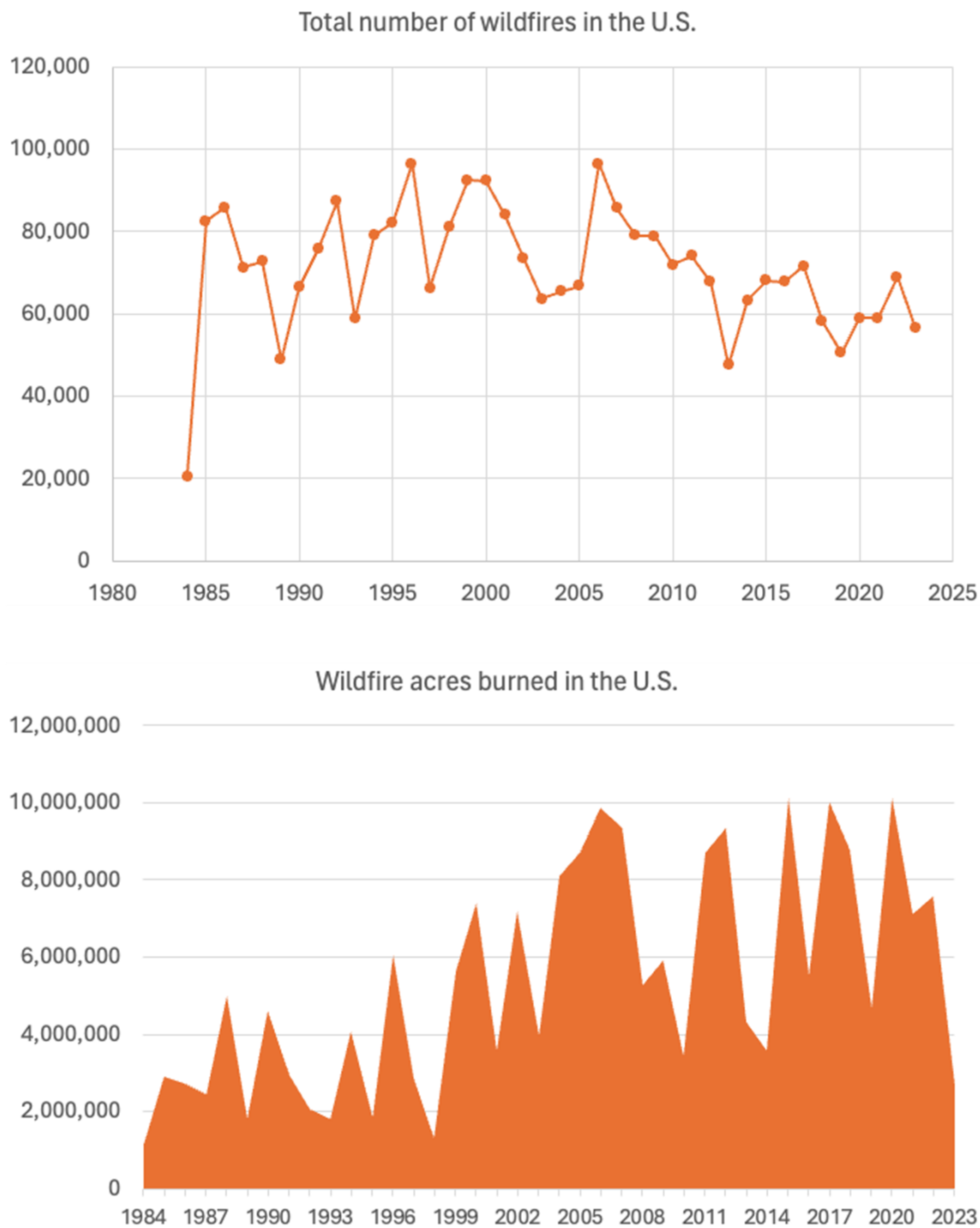
While there is no universally accepted definition of heat waves or EHEs, the quantitative definitions of those events are determined based on (1) the metric of heat (e.g., daily mean temperature [T_{mean}], daily maximum temperature [T_{max}], and humidity), (2) temperature thresholds (e.g., absolute threshold such as $T_{max} > 40°C$, and relative threshold like 95th percentile), and (3) durations such as number of persistent days.[24] In this dissertation, we used the county and calendar day-specific 95th percentile thresholds by using a 30-year historical daily T_{max} data spanning from 1980 to 2009, to take into account regional differences.

1.3 Climate Change and Wildfires

Prior studies have suggested that increases in heat waves and droughts are creating conditions that are conducive to large-scale wildfires.[6] Warmer temperatures can enhance atmospheric instability, leading to increases in lightning strikes from dry thunderstorm which is responsible for starting the wildfires, especially in areas with dense and dry vegetation.[25,26] Dry thunderstorms produce lightning but where most of its precipitation evaporates before reaching the ground, producing rainfall less than 2mm.[27]Additionally, wildfires release substantial amounts of CO_2 and other greenhouse gases into the atmosphere, thereby establishing a negative feedback loop where climate change intensifies and creates more favorable conditions for wildfires.[28]

In the U.S., the total acres burned by wildfires have steadily increased since 1984, reaching their peaking at 10,125,149 acres in 2015 and 10,122,336 acres in 2020 (**Figure 1.3**).[29] The 5th National Climate Assessment concluded that the extent and intensity of wildfire is increasing in the U.S. and this trend will continue in response to climate change.[6] In particular, the Western U.S. has experienced continuous warming accompanied by increases in frequency of wildfire, length of fire season as well as burnt area since 1980.[30,31] It is reported that there were 58,950 wildfires that burned approximately 10.1 million acres in 2020 in the U.S., and the West Coast (California, Oregon, and Washington) accounted for 58% of the nation's total acres burned.[32]

Figure 1.3. Total number of wildfires and wildfire acres burned in the U.S. from 1984 to 2020[29]



Wildfire smoke contains high concentrations of carbon monoxide (CO), nitrogen dioxide (NO_2), particulate matter (PM), polycyclic aromatic hydrocarbons

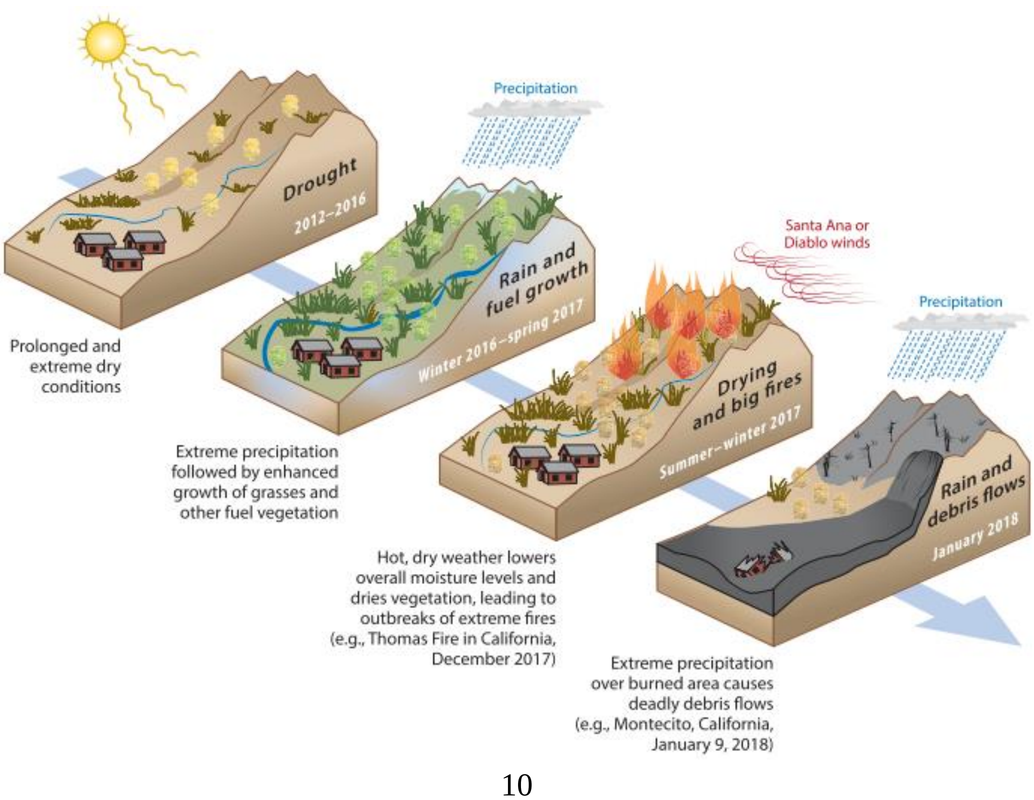
(PAHs), and volatile organic compounds (VOCs), all of which are known to adversely impact cardiopulmonary health outcomes and mortality.[33–36] One pollutant of notable concern within wildfire smoke is PM. Compared to ambient urban PM, wildfire-related PM is mostly carbonaceous and has more free radicals and greater potential to cause inflammation and oxidative stress.[37,38] This is supported by toxicological studies[39,40] as well as a recent epidemiological study.[41] Therefore, it is crucial to differentiate PM attributable to wildfire smoke when assessing its health impacts.[41] Additionally, previous studies further suggest that individuals with pre-existing respiratory disease, middle-aged and older adults, children, and individuals with low socio-economic status are known to be at greater risk of the adverse health outcomes due to wildfire air pollution exposure.[36,42,43]

The smoke from wildfires has the potential to travel over long distances. In July 2021, smoke from wildfires in Southern Canada and the Northwestern U.S. notably increased the levels of $PM_{2.5}$ even as far away as 5,000 km in New York state.[44] The year 2023 marked a record-breaking fire season in Canada, with wildfires starting in May, and peaking between June through September.[45] Overall, an estimated 6,551 fires burned 18.5 million hectares of land, far surpassing the annual average of 2.2 million hectares typically consumed by fires in Canada.[46] The impact of these wildfires was felt far and wide, as smoke plumes rose high into the atmosphere, carried by a steering coastal low to the Northeastern U.S.[47]

1.4 Climate Change and Compound Hazards

While individual hazards such as heatwaves, droughts, wildfires, and floods have been recognized as significant threats, recent studies have shed light on the interrelationships of these hazards.[5,6,48,49] Such individual hazards often arise from interactions between multiple physical processes, collectively referred to as compound hazards.[5] Specifically, these hazards often occur simultaneously (concurrent hazards) or consecutively (cascading hazards).[49] For example, in California, after the prolonged drought spanning from 2012 to 2016, extreme precipitation during the winter of 2016 enhanced growth of grasses and other fuel vegetation. Subsequently, a very dry and hot summer ensued, drying existing vegetation and the outbreak of extreme wildfires shortly thereafter (**Figure 1.4**).[5]

Figure 1.4. A set of consecutive extreme events in California during 2012-2018[5]



Failure to properly assessing compound hazards may lead to underestimation of the true and potentially catastrophic impacts.[48] In a recent systematic review, the authors studied 56 epidemiological studies that investigated the health impact of at least two of the environmental hazard exposures. The authors concluded that there is sufficient evidence supporting the synergistic effects of heat and air pollution (particularly for ozone and PM) exposure, underscoring that these exposures could yield more substantial effect than previously estimated by studies that considered these risk factors individually.[50]

The health impact of compound hazards has been assessed using various methods in environmental epidemiological studies. Chen et al. analyzed the compound effects of EHEs and wildfire smoke in California by categorizing the exposure into four types: days with EHEs alone, days with wildfires alone, days with both hazards, and days without either.[51] Another commonly used method involves introducing an interaction term between two different exposures (e.g., daily air pollutant concentration and ambient temperature) and conducting stratified analyses based on temperature or air pollutant concentrations thresholds. [52–54]

1.5 Chronic Kidney Disease, End-Stage Kidney Disease and Hemodialysis Patients

Chronic Kidney Disease (CKD) is defined based on the presence of either kidney damage, as indicated by protein loss in the urine, or decreased kidney function for three or more months, irrespective of cause.[55] The stages of CKD are determined by the GFR or eGFR. End-stage kidney disease (ESKD) typically refers to a reduction in kidney function, with a glomerular filtration rate (GFR) less than 15 ml/min/1.73m^2, persisting for 3 months or more.[56] The eGFR is a measurement for assessing kidney function which is calculated based on the patient's age, sex, race, and serum creatinine levels.[57] Creatinine, which is a waste product generated by muscle metabolism and filtered by kidneys, is a commonly used marker for kidney function.[58] (**Table 1.1**).

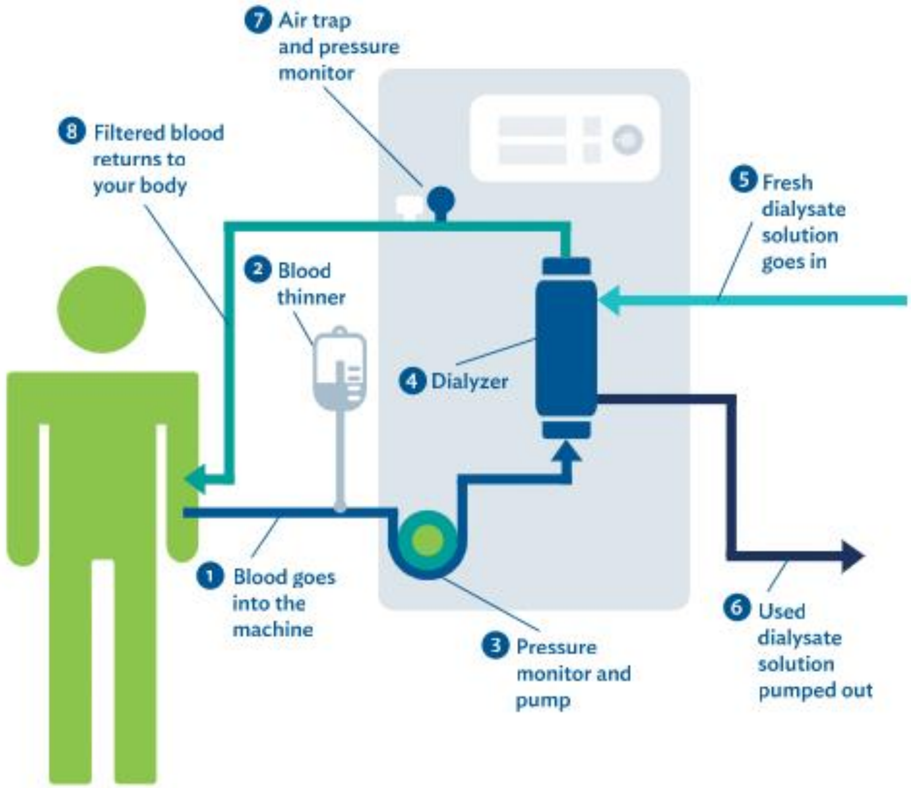
Table 1.1. Stages of CKD[55]

CKD stages	GFR (measured or estimated, ml/min/1.73m^2)	Terms
1	≥90	Normal or high
2	60 to 89	Mildly decreased
3a	45 to 59	Mildly to moderately decreased
3b	30 to 44	Moderately to severely decreased
4	15 to 29	Severely decreased
5	<15	Kidney failure

Depending on eGFR and clinical signs and symptoms, ESKD patients may require renal replacement treatment like hemodialysis (**Figure 1.5**) or kidney transplantation.[59] With the aging global population, the global burden of CKD and its severe manifestation, ESKD, is substantial, affecting 2.4 million of individuals worldwide in 2016.[60]. According to the 2023 Annual Report of the United States

Renal Data System, prevalent ESKD cases in the U.S. have steadily risen since 2001, reaching about 808,000 in 2021.[61] Medicare expenditure for ESKD patients totaled approximately $52.3 billion in 2021, with an average annual healthcare cost of around $68,000 per person with ESKD.[61] The growing prevalence of ESKD and its economic burden underscores the importance of comprehending and addressing the challenges faced by affected individuals and healthcare systems.

Figure 1.5. Overview of a hemodialysis treatment[62]



1.6 Potential Environmental Risk to Hemodialysis Patients

Previous studies have shown that EHEs can increase risk of developing CKD[63–66], risk of kidney function decline among CKD patients,[67] as well as risk of adverse health outcome among CKD patients[52,68,69]. The potential effect of EHEs exposure was proposed based on observations of high CKD incidence among agricultural workers in Central America.[70] Studies have suggested that the prevalent chronic kidney disease of unknown origin (CKDu) in the agricultural communities in the Mesoamerican area could be explained by the etiology that heat stress and recurrent dehydration due to exposure to high ambient temperature and extreme physical exertion could place burden to renal system.[71–74] This potential impact of heat exposure on kidney health is additionally evidenced by increased prevalence of kidney diseases among returnee Nepali migrant workers from the Gulf countries,[75] high prevalence of CKD among young farmers in Sri Lanka[76], and decreased kidney function and acute kidney injury development among sugarcane workers in Nicaragua.[72,77]

EHE can disproportionately impact ESKD patients because their liquid intake is strictly regimented and as such, they cannot cope with the higher temperature by increasing their liquid intake like healthy individuals.[78,79] Maintaining the balance of electrolytes is crucial especially for the ESKD patients undergoing hemodialysis treatments. The imbalance of serum electrolyte including sodium and potassium causes drastic change in blood pressure and inter-dialytic weight gain (IDWG),[80] and in the end, can result in potentially life-threatening disorder such as neurologic damage, cardiac arrythmias, sudden cardiac arrest, and mortality.[81–87] However, little is known about how ambient temperature affects the serum electrolyte levels among hemodialysis patients.[88]

ESKD patients may be particularly vulnerable to wildfire-related air pollution. Prior studies have shown that air pollution can increase risk of CKD[89,90], progression of CKD to ESKD[91], as well as risk of mortality and hospitalization among ESKD patients[52,92–94]. Several in vivo and in vitro studies found that $PM_{2.5}$, exposure induced renal tubular necrosis and impaired renal function.[95–97] Additionally, emerging studies have suggested that the mechanisms linking air pollution exposure and risk of CKD includes oxidative stress, inflammatory response, and abnormal metabolic changes inducing elevated hypertension and vascular injury which compromise renal function.[98,99] A longitudinal cohort study of U.S. veterans showed significant associations between $PM_{2.5}$ exposure and risk of incident CKD, eGFR decline (>30%), and progression to ESKD. Moreover, patients with ESKD are more vulnerable to air pollution exposure because the majority of these patients have impaired cardio-respiratory functions and comorbidities such as chronic obstructive pulmonary disease (COPD).[100–102]

1.7 Outline of Dissertation

We aim to fill the gap in knowledge on the association between exposure to environmental risk factors, including EHEs, wildfire smoke plumes, and wildfire-related $PM_{2.5}$, and various health outcomes such as serum electrolyte changes, hospitalization, and mortality among hemodialysis patients in the U.S. The specific aims for this dissertation are to:

1. **Examine the association between the ambient temperature and EHEs exposure and pre-hemodialysis serum level of electrolytes among hemodialysis patients in the Western U.S. from 2008 to 2018.** We hypothesized that the increase in ambient temperature and EHE exposure are associated with the decrease in the pre-hemodialysis serum level of sodium and potassium among hemodialysis patients.
2. **Quantify the mortality and hospitalization risk associated with exposure to 2023 Canadian wildfire-related air pollution in New England, the Mid-Atlantic, and the Midwest U.S.** Our hypothesis is that exposure to wildfire-related air pollution (wildfire smoke plume and wildfire-related $PM_{2.5}$) will increase the risk of mortality and hospitalization among hemodialysis patients.
3. **Investigate how EHEs modify the association between wildfire-related air pollution exposure and the risk of mortality and hospitalization among hemodialysis patients.** Our hypothesis is that exposure to EHEs and wildfire-related air pollution (wildfire smoke plume and wildfire-related $PM_{2.5}$) will increase the risks of all-cause mortality and hospitalization and among hemodialysis patients. Furthermore, we assessed the potential effect modification by EHEs on the association between wildfire-related air pollution exposure and the risks of mortality and hospitalization.

1.8 Conceptual Framework of Dissertation

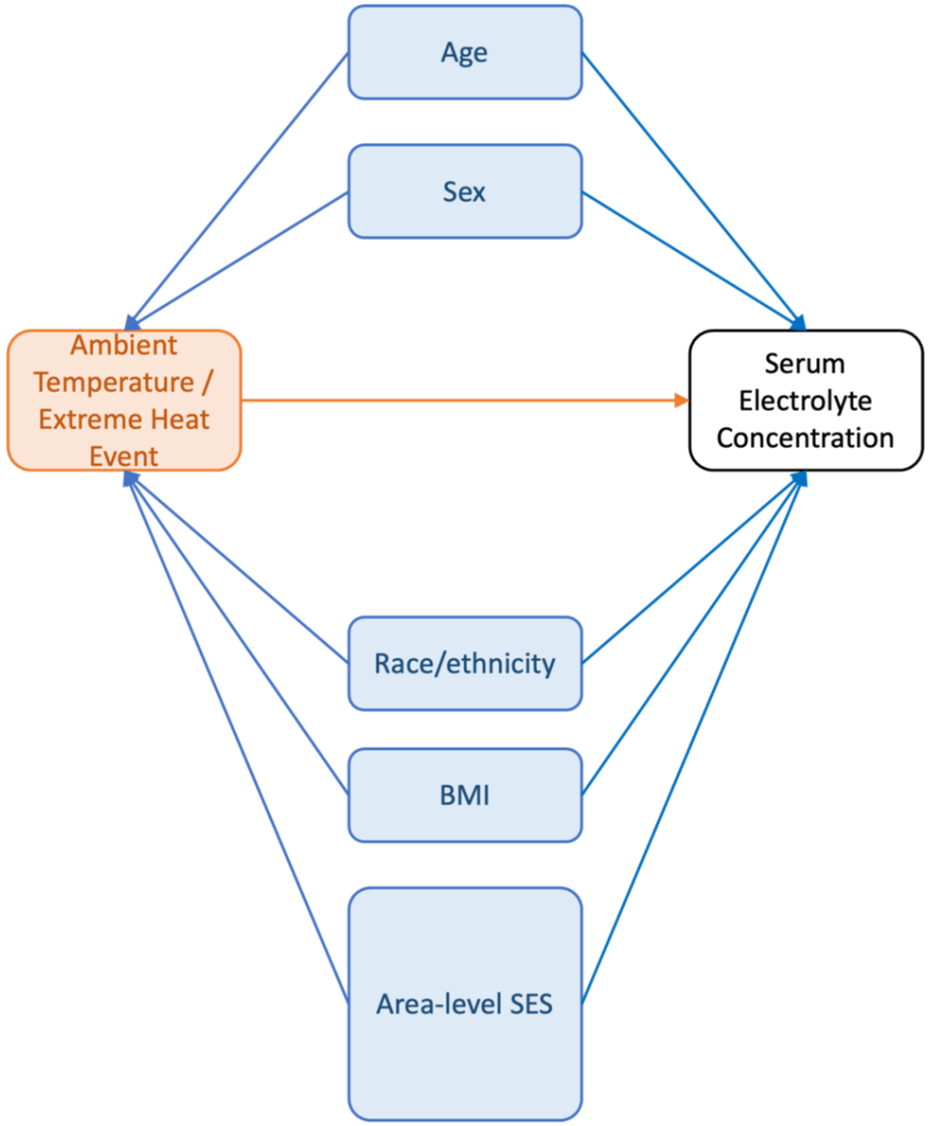


Figure 1.6. DAG for the association between exposure, outcome, and potential confounders for Chapter 2

The conceptual framework of Chapter 2 is presented in **Figure 1.6** using a directed acyclic graph (DAG). It is hypothesized that an increased in ambient temperature and presence of EHEs are associated with serum electrolyte (sodium and potassium) concentration changes among the hemodialysis patients. Age, sex, race/ethnicity, body mass index (BMI), and area-level SES are expected to 1) affect serum electrolyte concentration changes, 2) be associated with ambient temperature and EHEs with varying vulnerability or exposure level, and 3) be not in the pathway from ambient temperature and EHE exposure to serum electrolyte concentration changes.[103–105]

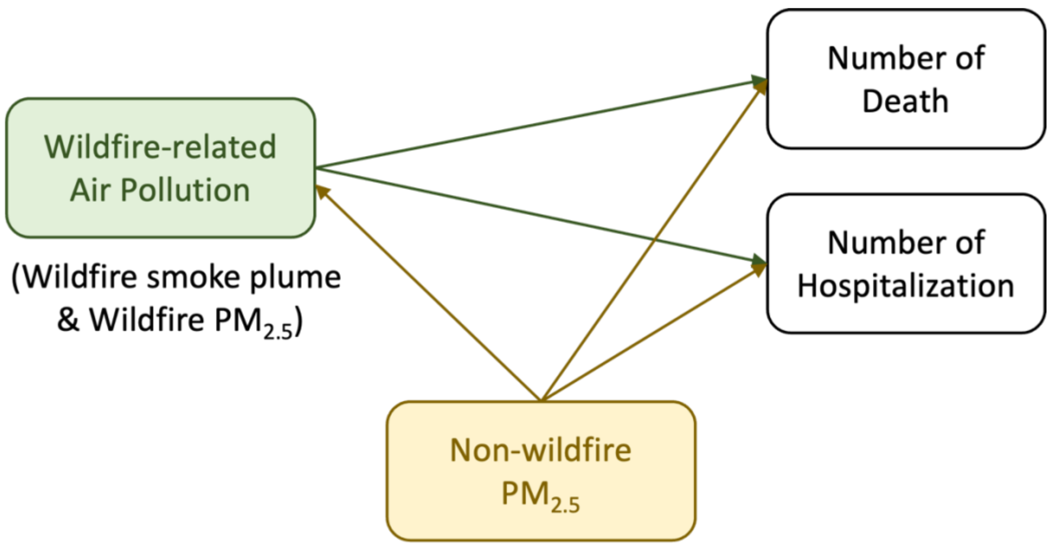


Figure 1.7. DAG for the association between exposure, outcome, and potential confounders for Chapter 3

The conceptual framework of Chapter 3 is presented in **Figure 1.7** using a directed acyclic graph (DAG). It is hypothesized that exposure to wildfire-related air pollution (wildfire smoke plume and wildfire-related $PM_{2.5}$) are associated with an increase in the risk of all-cause death and all-cause hospitalization among hemodialysis patients.[52,92,94]

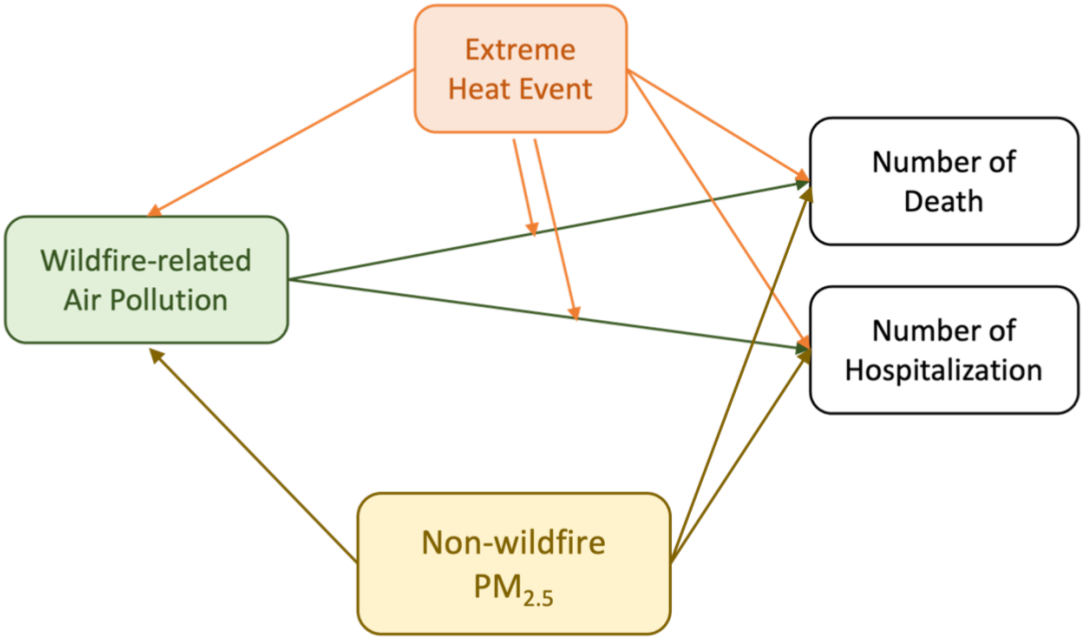


Figure 1.8. DAG for the association between exposure, outcome, and potential confounders for Chapter 4

The conceptual framework of Chapter 4 is presented in **Figure 1.8** using a directed acyclic graph (DAG). It is hypothesized that both exposures to EHEs and wildfire-related air pollution (wildfire smoke plume and wildfire-related $PM_{2.5}$) are associated with an increase in the risks of all-cause death and all-cause hospitalization among hemodialysis patients. Additionally, the effect modification by EHEs on the associations between wildfire-related air pollution exposure and the risks of mortality and hospitalization were assessed.[52,68,69,92,94]

Chapter 2: Association between Ambient Temperature and Extreme Heat Events with Serum Sodium and Potassium among Hemodialysis Patients in the Western U.S. (2008-2018)

2.1 Abstract

Introduction: Ongoing climate change is increasing the extent and intensity of extreme heat events (EHEs) in the Western U.S. These hazardous conditions may disproportionately impact hemodialysis patients by disrupting their electrolyte balance. This study investigated the association of exposure to ambient temperature and EHEs with serum electrolyte concentrations among hemodialysis patients in the Western U.S.

Methods: We analyzed health records of 58,527 hemodialysis patients who received hemodialysis treatment at Fresenius Kidney Care clinics in California, Oregon, and Washington between 2008 and 2018. Each patient's serum electrolyte (sodium and potassium) concentrations (mEq/L) were measured before each hemodialysis treatment. We used linear mixed-effects models with random intercepts to investigate the association between exposure to ambient temperature (10°C increase) and EHE with serum electrolyte concentration. All models adjusted for age, sex, race/ethnicity, BMI, and Social Deprivation Index.

Results: The average of baseline serum concentrations for sodium and potassium was 137.1mEq/L and 4.66mEq/L, respectively. Across all the months, a general trend was observed wherein a 10°C increase in daily average ambient temperature was associated with an increase in the mean serum sodium concentrations. The most significant increase was observed in July (0.46 mEq/L; 95% CI: 0.41, 0.50) and September (0.46

mEq/L; 95% CI: 0.42, 0.50) followed by August (0.31 mEq/L, 95% CI: 0.26, 0.36). Exposure to EHEs was associated with a 0.22 mEq/L (95% CI: 0.18, 0.26) increase in the mean serum sodium concentrations, with the effect being more pronounced among patients in Oregon, males, the oldest age group (≥75), White individuals, those who were overweight, and those residing in more socially deprived areas. We did not observe statistically significant changes in mean potassium concentrations.

Conclusions: Both increases in daily ambient temperature and exposure to EHEs were associated with increased serum sodium concentrations among hemodialysis patients in the Western U.S. EHEs can disproportionately affect electrolyte balance in hemodialysis patients as their limited liquid intake presents them from compensating for higher temperatures, unlike healthy individuals. This study underscores the urgent need of updating hemodialysis patient’s electrolyte level care guidelines to account for the potential impact of ambient temperature and EHEs.

2.2 Introduction

Climate change is increasing frequency of extreme heat events (EHEs) in the U.S. and this trend is projected to continue.[6,106] Annually, an average of 702 deaths were related to extreme heat from 2004 to 2018 in the U.S.[23] Previous studies have shown that EHEs can increase risk of developing chronic kidney disease (CKD),[63–66] risk of kidney function (eGFR) decline among CKD patients,[67] as well as risk of hospitalization and mortality among ESKD patients[52,68,69]. The potential effect of EHE exposure was proposed based on observations of high CKD incidence among agricultural workers in Central America.[70] Subsequent studies have suggested that the heat stress and recurrent dehydration resulting from exposure to high ambient temperature and extreme physical exertion could place burden to renal system, increasing the risk of acute kidney injury through mechanisms such as rhabdomyolysis, hyperosmolarity, hyperthermia, and extracellular volume depletion .[71–74,107]

The global burden of CKD and its end-stage manifestation, end-stage kidney disease (ESKD), is substantial, affecting 2.4 millions of individuals worldwide in 2016.[60] ESKD patients are required to undergo renal replacement treatment such as hemodialysis or kidney transplantation.[59] In the U.S., the most common type of renal replacement therapy is hemodialysis treatment, with more than 462,000 ESKD patients undergoing in-center hemodialysis in 2021.[61] Maintaining the balance of electrolytes is crucial especially for the ESKD patients undergoing hemodialysis treatments because the imbalance of serum electrolytes causes drastic change in blood pressure and inter-dialytic weight gain (IDWG),[80] and in the end, results in potentially life-threatening disorders such as neurologic damage, cardiac arrythmias, sudden cardiac arrest, and mortality.[81–87]

Previous studies have examined how seasonal variation and ambient temperature are associated with serum electrolyte abnormalities. Multiple investigations presented negative associations between temperature and sodium,[108,109] including low sodium concentrations during summer,[110,111] higher prevalence of hyponatremia (serum sodium concentration <135mEq/L) during the summer,[112] and hypernatremia (serum sodium concentration >145mEq/L) during the winter.[113] It is suggested that loss of sodium from sweating and excessive water intake might contribute to developing hyponatremia during the summer.[109,111,112] Several studies showed conflicting findings, such as higher prevalence of hypernatremia during the heat waves[114] and positive association between ambient temperature and sodium concentration[115]. Serum potassium concentrations are known to decrease in the summer, which can lead to hypokalemia (serum potassium concentration <3.5 mEq/L), because high ambient temperature is believed to promote glucose metabolism and increase cellular uptake of potassium.[109,116–119]

Prior studies have suggested that EHEs can disproportionately impact ESKD patients' electrolyte balance because their liquid intake is strictly regimented and as such, they cannot cope with the higher temperature by increasing their liquid intake like healthy individuals.[78,79] However, little is known about how ambient temperature affects the serum electrolyte concentration among hemodialysis patients[88] Cheung et al. observed 0.2mEq/L decrease in sodium and 0.01mEq/L decrease in potassium per 10°F increase (5.6°C increase) in ambient temperature among 1,445 hemodialysis patients in the U.S. during 1995-1999.[120] Among the 44 peritoneal dialysis patients in Taipei, Taiwan during 2004-2006, the monthly outdoor temperature showed negative correlation with serum sodium ($r = -0.71$, $p < 0.001$) and potassium ($r = -0.70$, $p < 0.001$).[109]

Significant changes in serum concentrations of sodium and potassium are associated with increased risk of hospitalization and mortality among hemodialysis patients.[80] Previous studies have highlighted that hyponatremia is particularly concerning as it is associated with elevated risks of neurological complications and mortality in hemodialysis patients.[121,122] Additionally, hyperkalemia has been associated with arrhythmias and sudden cardiac death among hemodialysis patients.[123] Therefore, understanding how ambient temperature affects hemodialysis patients' electrolytes concentration is important to reduce the risk of electrolyte imbalance and its severe adverse health impacts. This study aims to fill the gap in knowledge on the potential associations of ambient temperature and EHEs exposure with serum electrolyte concentration among hemodialysis patients.

2.3 Methods

2.3.1 Study Population

We conducted a retrospective cohort study that included patients aged 18 or older who were undergoing in-center hemodialysis treatment at the Fresenius Kidney Care (FKC) clinics in the Western U.S. (California, Oregon, and Washington), from 2008 to 2018 (N=58,527). The deidentified electronic health records included each patient's age, sex, race/ethnicity, height, weight, and the identification code of the visited clinic. To assign exposure to county-specific EHEs, the location of each clinic where patients received hemodialysis treatment was used as a proxy for their residence. This study was approved by the University of Maryland Institutional Review Board (Exempt Category #4). We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for cohort studies.[124]

2.3.2 Health Outcome

The primary health outcomes of this study were the changes in sodium and potassium concentrations (mEq/L). Each patient's serum concentration of sodium and potassium are typically measured once per month at the beginning of the hemodialysis treatment. The normal range of serum sodium and potassium concentrations are 135 to 145 mEq/L and 3.5 to 5.5 mEq/L, respectively.[125]

2.3.3 Exposure

We utilized the ambient temperature data from the fifth generation of the European Reanalysis (ERA5). The ERA5 is an integrated model data system developed and operated by the European Centre for Medium-Range Weather Forecasts (ECMWF), which merges daily observations from around the world with a weather prediction model.[126] In this study, we used a 10°C increase in daily average temperature for the entire year and occurrence of EHEs in each county during the warmer months (May to September) as the primary exposures of this study. EHE exposure of each county was estimated using one of the methods employed previously.[52] Briefly, a 30-year historical daily T_{max} data spanning from 1980 to 2009 was utilized to determine a 95th percentile threshold for each calendar day across each county. This was accomplished by employing a 31-day moving window centered around the date of interest. T_{max} for each calendar day during the study period was compared to their respective 95th percentile thresholds and assigned a value of 1 (EHE) if it exceeded the county and calendar day-specific thresholds, and 0 otherwise.

2.3.4 Covariates

We controlled for covariates including age (18-64, 65-74, and ≥75), sex (female and male), race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White, non-Hispanic Asian, and non-Hispanic Other), body mass index (BMI; underweight, <18.5; normal, 18.5–24.9; overweight, 25.0–29.9; obese, ≥30), and Social Deprivation Index (SDI) as covariates. The SDI is a composite metric of seven demographic characteristics obtained from the American Community Survey (ACS) 2008-2018: the percentages of (1) living in poverty, (2) less than 12 years of education, (3) single-parent households, (4) living in rented housing units, (5) living in the overcrowded housing unit, (6) households without a car, and (7) unemployed adults under 65 years of age.[127] In this study, the SDI was utilized to assess area-level socioeconomic status (SES) for each county. The SDI score ranges from 0 to 100 and higher score indicates greater socioeconomic deprivation.

2.3.5 Statistical Analysis

We estimated mean concentrations and 95% confidence intervals (CIs) of serum sodium and potassium using linear mixed-effects models with random intercepts which accounted for the correlation of repeated measures within patients. First, we estimated the mean changes in serum sodium and potassium with a 10°C increase in daily average ambient temperature, stratified by month and state. Additionally, we estimated the mean differences in serum sodium and potassium between EHE exposed and unexposed groups during May-September, stratified by age (18-64, 65-74, and ≥75), sex (female and male), race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White, non-Hispanic Asian, and non-Hispanic Other), BMI (underweight, <18.5; normal, 18.5–24.9; overweight, 25.0–29.9; obese, ≥30), and SDI (<40, 40-59, ≥60). All models adjusted for age (18-64, 65-74, and ≥75), sex (female and male), race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White, non-Hispanic Asian, and non-Hispanic Other), BMI (underweight, <18.5; normal, 18.5–24.9; overweight, 25.0–29.9; obese, ≥30), and SDI (continuous). In the stratified analyses, the selected effect modifier was not included as a covariate, and other covariates were treated as confounders.

We used R statistical software version 3.6.1 with the lme4, and *tidyverse* packages.[128,129] All statistical tests were two-tailed and based on a significance level of 0.05.

2.4 Results

Table 2.1 shows the baseline characteristics of the study population. This study included 58,527 patients across 222 hemodialysis clinics within 54 counties. Approximately 79% of the study population were in California at initial hemodialysis treatment during the study period, 58% were male, and 50% were non-Hispanic white. 47% of the study population were 18-64 years old and 34% were obese at initial hemodialysis treatment. Among all the patients included in the study, at the baseline, the average serum concentrations for sodium and potassium were 137.1 mEq/L (SD=3.7 mEq/L) and 4.66 mEq/L (SD=0.71 mEq/L), respectively. The average serum sodium concentration was 0.3 mEq/L higher for male patients compared to female patients (137.2 mEq/L vs. 136.9 mEq/L). Black patients showed the highest serum sodium concentration (138.0 mEq/L) and while Asian patients showed the lowest serum sodium concentration (136.7 mEq/L) and the lowest serum potassium concentration (4.61 mEq/L). The youngest group (age 18-64) showed the lowest serum sodium concentration (136.9 mEq/L) and the highest serum potassium concentration (4.75 mEq/L), while the oldest group (age ≥75) showed the highest serum sodium concentration (137.0 mEq/L) and the lowest serum potassium concentration (4.55 mEq/L).

Figure 2.1 shows the location of the 222 hemodialysis clinics and the county average temperature and yearly number of EHEs across the 54 counties from 2008 to 2018. The county average temperature ranged from 1.8°C to 22.9°C. The average yearly number of EHEs during the warmer months (May to September) ranged from 3 to 10 days.

Figure 2.2 shows the monthly average ambient temperature (°C) and serum electrolyte concentrations (mEq/L) for both the entire region (top panel) and each individual state (lower three panels). This was done by calculating monthly average for each patient, and then averaging all individuals over each month. During 2008-2018, across 54 counties, July (19.3°C) and August (18.9°C) represented the hottest months, while December (-0.9°C) and January (-0.2°C) were the coldest. The highest serum sodium concentrations were observed during April (137.1 mEq/L), while the lowest concentrations were observed during August and October (136.9 mEq/L). The serum sodium concentrations were below the overall average during January and June through October. The average serum potassium concentration was highest in June (4.80 mEq/L) and lowest in October (4.76 mEq/L). The serum potassium concentrations were above the overall average during months of April to August. For each state of California, Oregon and Washington, the serum sodium concentrations were below the overall average during January and June to September. The serum potassium concentrations were highest during April to July in California and June to September in Oregon and Washington.

Figure 2.3 illustrates the adjusted mean changes in serum sodium and potassium concentrations in response to a 10°C increase in daily average ambient temperature, stratified by month for both the entire region and individual states. A general trend was observed wherein an increase in daily average ambient temperature associated with an increase in the adjusted mean serum sodium concentrations, except for February, June, and November. The most significant increase in the adjusted mean serum sodium concentrations was observed in July and September, with a mean increase of 0.46 (95% CI: 0.41, 0.50) mEq/L and 0.46 (95% CI: 0.42, 0.50) mEq/L per 10°C increase in daily average ambient temperature. This was followed by August with a mean increase of 0.31 (95% CI: 0.26, 0.36) mEq/L. In California, the most significant increase in the adjusted mean serum sodium concentrations was observed in September (0.50 mEq/L; 95% CI: 0.45, 0.54), followed by July (0.43 mEq/L; 95% CI: 0.37, 0.49) and May (0.34 mEq/L; 95% CI: 0.30, 0.39). In Oregon, the highest increase was observed in July (0.66 mEq/L; 95% CI: 0.53, 0.79), followed by September (0.46 mEq/L; 95% CI: 0.34, 0.58), and August (0.42 mEq/L; 95% CI: 0.27, 0.57). Lastly, in Washington, the highest increase was in August (0.42 mEq/L; 95% CI: 0.28, 0.57), followed by July (0.41 mEq/L; 95% CI: 0.27, 0.55), and September (0.36 mEq/L; 95% CI: 0.22, 0.51). Unlike serum sodium concentrations, there was no consistent trend for mean serum potassium concentrations across the states.

Table 2.2 shows the adjusted mean differences in serum sodium and potassium between EHE exposed and unexposed groups during the warmer months (May-September), stratified by state, age, sex, race/ethnicity, BMI, and SDI. Among all the patients included in the study, exposure to EHEs were associated a 0.22 mEq/L (95% CI: 0.18, 0.26) increase in the adjusted mean serum sodium concentration. Overall, all the subgroups showed higher mean serum sodium concentration when exposed to EHEs. Patients in Oregon showed the most pronounced elevation in the adjusted mean serum sodium concentration (0.25 mEq/L; 95% CI: 0.13, 0.37), followed by California (0.22 mEq/L; 95% CI: 0.17, 0.26) and Washington (0.20 mEq/L; 95% CI: 0.08, 0.31). When stratified by age, the oldest group (≥75) showed the most pronounced increase in the adjusted mean serum sodium concentration (0.26 mEq/L; 95% CI: 0.18, 0.34), followed by age 65-74 (0.25 mEq/L; 95% CI: 0.17, 0.32) and the youngest group of age 18-64 (0.18 mEq/L; 95% CI: 0.12, 0.24). Hispanic patients demonstrated the most significant elevation in the adjusted mean serum sodium concentration (0.39 mEq/L; 95% CI: 0.32, 0.47) followed by White patients (0.16 mEq/L; 95% CI: 0.10, 0.22). Interestingly, Asian and Black patients did not show a statistically significant increase (0.13 mEq/L; 95% CI: -0.02, 0.28 and 0.05 mEq/L; 95% CI: -0.07, 0.16, respectively). Other racial/ethnic group showed a 0.38 (95% CI: 0.10, 0.66) mEq/L increase in the adjusted mean serum sodium concentration. When stratified by BMI, overweight patients showed the most prominent increase in the adjusted mean serum sodium concentration (0.25 mEq/L; 95% CI: 0.18, 0.32) followed by obese patients (0.21 mEq/L; 95% CI: 0.15, 0.27) and normal weight patients (0.19 mEq/L; 95% CI: 0.11, 0.27). The underweight patients did not show a statistically significant increase (0.03 mEq/L; 95% CI: -0.25, 0.31). Patients residing in more socially deprived counties (SDI 40-59 and ≥60) showed greater increase in the adjusted mean serum sodium (0.25 mEq/L and 0.24 mEq/L, respectively) compared to patients in less deprived counties (0.11 mEq/L).

The adjusted mean serum potassium concentration did not show a statistically significant change among all the patients (0.003 mEq/L; 95% CI: -0.004, 0.010). Only patients ≥75 years of age (0.020 mEq/L; 95% CI: 0.006, 0.034), underweight patients (0.050 mEq/L; 95% CI: 0.001, 0.099), and normal weight patients (0.015 mEq/L; 95% CI: 0.001, 0.028) showed a significantly higher mean serum potassium concentration when exposed to EHEs.

2.5 Discussion

We investigated the association of exposure to ambient temperature and EHEs with serum electrolyte concentrations among hemodialysis patients in the Western U.S. While the crude analysis comparing the monthly average ambient temperature and sodium concentrations showed a negative association, an increase in daily ambient temperature was associated with an increase in serum sodium concentrations. This positive association was particularly pronounced in July, August, and September. During the warmer months (May-September), the exposure to EHEs was associated with an increase in the mean serum sodium concentrations, with the effect being more pronounced among patients in Oregon, males, the oldest age group (≥75), White individuals, those who were overweight, and those residing in more socially deprived areas. We did not observe statistically significant changes in mean potassium concentrations.

Previous studies investigating the association between seasonal variation or ambient temperature and serum electrolyte abnormalities showed conflicting findings, with some showing an increase[114,115] and others decrease in serum sodium concentrations with increases in ambient temperature,[110–112] yet these studies primarily focused on the general population without impaired kidney function. While individuals with normal kidney function can maintain fluid and electrolyte homeostasis by increasing water intake and perspiration, hemodialysis patients may have impaired mechanisms for maintaining electrolyte homeostasis[109]. Their water intake is strictly regimented and as such, these patients may have greater perspiration than water intake,[109] which could explain the positive association between ambient temperature and serum sodium concentrations that we observed in this study. Moreover, our study population included relatively older individuals, with an average age of 63 and 46% of participants over 65 years of age. It is well-documented that the older population, particularly those with physical or cognitive impairment, are at greater risk of water-loss dehydration due to impaired thirst mechanisms.[114]

To our best knowledge, this is the first study that examined the association between daily ambient temperature, EHEs, and serum electrolyte change among hemodialysis patients, additionally investigating how these associations differ by region and demographic information. A few studies focused on hemodialysis patients[120] and peritoneal dialysis patients,[109] yet one of these studies utilized monthly average temperature, which does not provide a finer temporal scale for exposure measurement. In this study, we utilized daily average temperature and EHEs which are finer temporal scale. Additionally, a significant strength of this study lies in the inclusion of a representative sample of hemodialysis patients. FKC is the leading provider of dialysis services in the U.S., managing approximately 3,000 hemodialysis clinics. This significantly improves the generalizability of the study findings to a significant proportion of hemodialysis patients in the Western U.S.

This study has several limitations. For instance, exposure was assigned based on the temperature data from central monitoring stations, which does not capture spatial heterogeneity that may exist within the counties. However, potential exposure misclassification errors resulted from the use of monitoring station for each county is likely to be non-differential as it is independent of patients' serum electrolyte concentration, the outcome variable. The non-differential exposure misclassification, if it exists, would likely attenuate the risk estimates.[130] Additionally, due to the data availability, we were not able to account for the individual-level SES indicators, health behaviors, and nutritional status which could potentially lead to residual confounding. However, this study accounted for area-level sociodemographic characteristics by including the SDI as a covariate in the models.

Our findings underscore the need for enhanced preparedness to prevent electrolyte abnormalities among hemodialysis patients during EHEs. Typically, for efficient and safe delivery of treatment to the large population, dialysis facilities use standardized prescriptions with the dialysate sodium concentration of 140mEq/L and dialysate potassium concentration of 2.0-3.0mEq/L[131,132]. However, the deficiencies of a "one-size-fits-all" approach to dialysate prescription have been raised previously[123,131,133]. Our data highlights the need to pay heightened attention to the patients' serum electrolyte concentration change particularly during EHEs.

In conclusion, both an increase in daily ambient temperature and exposure to EHEs were associated with an increase in serum sodium concentration among hemodialysis patients in the Western U.S. These findings show the necessity to update guidelines for managing electrolyte levels in hemodialysis patients, taking into consideration the potential influence of ambient temperature and EHEs.

2.6 Tables

Table 2.1 Baseline Characteristics of Study Population in 222 FKC clinics across 54 counties

	N	(%)	Mean (SD) Sodium (mEq/L)	Mean (SD) Potassium (mEq/L)
All	58,527	(100)	137.1 (3.7)	4.66 (0.71)
State				
California	46,250	(79)	137.1 (3.7)	4.66 (0.70)
Oregon	7,230	(12)	137.1 (3.7)	4.64 (0.70)
Washington	5,047	(9)	136.8 (3.8)	4.71 (0.72)
Sex				
Female	24,592	(42)	136.9 (3.8)	4.63 (0.71)
Male	33,935	(58)	137.2 (3.7)	4.68 (0.70)
Race/ethnicity				
Hispanic	11,226	(19)	137.0 (3.7)	4.76 (0.72)
Non-Hispanic				
Black	5,042	(9)	138.0 (3.6)	4.68 (0.71)
White	29,624	(50)	137.2 (3.7)	4.64 (0.70)
Asian	3,291	(6)	136.7 (4.0)	4.61 (0.70)
Other*	880	(2)	136.8 (3.5)	4.71 (0.73)
Not Reported	8,464	(14)	136.7 (3.7)	4.62 (0.69)
Age				
18-64	27,794	(47)	136.9 (3.7)	4.75 (0.73)
65-74	13,908	(24)	136.9 (3.8)	4.61 (0.67)
≥75	12,988	(22)	137.0 (3.8)	4.55 (0.65)
Not Reported	3,837	(7)	137.9 (3.7)	4.63 (0.71)
BMI				
Underweight	1,336	(2)	136.6 (4.0)	4.61 (0.76)
Normal	15,296	(26)	136.8 (3.8)	4.69 (0.73)
Overweight	16,141	(28)	136.9 (3.7)	4.68 (0.70)
Obese	19,653	(34)	137.2 (3.7)	4.65 (0.68)
Not Reported	6,101	(10)	137.7 (3.7)	4.62 (0.71)
SDI				
<40	14,720	(25)	137.1 (3.6)	4.67 (0.68)
40-59	7,892	(14)	137.0 (3.7)	4.63 (0.69)
≥60	35,915	(61)	137.1 (3.8)	4.67 (0.71)

*Includes American Indian, Native Hawaiian, Samoan, and other

Table 2.2. Adjusted mean differences in serum sodium and potassium between EHE exposed and unexposed groups during May-September. Results are stratified by state, age, sex, race/ethnicity, BMI, and SDI. Linear mixed effects regression adjusted for age, sex, race/ethnicity, BMI, and SDI.

		β (95% CI)	
		Sodium (mEq/L)	**Potassium (mEq/L)**
All		**0.22 (0.18, 0.26)**	0.003 (-0.004, 0.010)
State	California	**0.22 (0.17, 0.26)**	0.004 (-0.004, 0.012)
	Oregon	**0.25 (0.13, 0.37)**	-0.002 (-0.024, 0.020)
	Washington	**0.20 (0.08, 0.31)**	0.001 (-0.023, 0.024)
Sex	Male	**0.23 (0.18, 0.28)**	0.004 (-0.006, 0.013)
	Female	**0.20 (0.14, 0.26)**	0.002 (-0.009, 0.013)
Age	18-64	**0.18 (0.12, 0.24)**	0.001 (-0.009, 0.012)
	65-74	**0.25 (0.17, 0.32)**	-0.006 (-0.020, 0.008)
	≥75	**0.26 (0.18, 0.34)**	**0.020 (0.006, 0.034)**
Race/ ethnicity	Hispanic	**0.39 (0.32, 0.47)**	0.004 (-0.009, 0.017)
	Black	0.04 (-0.08, 0.16)	0.003 (-0.019, 0.025)
	White	**0.16 (0.10, 0.22)**	0.005 (-0.005, 0.015)
	Asian	0.13 (-0.02, 0.28)	-0.020 (-0.046, 0.006)
	Other	**0.38 (0.10, 0.66)**	0.023 (-0.026, 0.072)
BMI	Underweight	0.03 (-0.25, 0.31)	**0.050 (0.001, 0.099)**
	Normal	**0.19 (0.11, 0.27)**	**0.015 (0.001, 0.028)**
	Overweight	**0.25 (0.18, 0.32)**	0.001 (-0.012, 0.013)
	Obese	**0.21 (0.15, 0.27)**	-0.003 (-0.015, 0.009)
SDI	SDI <40	**0.11 (0.00, 0.21)**	0.009 (-0.008, 0.026)
	SDI 40-59	**0.24 (0.16, 0.32)**	**-0.015 (-0.029, 0.000)**
	SDI ≥60	**0.25 (0.20, 0.30)**	0.008 (-0.002, 0.017)

2.7 Figures

Figure 2.1. County average temperature (°C) and average yearly number of EHEs from 2008 to 2018

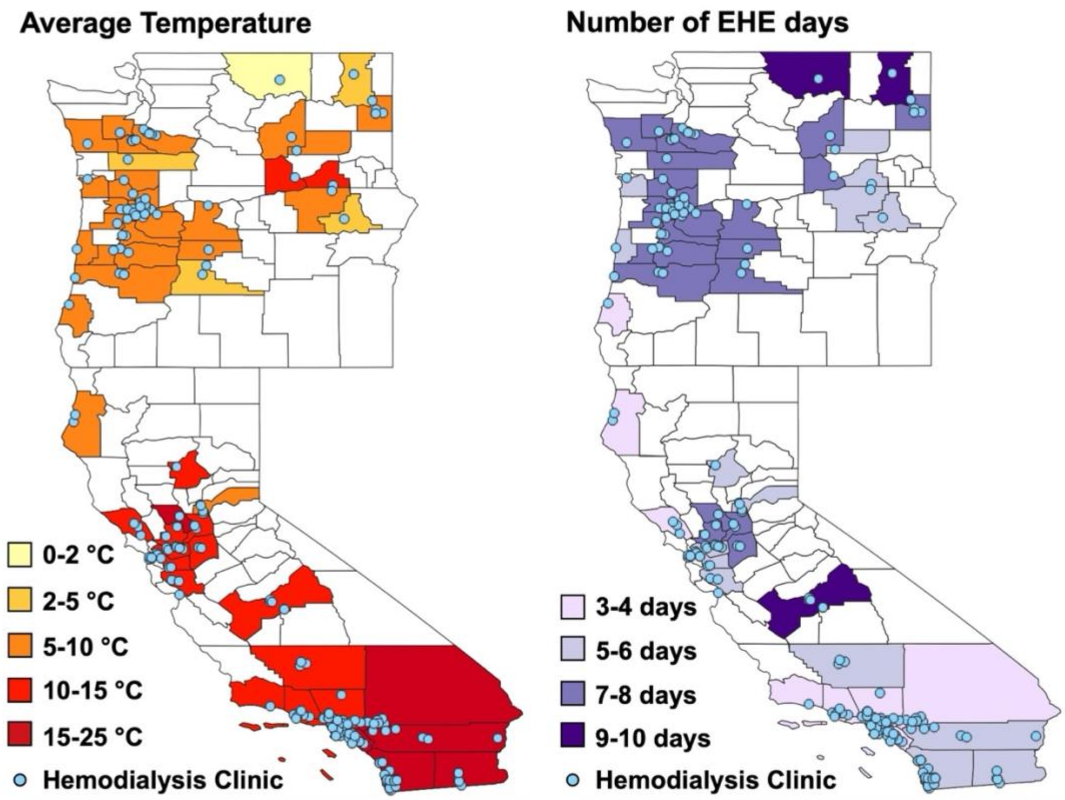


Figure 2.2. Monthly average ambient temperature (°C) and serum electrolyte concentration (mEq/L).

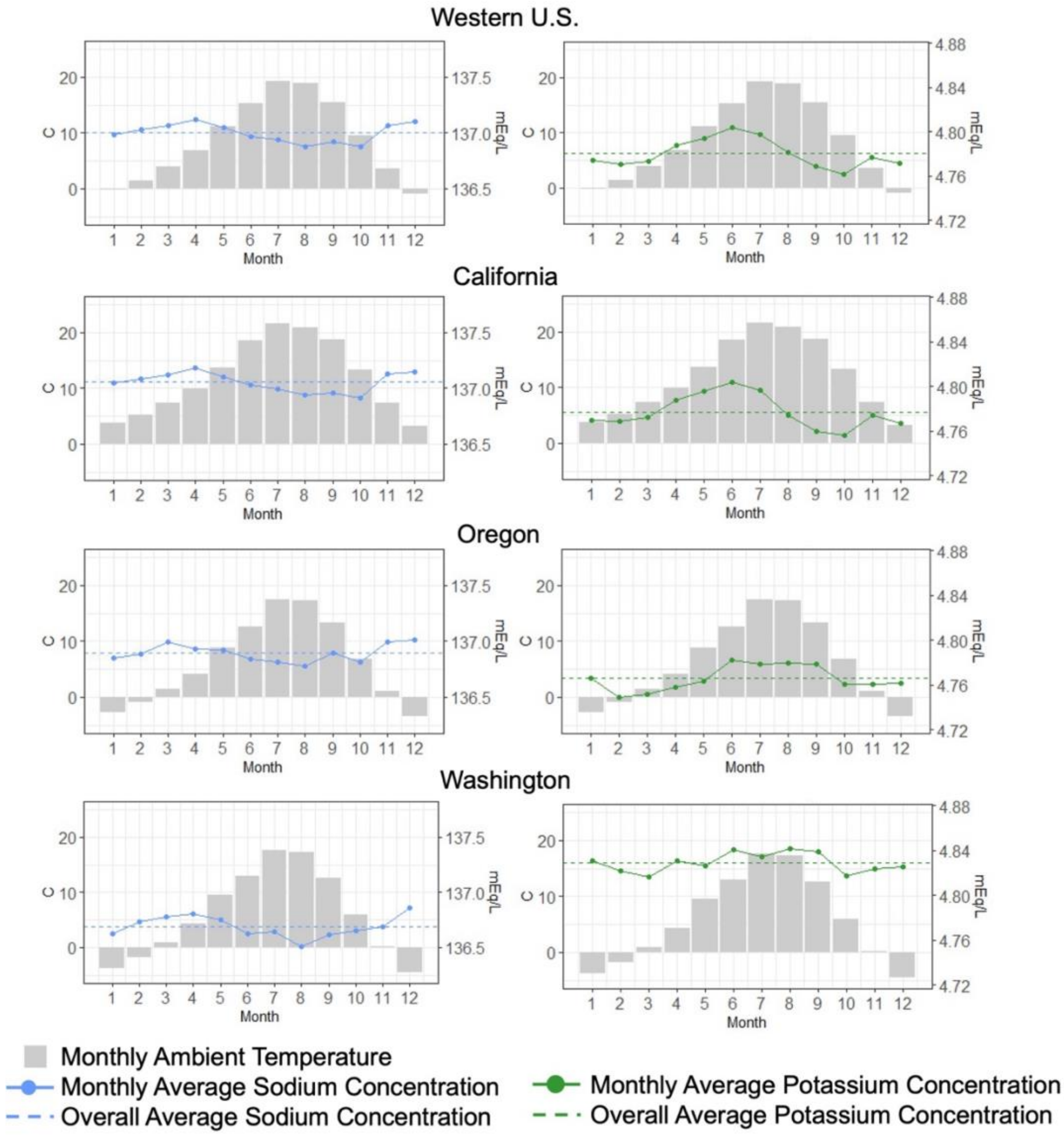
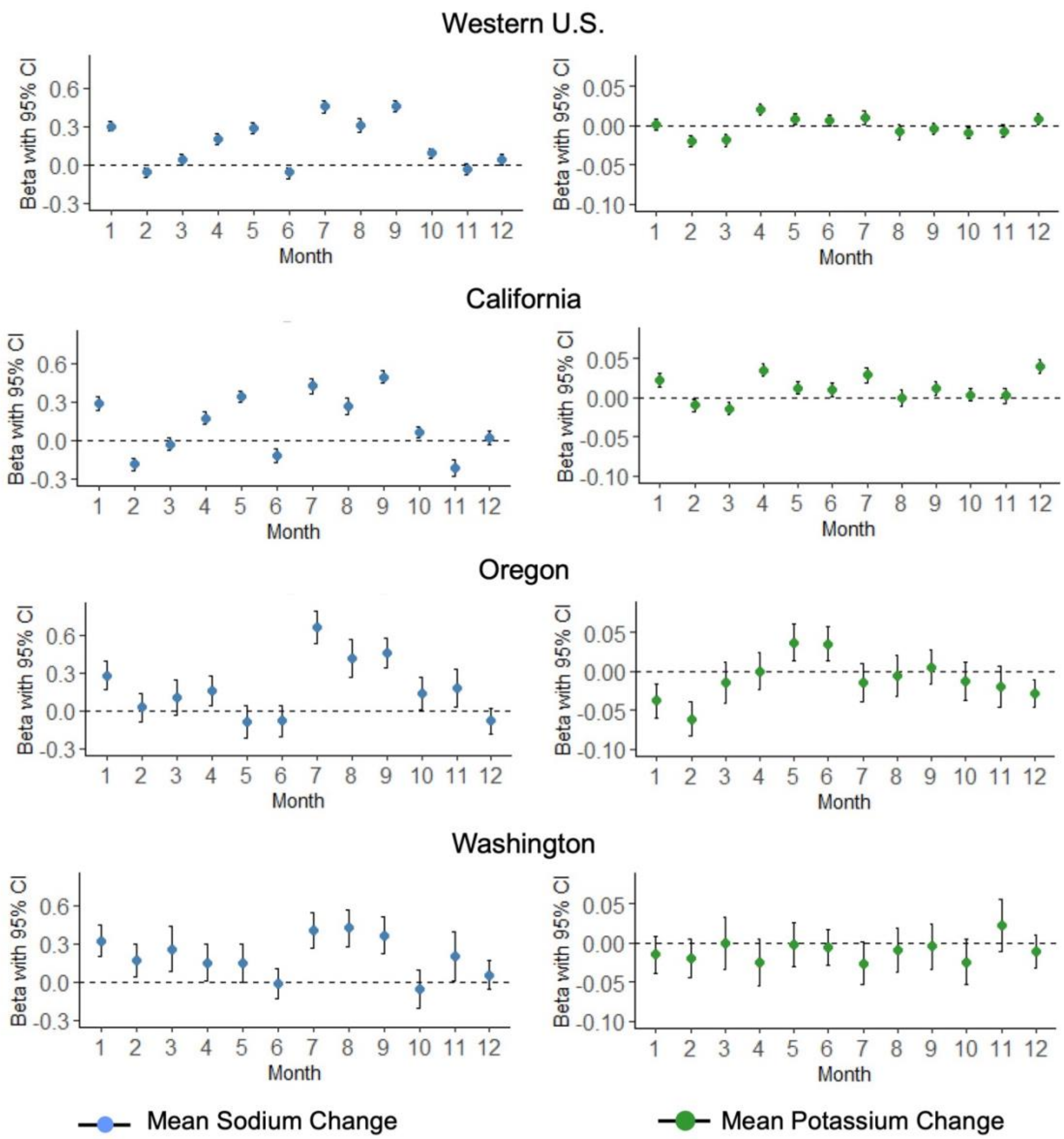


Figure 2.3. Adjusted mean change of serum sodium and potassium changes associated with 10°C increase in daily average ambient temperature, stratified by month. Linear mixed effects regression models adjusted for age, sex, race/ethnicity, BMI, and SDI.



Chapter 3: Canadian Wildfires 2023: Risk of Mortality and Hospitalization in Hemodialysis Patients in the U.S.

3.1 Abstract

Introduction: Smoke plumes from the 2023 Canadian wildfires negatively impacted air quality across large swaths of eastern US. However, a comprehensive assessment of its health impact is lacking. We investigate the association between exposure to wildfire-related air pollutants and risk of mortality and hospitalization among hemodialysis patients in New England, the Mid-Atlantic, and the Midwest U.S.

Methods: The study population includes the end stage kidney disease patients (N=52,995) receiving hemodialysis treatment at Fresenius Kidney Care clinics located in New England, the Mid-Atlantic, and the Midwest U.S. during June-July 2023. Daily number of all-cause deaths, all-cause hospitalizations, respiratory disease hospitalizations, and cardiovascular disease hospitalizations were counted for each hemodialysis clinic. Presence and absence of wildfire smoke plume and wildfire-related fine particulate matter ($PM_{2.5}$) concentration were assessed using both satellite-derived smoke polygons and ground-based $PM_{2.5}$ monitors. We constructed a retrospective observational study using a time-stratified case-crossover analysis with a conditional quasi-Poisson model to investigate the risk of mortality and hospitalization associated with exposures to wildfire-related air pollutants.

Results: The highest daily wildfire-related $PM_{2.5}$ concentration across the clinics was 251.1μg/m^3. The presence of wildfire smoke plume was associated with an 18% increase in risk of same day (lag0) all-cause mortality (rate ratio [RR]:1.18; 95%

confidence interval [CI], 1.13-1.24) and a 3% increase in risk of all-cause hospitalization (RR:1.03; 95% CI, 1.00-1.07). A 10-μg/m^3 increase in wildfire-related $PM_{2.5}$ was associated with a 139% increase in same day all-cause mortality (RR: 2.39; 95% CI, 1.79-3.18), and a 33% increase in all-cause hospitalization (RR:1.33; 95% CI, 1.10-1.62).

Conclusions: Our data suggest that air pollution from the 2023 Canadian wildfires resulted in increased risk of mortality and hospitalization among hemodialysis patients in New England, the Mid-Atlantic, and the Midwest U.S.

3.2 Introduction

The year 2023 marked a record-breaking fire season in Canada, with wildfires starting in May, and peaking between June through September.[45] Overall, an estimated 6,551 fires burned 18.5 million hectares of land, far surpassing the annual average of 2.2 million hectares typically consumed by fires in Canada.[46] The impact of these wildfires was felt far and wide, as smoke plumes rose high into the atmosphere, carried by a steering coastal low to the Northeastern U.S.[47] In response to the resulting high concentration of fine particulate matter ($PM_{2.5}$, particulate matter with aerodynamic diameter <2.5 microns) in New England regions, the U.S. Environmental Protection Agency (EPA) issued air quality advisories on May 31, June 6-8, July 18 and 28.[134]

The Fifth National Climate Assessment concluded that the extent and intensity of wildfire is increasing in the U.S. and this trend will continue in response to climate change.[6] Prior studies have suggested that increases in heat waves and droughts are creating conditions that are conducive to such large-scale wildfires.[6] Furthermore, warmer temperatures can enhance atmospheric instability, leading to increases in dry lightning strikes responsible for starting the wildfires, especially in areas with dense and dry vegetation.[25,26] Additionally, wildfires release substantial amounts of carbon dioxide and other greenhouse gases into the atmosphere, thereby establishing a feedback loop where climate change intensifies and creates more favorable conditions for wildfires.[28]

Wildfire smoke contains high concentrations of carbon monoxide (CO), nitrogen dioxide (NO_2), particulate matter (PM), polycyclic aromatic hydrocarbons

(PAHs), and volatile organic compounds (VOCs), all of which are known to adversely impact cardiopulmonary health outcomes and mortality.[33–36] One pollutant of notable concern within wildfire smoke is PM. Compared to ambient urban PM, wildfire-related PM is mostly carbonaceous and has more free radicals and greater potential to cause inflammation and oxidative stress.[37,38] This is supported by toxicological studies[39,40] as well as a recent epidemiological study.[41] Previous studies further suggest that individuals with pre-existing respiratory disease, middle-aged and older adults, children, and individuals with low socio-economic status are known to be in greater risk of the adverse health outcome due to wildfire air pollution exposure.[36,42,43]

End-stage kidney disease (ESKD) patients may be particularly vulnerable to wildfire-related air pollution. Prior studies have shown that air pollution can increase risk of chronic kidney disease (CKD)[89,90], progression of CKD to ESKD[91], as well as risk of mortality and hospitalization among ESKD patients[52,92–94]. Wildfires may pose additional risk to ESKD patients by disrupting access to dialysis service via road closure, facility closure, or interruption of electricity.[135] Moreover, as the global population ages, the prevalence of ESKD is expected to rise, further straining healthcare systems. The 2023 Annual Report of the U.S. Renal Data System reported that the number of prevalent ESKD patients in the U.S. has gradually increased since 2001 and reached approximately 808,000 in 2021.[61] Total Medicare expenditure for ESKD patients reached approximately $52.3 billion, with the yearly per person care costing approximately $68,000 in 2021.[61] Thus, there is a need to better characterize the burden of climate change fueled wildfires among ESKD patients to inform care practices and clinic-level preparedness.[135]

This study aims to bridge these knowledge gaps by examining the association of exposure to wildfire-related air pollution on the risk of mortality and hospitalization, focusing on the hemodialysis patients in Washington D.C. and the twenty-one states in New England, the Mid-Atlantic, and the Midwest U.S. affected by the 2023 Canadian wildfires. Our hypothesis is that exposure to wildfire-related air pollution (wildfire smoke plume and wildfire-related $PM_{2.5}$) will increase the risk of mortality and hospitalization.

3.3 Methods

3.3.1 Study Area

We focused on Washington D.C. and twenty-one states in New England (Connecticut, Maine, Massachusetts, New Hampshire, and Rhode Island), Mid-Atlantic (Delaware, Maryland, New Jersey, New York, Pennsylvania, Virginia, and West Virginia), and Midwest U.S. (Illinois, Indiana, Iowa, Kentucky, Michigan, Minnesota, Missouri, Ohio, and Wisconsin) that were impacted by the 2023 Canadian wildfires.

3.3.2 Wildfire-related Air Pollution

We quantified wildfire exposure at each Fresenius Kidney Care (FKC) hemodialysis clinic in the study area using two exposure metrics: i) wildfire smoke plume and ii) wildfire-related $PM_{2.5}$ concentration as previously described.[136–138]

To determine whether hemodialysis clinics were under wildfire smoke plume on a given day, we employed the Hazard Mapping System (HMS) from the National Oceanic and Atmospheric Administration's (NOAA), overlaying each clinic's geocoordinates. The HMS is a satellite image display system that provides the wildfire information across North America.[139–141] The HMS categorizes the density of smoke within its polygons as light, medium, and heavy based on the aerosol optical depth (AOD). A remote sensing study suggested that limiting the HMS smoke polygons to medium and heavy smoke closely represents surface smoke.[142] Hence, we created a dichotomous variable for 'wildfire smoke plume' for each hemodialysis clinic at daily basis, assigning it a value of 1 when the HMS polygon's density was categorized as 'medium' or 'heavy', and 0 otherwise.

The ambient daily $PM_{2.5}$ concentration from the U.S. EPA Air Quality System (AQS) was used to differentiate wildfire-related $PM_{2.5}$ from the ambient $PM_{2.5}$ which includes $PM_{2.5}$ from other sources, applying the multistep approach by previous study.[137] First, we matched each hemodialysis clinic with the $PM_{2.5}$ monitors located within a 20km radius, using the longitude and latitude information of the clinics and monitoring stations. The $PM_{2.5}$ concentrations across the monitors within a 20km radius were averaged for each hemodialysis clinic on a daily basis. Then, if a clinic was not under a wildfire smoke plume polygon, the estimated wildfire-related $PM_{2.5}$ was assigned a value 0 $\mu g/m^3$, and non-wildfire-related $PM_{2.5}$ was assigned the ambient daily $PM_{2.5}$ concentrations. However, if a clinic was under a wildfire smoke plume, the estimated wildfire-related $PM_{2.5}$ concentration for that particular day was computed by subtracting the seasonal non-smoke background $PM_{2.5}$ concentration from the ambient $PM_{2.5}$ concentration for that given day. Seasonal non-smoke background $PM_{2.5}$ concentrations were calculated as the median of the ambient $PM_{2.5}$ concentrations of sites without wildfire smoke plume during the summer (June-August). In cases where a smoke plume was detected but the ambient $PM_{2.5}$ concentration was lower than the seasonal background $PM_{2.5}$, a value of 0 $\mu g/m^3$ was assigned for the wildfire-related $PM_{2.5}$. Non-wildfire-related $PM_{2.5}$ was calculated by subtracting the wildfire-related $PM_{2.5}$ from the ambient $PM_{2.5}$ concentration.

Among the 1,096 hemodialysis clinics in the study area, we excluded the 364 clinics that did not have any adjacent AQS monitor. Vermont was not included in the study area because there was only one hemodialysis clinic, which did not have any adjacent AQS monitor. In total, 732 hemodialysis clinics were selected for our analysis.

3.3.3 Study Population and Health Outcomes

The study participants consisted of patients aged 18 years or older who were undergoing maintenance hemodialysis treatment at FKC clinics in the selected states between June 1st and July 31st 2023. The patient electronic health records included each patient's age, sex, race/ethnicity, clinic code, date and International Classification of Diseases (ICD-10) codes for hospitalization, and date of mortality. To assign each patient wildfire-related air pollution exposure, the location of each clinic where patients received hemodialysis treatment was used as a proxy for their residence. For each clinic, we counted the daily number of all-cause deaths, all-cause hospitalizations, hospitalizations for disease of the circulatory system (ICD-10 codes: I00-I99), and respiratory system (ICD-10 codes: J00-J99). This study was approved by the University of Maryland Institutional Review Board (Exempt Category #4). We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for cohort studies.[124]

3.3.4 Statistical Analysis

We conducted a time-stratified case-crossover analysis using a conditional quasi-Poisson regression model[143,144], to examine the association between wildfire exposures (wildfire smoke plume and wildfire-related $PM_{2.5}$) and the risk of mortality and hospitalization. In a time-stratified case-crossover study design, the time period is divided into fixed strata, such as month and day of the week, and referent days are selected within each stratum.[145] The exposure status of the individual during case period (immediately preceding the outcome) is then compared to the exposure status of the same individual during the control periods. This study design employing self-matching offers the advantage of controlling for all time-invariant individual level confounders including age, sex, and race/ethnicity.[146] A case-crossover design is particularly well-suited for studying short-term, transient effects of intermittent exposures on acute outcomes such as mortality and hospitalization.[146]

In traditional case-crossover analysis, conditional logistic regression is employed, using an expanded dataset for each individual case [145]. However, in this study, we utilized conditional quasi-Poisson regression, which simplifies computation by conditioning parameters on total health outcome counts within each stratum (year, month, day of week, and clinic).[143,144] This computationally efficient approach models the rate of events during each time period as a function of the exposure variable and allows for adjustment of overdispersion, autocorrelation, and varying rate denominators.[143] It has been established that this approach yields identical estimates to conditional logistic regression.[143,144] In our analysis, the aggregated daily mortality and hospitalization were used as the outcome variables, while wildfire smoke plume and wildfire-related $PM_{2.5}$ concentrations served as the two main exposure variables. We adjusted for non-wildfire-related $PM_{2.5}$ concentrations and population size (offset variable equal to the natural log of the monthly number of hemodialysis patients for each clinic). Measures of associations were reported as rate ratios (RRs) with 95% confidence intervals (95% CIs). The RRs for wildfire-related $PM_{2.5}$ was expressed as per 10-μg/m^3 increases. Furthermore, we employed the distributed lag non-linear model (DLNM) framework to assess lag effects for up to eight days following the exposure. DLNM enables the modeling of potential non-linear associations between exposures and health outcomes, capturing how this association changes over time, particularly considering the time elapsed since the onset of exposure.[147] Thus, DLNM was utilized to determine the risk of mortality and hospitalization and at various lag days. For example, 'lag 0' signifies the risk on the same day as the exposure, while 'lag 8' pertains to the risk eight days after exposure. Lag effect up to 8 days were chosen considering both model convergence and the Akaike Information Criterion (AIC).

Finally, we conducted stratified analyses by sex (male and female), baseline age (18-64, 65-74, and >74 years), and race/ethnicity (Hispanic, non-Hispanic Black, and non-Hispanic White) for estimating the risks of all-cause mortality and all-cause hospitalization using DLNM focused on lag 0. Due to low statistical power, presenting the results for the non-Hispanic Asian patients was not feasible. We used R statistical software version 3.6.1 with the *dlnm*, *gnm*, and *tidyverse* packages.[128,148–150] All statistical tests were two-tailed and based on a significance level of 0.05.

3.4 Results

In the selected study area, we had a total of 52,995 patients from 732 hemodialysis clinics located in 230 counties (**Table 3.1**). The majority of the patients were older than 64 years (53.8%), male (58.5%), and non-Hispanic White (39.8%).

Figure 3.1 shows the satellite image of wildfire smoke plume on June 6, 2023[151] (top) and Maximum wildfire-related $PM_{2.5}$ concentrations and number of wildfire smoke days at the 732 hemodialysis clinics during June-July 2023 (bottom). The daily maximum wildfire-related $PM_{2.5}$ concentrations ranged from 0 to 251.1 $\mu g/m^3$. The number of wildfire smoke days ranged from 16 to 48 days, with an average of 33 (SD=6) days.

Table 3.2 shows health outcomes and $PM_{2.5}$ concentrations stratified on the presence/absence of a wildfire smoke plume. Notably, there were more clinic-days with wildfire smoke plumes (N=24,404) compared to clinic-days without (N=20,122). The average all-cause mortality rate was higher on days with wildfire smoke plumes (5.1 per 10,000 hemodialysis patients) than on days without (4.5 per 10,000 hemodialysis patients). The average all-cause hospitalization rate higher on wildfire smoke plume days (48.4 vs. 45.7). In contrast, the hospitalization rate for respiratory diseases was slightly lower during wildfire smoke plume days (3.9 vs. 4.0). The hospitalization rate for cardiovascular diseases was higher on wildfire smoke plume days (6.6 vs. 6.2). Finally, the average $PM_{2.5}$ concentration was 23.7 $\mu g/m^3$ on days with wildfire smoke plumes vs. 10.3 $\mu g/m^3$ on days without. The average of estimated wildfire-related $PM_{2.5}$ concentration was 16.5 $\mu g/m^3$ on days with wildfire smoke plumes.

The lag-specific risks of mortality and hospitalizations associated with exposure to wildfire smoke plume and a 10-$\mu g/m^3$ increase in wildfire-related $PM_{2.5}$ are shown in **Figure 3.2**. We observed an 18% increase in risk of all-cause mortality (lag 0) during days with wildfire smoke plume (RR_{Lag0}: 1.18; 95% CI, 1.13-1.24), with the risk declining over the subsequent 3 days. The risk of same day (Lag0) all-cause mortality was 139% higher for 10-$\mu g/m^3$ increase in wildfire-related $PM_{2.5}$ (RR_{Lag0}: 2.39; 95% CI, 1.79-3.18). The presence of wildfire smoke plume was associated with a 3% higher risk of same day all-cause hospitalization (RR_{Lag0}: 1.03; 95% CI, 1.00-1.07), with the risk declining over the subsequent 5 days. We observed a 33% increase in same day all-cause hospitalization for a 10-$\mu g/m^3$ increase in wildfire-related $PM_{2.5}$ (RR_{Lag0}: 1.33; 95% CI, 1.10-1.62). By comparison, the wildfire smoke plume related risk of hospitalization was considerably higher for respiratory conditions, with an 11% increase in same day hospitalization (RR_{Lag0}: 1.11; 95% CI, 1.06-1.16). The highest risk of wildfire-related $PM_{2.5}$ exposure was observed for respiratory hospitalizations, with a 10-$\mu g/m^3$ increase in exposure associated with a 144% increase in same day hospitalization (RR_{Lag0}: 2.44; 95% CI, 1.83-3.24). The risk of cardiovascular disease hospitalizations was highest at lag 1 (RR_{Lag1}: 1.06; 95% CI, 1.04-1.08). The wildfire-related $PM_{2.5}$ was associated with reduced cardiovascular disease hospitalizations up to lag 3 days with the highest risk observed at lag 5 (RR_{Lag5}: 1.05; 95% CI, 0.95-1.15).

We further stratified the analysis for all-cause mortality (**Figure 3.3 top panel**) and all-cause hospitalization (**Figure 3.3 bottom panel**) by sex (male and female), baseline age (18-64, 65-74, and >74 years), and race/ethnicity (Hispanic, non-Hispanic Black, and non-Hispanic White), presenting the RRs at lag 0 (RR_{Lag0}). Female patients showed higher RR for 10-μg/m^3 increase in wildfire-related $PM_{2.5}$ compared to male patients (RR_{Lag0}: 1.60 vs. RR_{Lag0}: 1.38). The oldest group (age >74) showed the highest mortality RR for wildfire smoke plume exposure (RR_{Lag0}: 1.26), while the youngest group (age 18-64 years) highest mortality RR for a 10-μg/m^3 increase in wildfire-related $PM_{2.5}$ (RR_{Lag0}: 2.29). Hispanic patients showed the highest mortality RR for both wildfire smoke plume exposure (RR_{Lag0}: 1.93) and 10-μg/m^3 increase in wildfire-related $PM_{2.5}$ (RR_{Lag0}: 2.07). Male patients showed higher RRs of hospitalization compared to female patients for both wildfire smoke plume exposure (RR_{Lag0}: 1.06 vs. 1.01) and 10-μg/m^3 increase in wildfire-related $PM_{2.5}$ (RR_{Lag0}: 1.24 vs. 0.91). Patients aged 65-74 showed the lowest hospitalization RR for wildfire smoke plume exposure (RR_{Lag0}: 0.92) and lowest RR for a 10-μg/m^3 increase in wildfire-related $PM_{2.5}$ (RR_{Lag0}: 1.18) among the age groups. Black patients showed the highest hospitalization RR for wildfire smoke plume exposure among all (RR_{Lag0}: 1.09), while Hispanic patients showed the highest RR for 10-μg/m^3 increase in wildfire-related $PM_{2.5}$ (RR_{Lag0}: 1.61).

3.5 Discussion

We investigated how exposure to the 2023 Canadian wildfire smoke influenced the risk of mortality and hospitalization among hemodialysis patients in New England, the Mid-Atlantic, and the Midwest U.S. using wildfire smoke plume and wildfire-related $PM_{2.5}$. Both the presence of wildfire smoke plume and wildfire-related $PM_{2.5}$, showed the most pronounced effects at lag 0 for all-cause mortality, all-cause hospitalization, and respiratory hospitalization. In terms of all-cause mortality, Hispanic patients were identified as the most vulnerable population. Regarding all-cause hospitalization, both male patients and Hispanic patients showed pronounced RRs.

Climate change is extending the wildfire season and escalating the intensity and extent of wildfires[6], which is a trend that coincides with the growing population of ESKD patients due to aging demographics. This study underscores the potential impact of these intersecting factors on the burden faced by this high-risk population. It also emphasizes a significant shift, where wildfire smoke is no longer solely a local issue in the Western U.S., underscoring the need for adaptation strategies in other regions to address the risks posed by these climate-related hazards.

Prior studies have primarily focused on more localized effects of wildfires, particularly in Western U.S. where wildfires occur most frequently[42,43,136,138,152–161]. However, as projections indicate a rise in the intensity and extent of these fires, it is becoming evident that wildfire smoke and its associated air pollutants can travel vast distances, extending from Southern Canada to as far as 5,000km away in Northeastern U.S.[6,44] This was evidenced by the devastating impact of Canadian wildfires in 2023, which reached as far as Greater Northeastern and Midwestern U.S., carried by the winds. Studies on wildfires in Quebec, Canada in 2002 further elucidate this phenomenon, demonstrating the long-range transboundary $PM_{2.5}$ reaching the east coast of the U.S.[162–164] One of these studies reported 49.6% increase in respiratory hospitalization and 64.9% increase in cardiovascular hospitalization when the smoke plume was present compared to before the smoke plume had arrived.[162]

Notably, our findings showed a negative association between 10-$\mu g/m^3$ increase in wildfire-related $PM_{2.5}$ and cardiovascular hospitalization for up to lag 3, while the wildfire smoke plume exposure showed a positive association during the same lag period. Since the wildfire-related $PM_{2.5}$ concentration was estimated based on both satellite-derived data (HMS) and ground-based monitoring data (AQS), it is prone to larger measurement errors and has potential to lead to larger uncertainties in the statistical estimates. Additionally, this mixed finding for cardiovascular outcome aligns with previous review studies, which concluded that wildfire smoke or wildfire $PM_{2.5}$ increases all-cause mortality and respiratory health effects, but its impact on cardiovascular mortality and morbidity remains mixed and inconclusive.[35,165] They suggested that wildfire-related $PM_{2.5}$ may not fully represent the diverse chemicals present in wildfire smoke and this incomplete characterization could explain inconsistencies in cardiovascular outcomes.[165] Another explanation could be that patients with severe cardiovascular diseases may not be captured in cardiovascular hospitalization cases as they may succumb to their condition before being hospitalized.

To our knowledge, this is the first study that examined the potential health impact of the 2023 Canadian wildfires. Moreover, a significant strength of this study lies in the inclusion of a representative sample of hemodialysis patients. In the U.S., FKC is the leading provider of dialysis services, managing nearly 3,000 hemodialysis facilities. This also allowed us to encompass a study population across a broad geographic area. Finally, we used two distinct metrics to assess wildfire air pollution exposure: the presence of wildfire smoke plumes and wildfire-related $PM_{2.5}$, by utilizing both satellite-derived data and ground-based air pollution measurements.

One limitation of this study is the possibility for exposure misclassification regarding wildfire smoke plumes. By utilizing satellite observation, HMS data identifies smoke plumes from the ground to high altitudes. Consequently, it might not precisely represent air quality near the surface, particularly in downwind areas where the dispersion of smoke plumes may differ. Nevertheless, a remote sensing investigation indicated that restricting the smoke polygons to medium and heavy smokes closely reflects surface smoke, highlighting the need for cautious consideration when employing the HMS smoke product to evaluate the public health implications of wildfire smoke.[142] Moreover, while assessing wildfire smoke plume and $PM_{2.5}$ exposure at clinic-level, there might be spatial heterogeneity within the clinic-level area. Nevertheless, any potential exposure misclassification due to clinic-level measures are likely to be non-differential. This implies that such errors are unrelated to patients' mortality and hospitalization, which serve as the outcome variables. In the presence of non-differential exposure misclassification, if it exists, the risk estimates would likely be attenuated.[130]

Our findings underscore the need for enhancing awareness among kidney care providers regarding health threats posed by wildfires. Hemodialysis clinics can play a crucial role in this regard by implementing early warning systems to notify patients about anticipated wildfire smoke and air pollution.[135] Encouraging patients to limit outdoor activities and use protective measures such as N95 masks can significantly reduce their exposure to harmful pollutants. Moreover, hemodialysis clinics can utilize pulse oximeters to monitor the oxygen saturation level of their patients. In the event of a direct wildfire threat, clinics should have evacuation protocols in place to ensure patient safety. Providing alternative treatment options can help minimize disruptions to patients' hemodialysis schedules and ensure continuity of care. By proactively implementing these measures, healthcare providers can better protect patients during wildfires that increasingly transcend regional boundaries.

In conclusion, exposure to the 2023 Canadian wildfire smoke plume and wildfire-related $PM_{2.5}$ exposure was associated with increased risk of mortality and hospitalization among hemodialysis patients in New England, the Mid-Atlantic, and the Midwest U.S. Our research focuses on particularly among hemodialysis patients, who represent one of the most vulnerable populations. Targeting interventions toward this vulnerable group can potentially contribute to mitigating the health risks of broader populations as well.

3.6 Tables

Table 3. 1. Characteristics of Study Population

Characteristics	
Counties, N	230
Clinics, N	732
Patients, N	52,995
Baseline Age [a], No. (%)	
18-64	24,474 (46.1)
65-74	14,391 (27.2)
>74	14,130 (26.7)
Sex, No. (%)	
Female	22,019 (41.5)
Male	30,976 (58.5)
Race/ethnicity, No. (%)	
Hispanic	6,312 (11.9)
Non-Hispanic	
Black	20,696 (39.1)
White	21,103 (39.8)
Asian	2,040 (3.8)
Other	399 (0.8)
NA	2,445 (4.6)

[a] Age at initial treatment during the study period (June-July 2023)

Table 3.2. Summary of health outcomes and $PM_{2.5}$ concentrations stratified by wildfire smoke exposure at all hemodialysis clinics

	All	Wildfire Smoke Plume Stratification	
		Present	Absent
Clinic-day, N	44,526	24,404	20,122
Mortality, N	1,431	836	595
Average mortality, rate [a]	4.8	5.1	4.5
Hospitalization, N			
All-cause	14,768	8,325	6,443
Respiratory	1,220	665	556
Cardiovascular	2,069	1,162	907
Average hospitalization, rate [b]			
All-cause	47.1	48.4	45.7
Respiratory	4.0	3.9	4.0
Cardiovascular	6.5	6.6	6.2
Average $PM_{2.5}$ ($\mu g/m^3$)			
Overall	17.7	23.7	10.3
Wildfire-related	9.1	16.5	0
Non-wildfire-related	8.6	7.2	10.3

[a] Mortality rate: 10,000 × (Daily number of death / Monthly number of hemodialysis patients who visited the clinic)
[b] Hospitalization rate: 10,000 × (Daily number of hospitalization / Monthly number of hemodialysis patients who visited the clinic)

3.7 Figures

Figure 3.1. Terra satellite image showing wildfire smoke plume on June 6, 2023[151] (top) and Maximum wildfire-related $PM_{2.5}$ concentrations and number of wildfire smoke days at the 732 hemodialysis clinics during June-July 2023 (bottom)

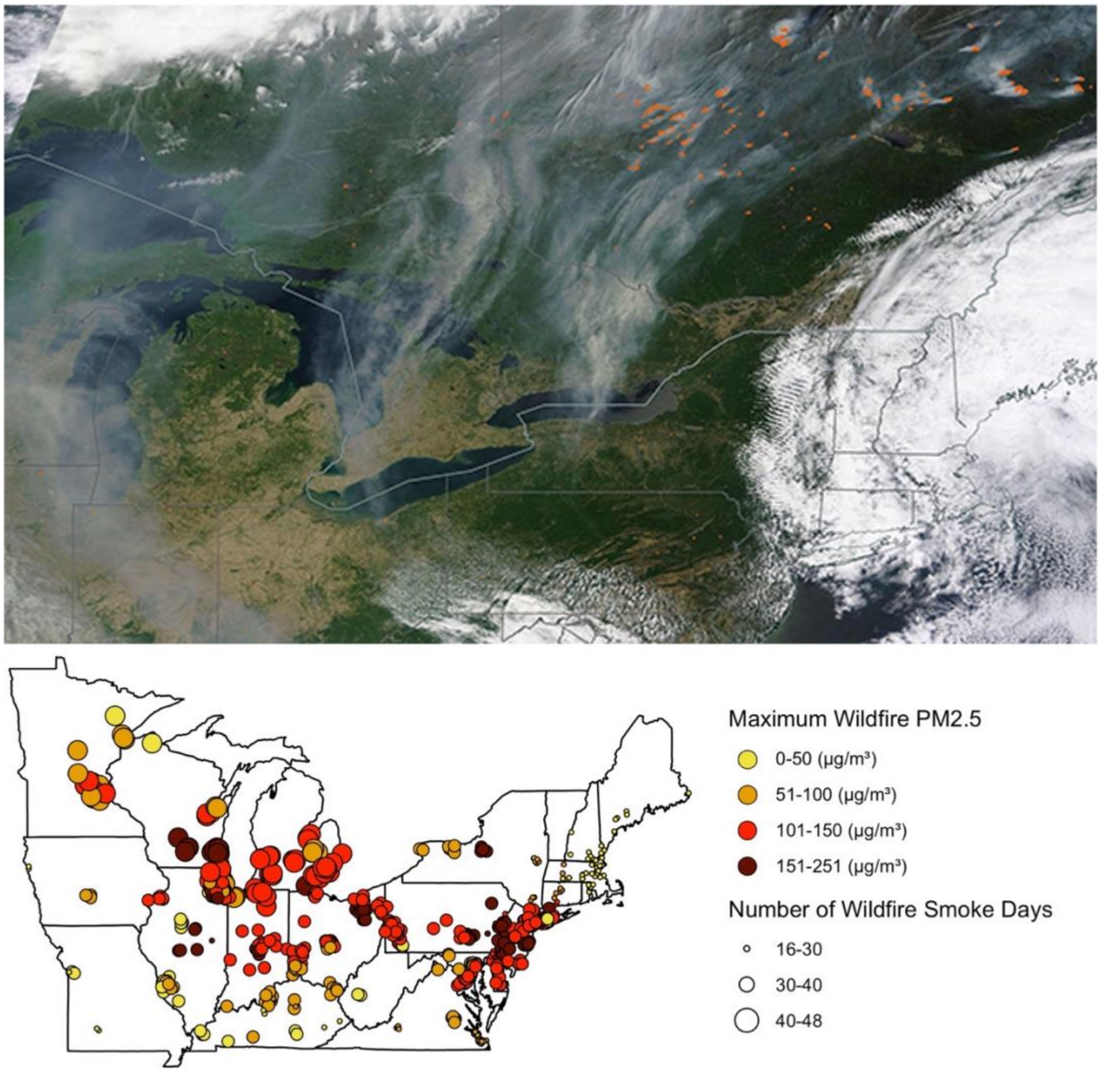


Figure 3.2. Lag-specific associations between exposure to wildfire smoke plume and a 10-μg/m^3 increase in wildfire-related $PM_{2.5}$ and risk of mortality and hospitalization. CI, confidence interval; RR, rate ratio. All models were adjusted for non-wildfire-related $PM_{2.5}$.

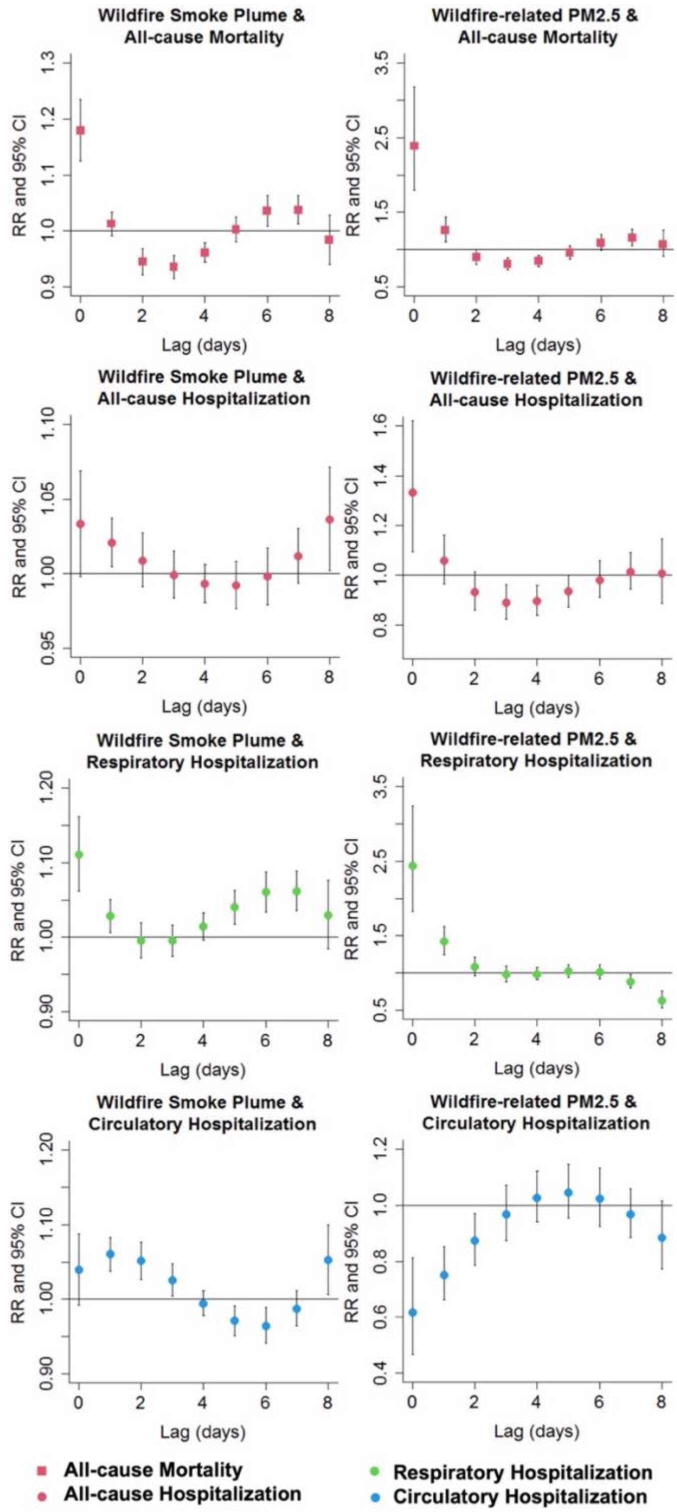
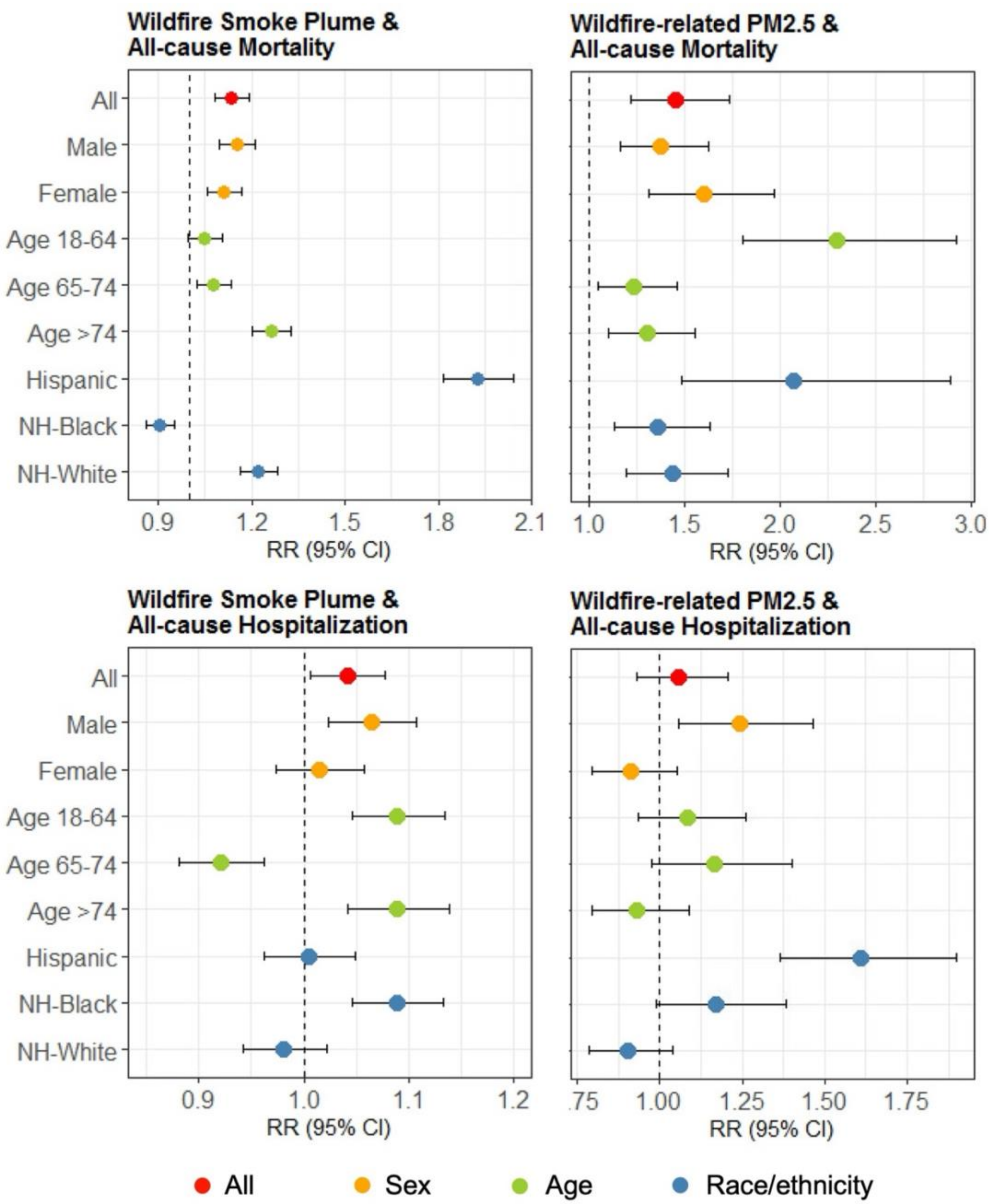


Figure 3.3. RR at lag 0 (RR $_{Lag0}$) for all-cause hospitalization (top) and all-cause mortality (bottom) stratified by sex, age, and race/ethnicity. CI, confidence interval; RR, rate ratio. All models adjusted for non-wildfire-related $PM_{2.5}$.



NH-Black: Non-Hispanic Black, NH-White: Non-Hispanic White, NH-Asian: Non-Hispanic Asian
Due to low statistical power, presenting the mortality RRs for the NH-Asian patients was not feasible.

Chapter 4: Exposure to Wildfire Smoke and Risk of Mortality and Hospitalization among Hemodialysis Patients in the Western U.S.: Effect Modification by Extreme Heat Events

4.1 Abstract

Introduction: Ongoing climate change is increasing the extent of wildfires and extreme heat events (EHEs) in the Western United States. Prior studies have the investigated impact of such extreme events separately, but there is a paucity of data regarding how simultaneous occurrences of wildfires and EHEs impact vulnerable populations such as hemodialysis patients.

Methods: We analyzed health records of 55,223 hemodialysis patients received hemodialysis treatment at Fresenius Kidney Care clinics in California, Oregon, and Washington during the warmer months of 2010–2018. Each patient's exposure to wildfire smoke (wildfire smoke plume and wildfire-related $PM_{2.5}$) and EHEs was estimated using dialysis clinic locations. We employed a time-stratified case-crossover analysis with a conditional quasi-Poisson model to investigate the risks of mortality and hospitalization associated with exposure to wildfire smoke and EHEs. We used a likelihood ratio test to assess potential interaction effects of wildfire smoke and EHEs. Additionally, we conducted stratified analyses to estimate effect modification by EHEs.

Results: The presence of a wildfire smoke plume was associated with a 19% increase in same-day (lag 0) risk of mortality (Rate Ratio [RR]: 1.19; 95% Confidence Interval [CI]: 1.11, 1.27), while a 10-$\mu g/m^3$ increase in wildfire-related $PM_{2.5}$ was associated with a 3% increase in mortality risk. We observed considerably higher risk of mortality

when patients were simultaneously exposed to both wildfire smoke plume and an EHE compared to wildfire smoke plume alone in the absence of EHE (52% vs 15%, respectively, increase in risk). We did not observe such a significant interaction when estimating the risk of all-cause hospitalization.

Conclusions: The all-cause mortality risks associated with wildfire smoke plume and wildfire-related $PM_{2.5}$ were more prominent during EHE days. This study underscores the urgent need of updating patient care guidelines to account for the increasing extent of such compound hazards.

4.2 Introduction

Climate change is contributing to a substantial increase in the Earth's global surface temperature, with the year 2022 exceeding the long-term (1951-1980) average by 0.89°C.[166] The 5th National Climate Assessment concluded that both frequency and intensity of extreme heat events (EHEs) are increasing in the U.S.,[6] a trend which will continue in response to climate change.[4] EHEs represent the leading cause of weather-related deaths in the U.S.[22], with an average of 702 deaths annually between 2004 and 2018.[23]

EHEs and drought increase the risk of wildfires by contributing to the drying of the vegetation which subsequently promotes rapid spread of wildfires.[33,167] Since the 1980s, the Western U.S. has experienced continuous warming accompanied by increased frequency of wildfire and length of fire season, with many global climate models suggesting this trend will continue.[30,31] The National Interagency Coordination Center reported that there were 58,950 wildfires that burned approximately 10.1 million acres in 2020 in the U.S., and the West Coast (Washington, Oregon, and California) accounted for 58% of the nation's total acres burned.[32]

Wildfire smoke contains high concentrations of hazardous air pollutants, including particulate matter (PM), carbon monoxide, nitrogen dioxide, volatile organic compounds, and polycyclic aromatic hydrocarbons.[33] The smoke plume from a wildfire has the potential to travel over long distances, impacting communities that are geographically distant from the fire sources.[163] For example, in July 2021, smoke from wildfires in Southern Canada and the Northwestern U.S. contributed to New

York state exceeding the National Ambient Air Quality Standard (NAAQS) for fine particulate matter (aerodynamic diameter < 2.5 microns; $PM_{2.5}$).[44] In comparison to urban ambient PM, wildfire-related PM is predominantly carbonaceous and contains higher levels of free radicals, increasing its potential to induce inflammatory and oxidative responses.[37,38] Prior toxicological studies have demonstrated that PM from wildfires is more toxic than PM from other sources of air pollution.[39,40] Therefore, it is crucial to differentiate PM attributable to wildfire smoke from background PM when assessing its health impacts.[41] Certain populations, including individuals with pre-existing respiratory disease, older adults, children, pregnant women, and individuals with low socioeconomic status, are considered to be particularly vulnerable to the adverse health effects of wildfire-related air pollution exposure.[36,42,43]

Hazards like wildfire do not exist in a vacuum. The Fifth National Climate Assessment concluded that communities across the U.S. are increasingly facing threats from climate change-related compound hazards where two or more hazards occur simultaneously or in close succession.[6] In a recent systematic review, researchers identified a total of 56 environmental epidemiological studies that examined at least two climate change-related exposures, including air pollution, temperature, and pollen.[50] The authors of the review concluded that there is sufficient evidence supporting the synergistic effects of heat and air pollution exposure. They also underscored the need for future research to investigate the potential impact of compound environmental exposures, given that individuals are often exposed to multiple environmental risk factors simultaneously.[50] Furthermore, compound hazards may disproportionately impact individuals living with chronic diseases, such as end-stage kidney disease (ESKD).[52]

The global burden of ESKD is increasing, with a 2.4 million ESKD patients across the globe in 2016.[60] With the aging global population, ESKD prevalence is projected to increase, placing greater strain on healthcare systems. According to the 2023 Annual Report of the United States Renal Data System (USRDS), prevalent ESKD cases in the U.S. have steadily risen since 2001, reaching about 808,000 in 2021.[61] ESKD patients require renal replacement treatment such as in-center hemodialysis or kidney transplantation.[59] Medicare expenditure for ESKD patients totaled approximately $52.3 billion in 2021, with an average annual healthcare cost of around $68,000 per person with ESKD.[61]

Given the projected increases in wildfire activity in the Western U.S. tied to ongoing climate change and ESKD burden associated with an aging population, there is a need to investigate how wildfire-related air pollution impacts mortality and hospitalization risk among ESKD patients. Likewise, additional data is needed to understand if joint occurrences of wildfires and EHEs further exacerbate the risk. This study aims to bridge these knowledge gaps by examining (1) how exposure to wildfire-related air pollution (wildfire smoke plume and wildfire-related $PM_{2.5}$) and EHEs impact the risks of mortality and hospitalization among hemodialysis patients, and (2) the potential effect modification by EHEs on the association between wildfire-related air pollution exposure and the risks of mortality and hospitalization. Our hypothesis is that exposure to wildfire-related air pollution and EHEs will increase the risks of mortality and hospitalization among ESKD patients, and that the risks associated with wildfire-related air pollution exposure will be more pronounced in the presence of EHEs.

4.3 Methods

4.3.1 Study Population and Health Outcomes

Deidentified electronic health records of in-center hemodialysis patients were obtained from Fresenius Kidney Care (FKC). The study participants consisted of patients aged 18 or older who were undergoing hemodialysis treatment at FKC clinics located in the Western U.S. (Washington, Oregon, and California) during the warmer months, spanning from May to September, between June 2010 and September 2018. The relevant health records included the information on each patient's age, sex, race/ethnicity, identification code of the treatment clinic visited, and the dates of hospital admissions and deaths. Daily counts for all-cause hospitalizations and all-cause deaths were calculated for each clinic, respectively. This study was approved by the University of Maryland Institutional Review Board (Exempt Category #4). We followed the Strengthening the Reporting of Observational studies in Epidemiology (STROBE) guidelines for cohort studies.[124]

4.3.2 Exposure

Presence of Wildfire Smoke Plume and Wildfire-related $PM_{2.5}$ Concentration

We quantified wildfire-related air pollution exposure at each hemodialysis clinic using two exposure metrics: (1) wildfire smoke plume and (2) wildfire-related $PM_{2.5}$ concentration as previously described.[136–138]

To assess for the presence of a wildfire smoke plume on a given day, we overlaid the clinic's geocoordinates with the Hazard Mapping System (HMS) from the National Oceanic and Atmospheric Administration's (NOAA), which is a satellite image display system that provides the wildfire information for North America (**Figure 4.1**).[139–141] The HMS classifies the density of smoke within its polygons as light, medium, and heavy based on the aerosol optical depth (AOD). A recent remote sensing study suggested that restricting the HMS polygons to medium and heavy smoke classes more closely represents surface smoke.[142] Hence, we established a binary exposure indicator for 'wildfire smoke plume' for each clinic on a daily basis, assigning it a value of 1 when the HMS polygon's density was classified as 'medium' or 'heavy', and 0 if otherwise.

To differentiate wildfire-related $PM_{2.5}$ from the overall $PM_{2.5}$ originating from other sources, we utilized a multi-step approach employing daily ambient $PM_{2.5}$ concentration data from the U.S. Environmental Protection Agency (EPA) Air Quality System (AQS), following a previously established method.[137] First, we matched each hemodialysis clinic with all $PM_{2.5}$ monitors within a 20km radius. Then, we averaged $PM_{2.5}$ concentrations from different AQS monitors for each clinic on a daily basis. If a given clinic was not under a wildfire smoke plume polygon, the estimated wildfire-related $PM_{2.5}$ for that clinic was assigned a value of 0 $\mu g/m^3$, while non-wildfire-related $PM_{2.5}$ was assigned the recorded ambient $PM_{2.5}$ concentrations.

However, if a clinic fell under a wildfire smoke plume, the estimated wildfire-related $PM_{2.5}$ concentration for that specific day was calculated by subtracting the seasonal non-smoke background $PM_{2.5}$ concentration from the ambient $PM_{2.5}$ concentration for that given day. Seasonal non-smoke background $PM_{2.5}$ concentrations were computed as the median of the ambient $PM_{2.5}$ concentrations of sites without wildfire smoke plumes for each season (Spring: Mar-May, Summer: Jun-Aug, and Fall: Sept-Nov) within the same year. In instances where the ambient $PM_{2.5}$ concentration was lower than the seasonal non-smoke background $PM_{2.5}$, a value of 0 $\mu g/m^3$ was assigned for the wildfire-related $PM_{2.5}$. Non-wildfire-related $PM_{2.5}$ was computed by subtracting the wildfire-related $PM_{2.5}$ from the ambient $PM_{2.5}$ concentration. Of the 190 FKC clinics in the Western U.S., 15 clinics were excluded from the analyses because they were without an air pollution monitoring station within a 20km radius. An additional 14 clinics were excluded due to having a high percentage of missing concentration data for $PM_{2.5}$ (>30%).

Extreme Heat Event (EHE)

To identify EHEs for each county, this study utilized daily maximum temperature (T_{max}) data from the fifth generation of the European Reanalysis (ERA5). The ERA5 is an integrated model data system developed and operated by the European Centre for Medium-Range Weather Forecasts (ECMWF), which merges daily observations from around the world with a weather prediction model.[126] EHE exposure was assigned to each county using one of the previously described methods.[52] Briefly, a 30-year baseline daily T_{max} data from 1980 to 2009 was used to determine a 95th percentile threshold for each calendar day within each county. This was accomplished by employing a 31-day moving window centered around the date of interest. Temperature for each calendar day during the study period was compared to their respective 95th percentile thresholds and assigned a value of 1 (EHE) if it exceeded the county and calendar day-specific thresholds.

4.3.3. Statistical Analysis

We conducted a time-stratified case-crossover analysis employing a conditional quasi-Poisson model to examine the association of wildfire exposure (wildfire smoke plume and wildfire-related $PM_{2.5}$) and EHEs with all-cause mortality and all-cause hospitalization risk. In this study design, the time period is divided into fixed strata, such as month and day of the week, and referent days are selected within each stratum.[145] The exposure status of the individual during the case period is compared to the exposure status of the same individual during the control periods. This approach, which utilizes self-matching, offers the advantage of controlling for all time-invariant individual-level confounders including sex, age, and race/ethnicity.[146] The case-crossover design is particularly suitable for investigating transient effects of intermittent exposures on acute outcomes.[146]

In traditional case-crossover analysis, conditional logistic regression is typically utilized, employing an expanded dataset for each individual case.[145] However, in this study, we instead used conditional quasi-Poisson regression which streamlines the calculation process by conditioning parameters on the counts of a health outcome within each stratum (clinic, year, month, and day of week). This approach models the rate of events during each time period as a function of the exposure variable and permits adjustment of overdispersion, autocorrelation, and varying rate denominators.[143] Previous studies have shown that this approach produces identical estimates to conditional logistic regression. [143,144] In the present study, the number of daily deaths and hospitalizations were used as the outcome variables, while wildfire smoke plume, wildfire-related $PM_{2.5}$ concentrations, and EHEs served as the three main exposure variables. For the analyses involving exposure to wildfire smoke plume and wildfire-related $PM_{2.5}$, we adjusted for non-wildfire-related $PM_{2.5}$ as a potential confounder. To adjust for varying populations, we included an offset variable equivalent to the natural logarithm of the monthly number of hemodialysis patients for each clinic. Measures of associations were reported as rate ratios (RRs) with 95% confidence intervals (95% CIs). The RRs for wildfire-related $PM_{2.5}$ was expressed as per 10-μg/m^3 increases. Furthermore, we employed the unconstrained distributed lag model (DLM) framework to assess lag effects for up to one day following the exposure. In this case, 'lag 0' represents the risk associated with the same day as the exposure, while 'lag 1' pertains to the risk one day after exposure.[147]

Finally, this study examined the potential effect modification of EHEs on the association of exposure to wildfire smoke plume and wildfire-related $PM_{2.5}$ with mortality and hospitalization. Initially, we compared the models without interaction term and with interaction term using likelihood ratio tests. Subsequently, we conducted EHE-stratified analyses for exposure to wildfire smoke plume and wildfire-related $PM_{2.5}$, both for the same-day (lag 0) and lag 1 exposure.

A sensitivity analysis was conducted by using all types of smoke plume, assigning a value of 1 for the presence of wildfire smoke plume when the HMS polygon's density was classified as 'light', 'medium' or 'heavy', and 0 if otherwise. Wildfire-related $PM_{2.5}$ concentrations were estimated based on those all types of wildfire smoke plume. For our analyses, we utilized R statistical software version 3.6.1 with the *dlnm*, *dplyr,* and *gnm* packages.[128,148,149,168] All statistical tests were two-tailed and based on a significance level of 0.05.

4.4 Results

This study included 55,223 patients across 161 hemodialysis clinics within 45 counties within California, Oregon, and Washington (**Table 4.1**). There was a total of 5,379 all-cause deaths and 61,627 all-cause hospitalizations during the study period (May to September, from June 2010 to September 2018). Approximately 50.6% of the study population were 18-64 years old at hemodialysis initiation, 58.4% were male, and 42.0% were non-Hispanic White.

Table 4.2 provides a summary of daily total $PM_{2.5}$ and wildfire-related $PM_{2.5}$ concentrations for each clinic, and daily T_{max} for each county. The daily total $PM_{2.5}$ concentrations for each hemodialysis clinic ranged from 0 to 485.8 $\mu g/m^3$, with an average of 10.2 $\mu g/m^3$. The daily wildfire-related $PM_{2.5}$ concentrations ranged from 0 to 480.8 $\mu g/m^3$, with an average of 13.7 $\mu g/m^3$. The daily non-wildfire-related $PM_{2.5}$ concentrations varied between 0 and 130.6 $\mu g/m^3$, averaging at 9.8 $\mu g/m^3$. T_{max} in the study area ranged from -0.8 to 48.1°C with an average of 24.9°C. The average number of days with wildfire smoke plume per month per clinic was one day. Meanwhile, each county had an average of one day of EHE exposure per month.

Figure 4.2 shows $PM_{2.5}$ concentrations, T_{max}, and health outcomes stratified by the presence of EHEs and wildfire smoke plume during the warmer season (May-September). A total of 634 (0.04%) clinic-days experienced joint occurrences of wildfire smoke plume and EHEs while 93% of clinic-days had neither a wildfire smoke plume nor an EHE. The average total $PM_{2.5}$ concentration was highest when both wildfire smoke plume and EHEs were present (24.0 $\mu g/m^3$) compared to days with wildfire smoke plume alone (19.6 $\mu g/m^3$), EHE alone (11.6 $\mu g/m^3$), or absence of both wildfire smoke plume and EHE (9.7 $\mu g/m^3$). Likewise, the average wildfire $PM_{2.5}$ concentration was higher during the EHE days compared to non-EHE days (17.7 $\mu g/m^3$ vs. 13.3 $\mu g/m^3$). T_{max} was higher during wildfire smoke plume days compared to non-wildfire smoke plume days (35.7°C vs. 34.8°C during EHE days and 29.1°C vs. 25.6°C during non-EHE days). The mortality rate was lowest in the absence of both wildfire smoke plume and EHE (3.4 per 10,000 patients). The hospitalization rate was highest when both wildfire smoke plume and EHE existed (80.0 per 10,000 patients).

Table 4.3 illustrates the time-dependent association between exposure to wildfire smoke plume, wildfire-related $PM_{2.5}$, EHEs, and risk of mortality and hospitalization. The presence of wildfire smoke was associated with a 19% higher same day (lag 0) mortality risk (RR_{Lag0}: 1.19; 95% CI: 1.11, 1.27) and a 4% increase in hospitalization risk at lag 1 (RR_{Lag1}: 1.04; 95% CI: 0.99, 1.09) after adjusting for non-wildfire-related $PM_{2.5}$. A 10-$\mu g/m^3$ increase in wildfire-related $PM_{2.5}$ was associated with a 3% increase in risk of mortality (RR_{Lag0}: 1.03; 95% CI: 1.02, 1.06) and a 1% increase in hospitalization risk (RR_{Lag0}: 1.01; 95% CI: 1.00, 1.03). Exposure to EHEs was associated with a 3% higher risk of mortality (RR_{Lag0}: 1.03; 95%CI: 0.97, 1.10) and a 4% higher risk of same day hospitalization (RR_{Lag0}: 1.04; 95% CI: 0.99, 1.08), although the risks were borderline significant. We performed sensitivity analysis by including the 'light' smoke plumes in the exposure metric (**Supplemental Table 4.1**). Inclusion of light smoke plume decreased the RR_{Lag0} for wildfire smoke plume exposure and mortality from 1.19 (95% CI: 1.11, 1.27) to 1.02 (95% CI: 0.98, 1.06).

Model comparison test results (F-test and p-value) examining the inclusion of interaction term and EHE-stratified analyses are shown in in **Table 4.4**. For mortality, we observed a significant interaction between EHEs and wildfire smoke plume at both lag 0 (F = 7.08, $p < 0.01$) and lag 1 (F = 11.7, $p < 0.01$). When we stratified the analysis by presence/absence of EHE, a considerably higher RR of smoke plume related mortality was observed during EHE days (RR_{Lag0}: 1.52; 95% CI: 1.25, 1.86) vs. non-EHE days (RR_{Lag0}: 1.15; 95% CI: 1.08, 1.23). The mortality RR for a 10-$\mu g/m^3$ increase in wildfire-related $PM_{2.5}$ was more pronounced during EHE days at lag 1 (RR_{Lag1}: 1.10 vs. 1.02). We did not observe significant interactions for all-cause hospitalization (wildfire smoke plume and EHE: F = 0.00, $p = 0.96$; and wildfire-related $PM_{2.5}$ and EHE: F = 1.13, $p = 0.29$). We performed additional sensitivity analysis by including light density smokes, (**Supplemental Table 4.2**), which attenuated the RRs.

4.5 Discussion

We observed a significant interaction between EHEs and wildfire-related air pollution exposure among the in-center hemodialysis patients in the Western U.S. from June 2010 to September 2018. The interaction effects were significant for all-cause mortality but not for all-cause hospitalizations. Furthermore, we observed that wildfire smoke plume-related risk of mortality was considerably higher when the smoke plume and EHE occurred simultaneously as opposed to the smoke plume itself in the absence of EHE (52% vs. 15%).

Our novel findings regarding the joint impact of wildfire exposure and EHEs builds upon the prior studies that have looked at these risk factors separately. In a recent study, Remigio et al. investigated the impact of EHEs on ESKD patients receiving in-center hemodialysis treatments at FKC clinics in Boston, New York, and Philadelphia from 2001 to 2012 reported 27% and 31% higher risk of hospitalization and all-cause mortality, respectively.[68] In subsequent expanded studies that include data from 28 northeastern U.S. counties spanning from 2001 to 2016, Remigio et al. reported a 5% increased risk of all-cause mortality for every 10-μg/m^3 increase in $PM_{2.5}$ (cumulative RR for $Lag_{0\text{-}3}$=1.05, 95% CI: 1.00,1.10) among ESKD patients.[52] In another study using health records of hemodialysis patients in 253 counties across the U.S., obtained from the USRDS for the years 2008 to 2012, Xi et al. reported that a 10-μg/m^3 increase in wildfire-related $PM_{2.5}$ was associated with a 4% increase in all-cause mortality on the same day (RR=1.04; 95% CI: 1.01, 1.07), similar to what we observed in this study.[92]

To our knowledge, this is the first study to investigate the combined effect of wildfire smoke plume, wildfire-related $PM_{2.5}$ and EHEs among hemodialysis patients. Previous research has mainly focused on examining the interaction between extreme heat and air pollution, not wildfire smoke plume specifically.[52,169,170] An additional strength of this study is the inclusion of a representative sample of hemodialysis patients. FKC is a prominent provider of dialysis services, accounting for approximately 57% of all dialysis services provided in the U.S.[171] This extensive representation enhances the generalizability of the study's findings to a significant portion of in-center hemodialysis patients in the Western U.S.

One limitation of this study is the potential for exposure misclassification regarding wildfire smoke plumes. HMS relies on satellite observation and detects smoke plumes from the ground to high altitudes. Therefore, it may not accurately represent air quality near the ground, especially in downwind regions, where the smoke plumes dispersion may vary. However, a remote sensing study suggested that limiting the HMS smoke polygons to medium and heavy smoke closely represents surface smoke, underscoring the importance of careful consideration when utilizing the HMS smoke product to assess the health impacts of wildfire smoke. [142] In our analysis, we restricted to medium and heavy wildfire smoke plumes, and additionally conducted sensitivity analyses by including light density plumes. The results exhibited more pronounced mortality risk when restricted to medium and heavy smokes (RR_{Lag0}: 1.19 vs. 1.02). Finally, the spatial resolution for exposure assessment was at the clinic-level (wildfire smoke plume and wildfire-related $PM_{2.5}$) and county-level (EHE). Such approach does not capture the true heterogeneity in exposure that exists between patients receiving treatment in the same clinic or residing in the same county. Regardless, such measurement errors were likely to be non-differential in nature, thus, our risk estimates were likely attenuated.[130]

A growing body of literature in recent years has shed light on the public health threats posed by ongoing climate change. However, there remains a notable gap in research when it comes to understanding how extreme environmental hazards impact hemodialysis patients. Given extreme events are projected to increase in frequency and intensity into the foreseeable future despite mitigation efforts[4,6], there is an urgent need to develop early warning systems that can inform clinic-level protocols designed to safeguard hemodialysis patients. Effective early warning systems should take into consideration on present weather and wildfire conditions combined with future forecast (ranging from a few days to weeks or months), along with individual and area-level characteristics to provide meaningful outlook to inform clinic-level decision-making. These systems should also facilitate communication regarding risks and prevention strategies while continuously evaluating and refining their effectiveness.[172,173] Implementing such early warning systems can encourage hemodialysis patients to adjust their behaviors, for instance, spending less time outdoors when higher air pollution or heat exposure is projected. Such effort may contribute to reducing treatment costs for hemodialysis patients, which reached approximately $52.3 billion in the U.S. in 2021.[174] The findings of this study can aid in bolstering the resilience for hemodialysis patients in the Western U.S., a region that is experiencing the most severe effects of climate change, marked by an increasing frequency of heatwaves, droughts, and wildfires.

In conclusion, we found evidence of potential modification by EHEs on the relationship between all-cause mortality risk and wildfire-related air pollution exposure, with the association being more prominent on EHE days. These findings underscore the necessity for enhanced preparedness measure to protect this vulnerable population from the effects of these environmental hazards.

4.6 Tables

Table 4.1. Characteristics of study population

Characteristics	
Counties, n	45
Clinics, n	161
Patients, n	55,223
All-cause mortality, n	5,379
All-cause hospitalization, n	61,627
Age at initial treatment, n (%)	
18-64	27,958 (50.6)
65-74	13,209 (23.9)
≥75	11,588 (21.0)
Not Reported	2,468 (4.5)
Sex, n (%)	
Female	22,998 (41.6)
Male	32,225 (58.4)
Race/ethnicity, n (%)	
Hispanic	10,242 (18.5)
Non-Hispanic Black	5,230 (9.5)
Non-Hispanic White	23,199 (42.0)
Asian American	3,050 (5.5)
Other	965 (1.7)
Not Reported	12,537 (22.7)

Table 4.2. Daily measures of $PM_{2.5}$ concentrations for each clinic and daily measures of T_{max} for each county, in the Western U.S. (Jun 2010 - Sept 2018) during the warmer season (May through September)

		Mean (SD)	Min	Med	Max
Daily $PM_{2.5}$ $\mu g/m^3$ (clinic-level)	Total $PM_{2.5}$	10.2 (7.7)	0	9.3	485.8
	Wildfire-related $PM_{2.5}$ [1]	13.7 (24.8)	0	5	480.8
	Non-wildfire-related $PM_{2.5}$ [2]	9.8 (5.7)	0	9.2	130.6
Daily T_{max} °C (county-level)		24.9 (7.5)	-0.8	25.0	48.1
Number of wildfire smoke days per month per clinic		1 (3)	0	0	28
Number of EHE days per month per county		1 (2)	0	0	14

[1] During the days with wildfire smoke plume
[2] During the days without wildfire smoke plume

Table 4.3. Rate ratios and 95% confidence intervals for risk of mortality and hospitalization associated with exposure to wildfire smoke plume, wildfire-related $PM_{2.5}$, and EHEs

	Lag	Mortality	Hospitalization
Presence of wildfire smoke plume*	Lag_0	**1.19 (1.11, 1.27)**	1.01 (0.96, 1.06)
	Lag_1	1.03 (0.96, 1.10)	1.04 (0.99, 1.09)
Wildfire-related $PM_{2.5}$ 10 $\mu g/m^3$ increase*	Lag_0	**1.03 (1.02, 1.06)**	**1.01 (1.00, 1.03)**
	Lag_1	**1.02 (1.00, 1.04)**	1.01 (0.99, 1.03)
EHEs	Lag_0	1.03 (0.97, 1.10)	1.04 (0.99, 1.08)
	Lag_1	0.98 (0.92, 1.05)	1.01 (0.97, 1.05)

* Adjusted for non-wildfire-related $PM_{2.5}$

Table 4.4. Risks of mortality and hospitalization associated with exposure to wildfire (wildfire smoke plume and wildfire-related $PM_{2.5}$), stratified by EHE. All models adjusted for non-wildfire-related $PM_{2.5}$.

Outcome	Exposure	Lag	RR (95% CI) adjusted for EHE	Interaction with EHE		EHE Stratification	
				F-test	*p*-value	EHE Days	Non-EHE Days
Mortality	Wildfire Smoke Plume	Lag0	**1.18 (1.11, 1.26)**	F(7.08)	**<0.01**	**1.52 (1.25, 1.86)**	**1.15 (1.08, 1.23)**
		Lag1	1.03 (0.96, 1.10)	F(11.7)	**<0.01**	**1.45 (1.19, 1.78)**	1.00 (0.93, 1.07)
	Wildfire-related $PM_{2.5}$	Lag0	**1.03 (1.01, 1.05)**	F(1.37)	0.24	1.00 (0.94, 1.06)	**1.04 (1.02, 1.06)**
		Lag1	**1.02 (1.01, 1.04)**	F(3.37)	0.07	**1.10 (1.02, 1.20)**	**1.02 (1.00, 1.04)**
Hospitaliz-ation	Wildfire Smoke Plume	Lag0	1.01 (0.96, 1.05)	F(0.00)	0.96	1.00 (0.87, 1.15)	1.01 (0.96, 1.06)
		Lag1	1.04 (0.99, 1.09)	F(0.01)	0.91	1.05 (0.91, 1.21)	1.04 (0.99, 1.09)
	Wildfire-related $PM_{2.5}$	Lag0	1.01 (0.99, 1.03)	F(1.13)	0.29	1.03 (0.99, 1.07)	1.01 (0.99, 1.03)
		Lag1	1.01 (0.99, 1.03)	F(0.39)	0.53	1.00 (0.97, 1.04)	1.01 (0.99, 1.03)

4.7 Figures

Figure 4.1. Hemodialysis clinics in the Western U.S. (Washington, Oregon, and California) and HMS image depicting the presence of wildfire smoke plume on June 24, 2018. A significant number of hemodialysis clinics were affected by wildfire smoke plume.

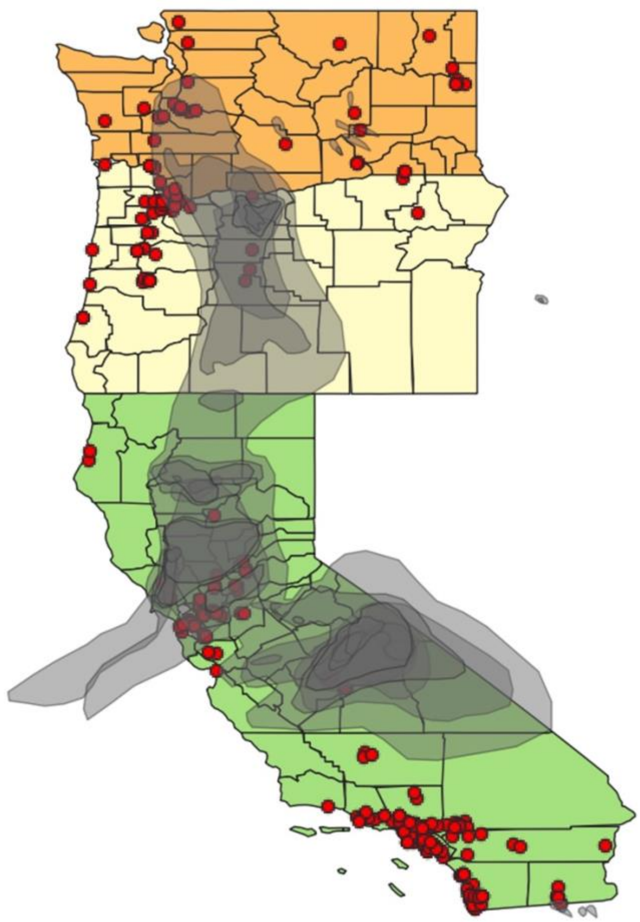
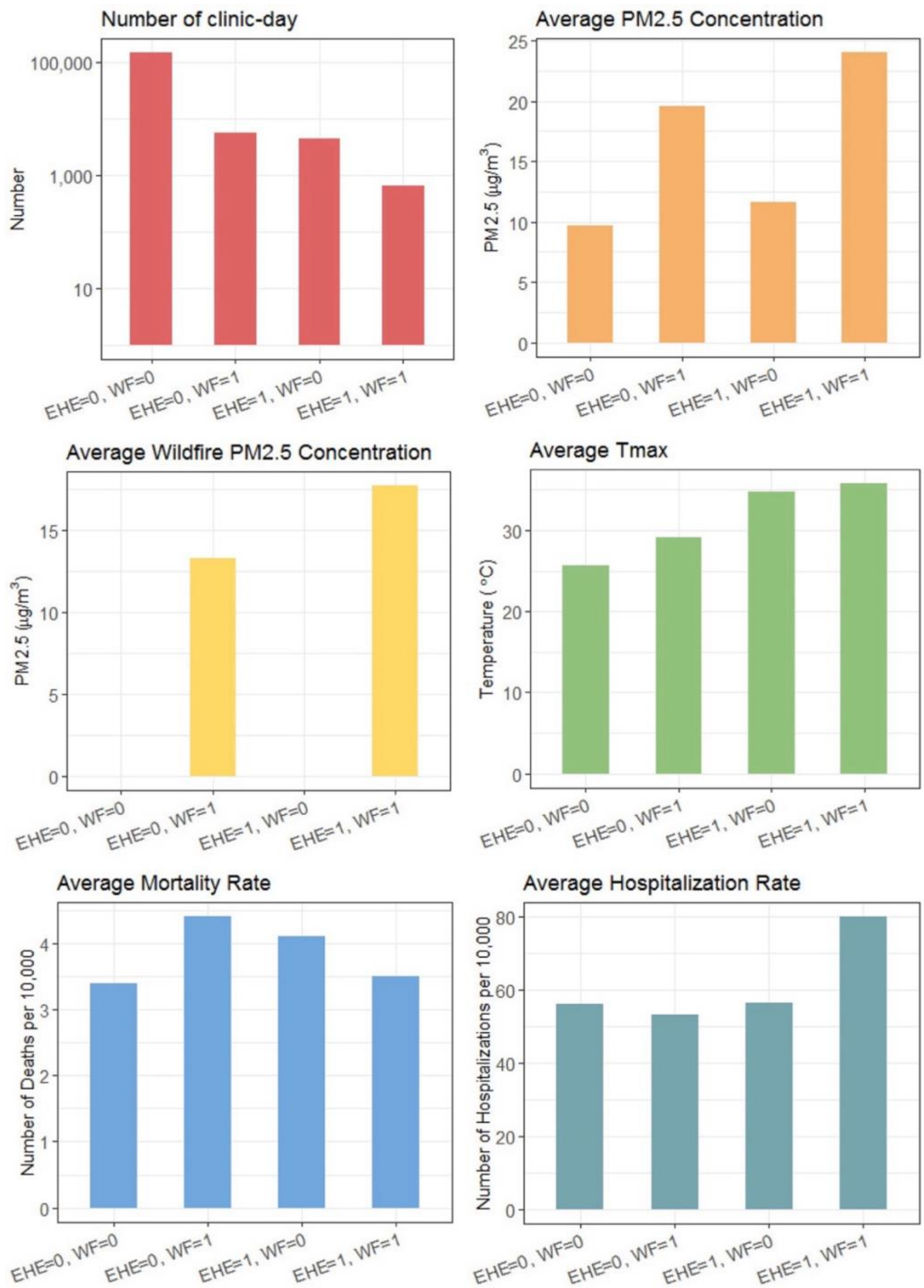


Figure 4.2. Summary of daily $PM_{2.5}$ concentrations, T_{max}, and health outcomes stratified by the presence of EHEs and wildfire smoke plume



EHE=0, days with EHE; **EHE=1**, days without EHE; **WF=1**, days with wildfire smoke plume; **WF=0**, days without wildfire smoke plume; **Mortality rate**: 10,000 × (Daily number of death / Monthly number of hemodialysis patients who visited the clinic); **Hospitalization rate**: 10,000 × (Daily number of hospitalization/Monthly number of hemodialysis patients who visited the clinic)

Chapter 5: Conclusions & Public Health Significance

5.1 Overall Conclusions

This dissertation provides a comprehensive examination of the associations between exposure to EHEs, wildfire-related air pollution, and health outcomes among hemodialysis patients in the U.S. The main findings from this dissertation are:

1. Both increases in daily temperature and exposure to EHEs during the warmer season were associated with increased serum sodium concentrations among hemodialysis patients in the Western U.S.
2. Exposure to the 2023 Canadian wildfire smoke plume and wildfire-related $PM_{2.5}$ exposure was associated with an increased risk of mortality and hospitalization among hemodialysis patients in New England, the Mid-Atlantic, and the Midwest U.S.
3. We found evidence of potential modification of EHEs, with the all-cause mortality risks associated with wildfire-related air pollution exposure (wildfire smoke plume and wildfire-related $PM_{2.5}$) being more prominent during EHE days among hemodialysis patients in the Western U.S.

5.2 Public Health Implications

A growing body of literature in recent years has shed light on the public health threats posed by ongoing climate change. However, there remains a notable gap in the research on how extreme environmental hazards impact vulnerable hemodialysis patients. The potential impact of heat exposure on kidney health is evidenced by the prevalent chronic kidney disease in the agricultural communities in the Mesoamerican area, explained by the etiology that heat stress and recurrent dehydration placing burden to renal system.[71–74] EHEs can disproportionately affect ESKD patients because heat exposure induces impaired thermoregulation and impaired breathing pattern intended to cope with increase in core temperature[19]. This, coupled with systemic inflammation, exacerbates pre-existing cardiovascular, respiratory, and renal diseases.[20] Likewise, wildfire-related air pollution can excessively affect ESKD patients by inducing oxidative stress, inflammatory response, and abnormal metabolic changes inducing elevated hypertension and vascular injury which exacerbates pre-existing comorbidities and impaired cardio-respiratory functions.[98–102]

This dissertation focused on hemodialysis patients and demonstrated that (1) higher daily temperature and exposure to EHEs are associated with increased serum sodium concentrations among hemodialysis patients, (2) exposure to wildfire smoke plume and wildfire-related $PM_{2.5}$ exposure was associated with an increased risk of mortality and hospitalization, and (3) the association between wildfire-related air pollution exposure and mortality was more pronounced during EHE days. Our findings underscore the necessity for enhanced preparedness measures to protect hemodialysis patients from the effects of such environmental hazards.

Given extreme events are projected to increase in frequency and intensity into the foreseeable future despite mitigation efforts[4,6], there is an urgent need to develop early warning systems that can inform clinic-level protocols designed to safeguard hemodialysis patients. Effective early warning systems should take into consideration on present weather and wildfire conditions combined with future forecast (ranging from a few days to weeks or months), along with individual and area-level characteristics to provide meaningful outlook to inform clinic-level decision-making. These systems should facilitate communication regarding risks and prevention strategies while continuously evaluating and refining their effectiveness.[172,173]

Such effort may contribute to reducing treatment costs for hemodialysis patients, which reached approximately $52.3 billion in the U.S. in 2021, with an average annual healthcare cost of around $68,000 per person with ESKD.[174] The growing prevalence of ESKD and its economic burden underscores the importance of comprehending and addressing the challenges faced by affected individuals and healthcare systems. The findings of this study are crucial in bolstering the resilience for hemodialysis patients in the U.S., where experiencing the most severe effects of climate change, marked by an increasing extent of heatwave, drought, and wildfire.

Our research focuses on hemodialysis patients, who represent one of the most vulnerable populations. By implementing interventions protecting hemodialysis patients, we can not only directly improve health outcome of this population but also benefit broader population facing similar climate change-related hazards.

5.3 Limitations

The studies in this dissertation had several limitations. For the study on serum electrolyte level using individual-level data analysis, we were not able to account for the individual-level socioeconomic status (SES) and nutritional status which may result in residual confounding. Constructing a prospective cohort study with the incorporation of surveys to gather such information could address this limitation.

For the studies examining wildfire-related air pollution exposure, we could not include the clinics that did not have at least one $PM_{2.5}$ monitor within a 20km radius, as well as the clinics that had missing values in daily $PM_{2.5}$ concentrations exceeding 70%. Incorporating imputations for these missing values was not feasible because most missing values were due to the monitors not operating for prolonged periods, such as several weeks likely due to technical issues. Instead of using ground-based monitoring data, using the simulated air quality data such as Climate-Weather Research and Foresting and Community Multiscale Air Quality (CWRF-CMAQ)[175] can help mitigate issues associated with missing values.

Finally, the spatial resolution for exposure assessment was clinic-level (wildfire smoke plume and wildfire-related $PM_{2.5}$) and county-level (EHE). Such approach does not capture the true heterogeneity in exposure that may exist between patients receiving treatment in the same clinic or residing in the same county. Regardless, such measurement errors were likely to be non-differential in nature, thus, our risk estimates were likely attenuated.[130]

5.4 Future Directions

Constructing a prospective cohort study with a survey on health behavior, socio-economic status

We conducted retrospective cohort studies by utilizing the electronic health records of patients who were undergoing maintenance hemodialysis treatment at FKC clinics in the U.S. As we had to rely on existing data, we were unable to assess certain potential confounders, such as individual-level SES and health behaviors. However, construction of a prospective cohort study by recruiting participants and tracking them over time can address these limitations. Incorporating survey questions related to residential address, individual-level SES such as household income and education level, as well as health behaviors including smoking status, alcohol consumption, and nutritional intake enables assessing a wide range of risk factors and individual-level potential confounders. Moreover, such a study design can facilitate the examination of long-term health effect, such as chronic conditions including diabetes and cardiovascular diseases, cancer onset, or mortality.

Examining the association between air pollution exposure and oxygen saturation level

The FKC installed Crit-Line IV Monitors in 2019 which measures patients' oxygen saturation (SaO_2) in the extracorporeal circuit every minute during the hemodialysis treatment.[176] This oxygen saturation measure has the potential to serve as a marker to identify the risk of morbidity and mortality among ESKD patients.[100] Hypoxemia (SaO_2 <90%) is a sign of an impaired breathing or circulation, and is a primary cause of respiratory morbidity and mortality.[177] Previous studies examined the association between air pollution exposure and oxygen saturation, but they are limited to panel studies of the elderly with relatively small sample size less than 100.[177–183] Utilizing the oxygen saturation level data has the potential to allow for studying the association between wildfire-related air pollution and respiratory impairment.

Utilizing various wildfire-related air pollution measurements

With advancements in the availability and accessibility of satellite-derived data, utilizing these data in public health studies have enabled assessing the wildfire-related exposure and its health impact at finely configured temporal and spatial scales. This study measured the exposure to wildfire smoke plume and wildfire-related $PM_{2.5}$ using the Hazard Mapping System (HMS) from the National Oceanic and Atmospheric Administration (NOAA), which displays smoke plume polygons at a 15km resolution.[139–141] The other wildfire data sources commonly used in public health studies include the GEOS-Chem chemical transport model which integrates meteorological data from Goddard Earth Observing System (GEOS-5) with satellite observations of fire counts and burned area from the Global Fire Emissions Database (GFED3),[155] and Chemistry (WRF-Chem) model with GOES satellite images [43]. With considerations on the appropriate spatial and temporal resolution of the study design and health outcome measurement, a range of satellite-derived data can be employed to assess wildfire exposure.

Appendices

Supplementary materials for Chapter 4

Table S4.1. Rate ratios and 95% confidence intervals for risk of mortality and hospitalization associated with exposure to wildfire smoke plume, wildfire-related $PM_{2.5}$, and EHEs. Wildfire smoke plume and wildfire-related $PM_{2.5}$ estimated using all types of smoke plume including light, medium, and heavy.

	Lag	Mortality	Hospitalization
Presence of wildfire smoke plume*	Lag_0	1.02 (0.98, 1.06)	1.02 (0.99, 1.04)
	Lag_1	1.02 (0.98, 1.06)	**1.04 (1.01, 1.07)**
Wildfire-related $PM_{2.5}$ 10 $\mu g/m^3$ increase*	Lag_0	**1.02 (1.00, 1.04)**	**1.01 (1.00, 1.03)**
	Lag_1	1.01 (0.99, 1.03)	**1.01 (1.00, 1.03)**
EHEs	Lag_0	1.03 (0.97, 1.10)	1.04 (0.99, 1.08)
	Lag_1	0.98 (0.92, 1.05)	1.01 (0.97, 1.05)

* Adjusted for non-wildfire-related $PM_{2.5}$

Table S4.2. Risks of mortality and hospitalization associated with exposure to wildfire (wildfire smoke plume and wildfire-related $PM_{2.5}$), stratified by EHE. Wildfire smoke plume and wildfire-related $PM_{2.5}$ estimated using all types of smoke plume including light, medium, and heavy. All models adjusted for non-wildfire-related $PM_{2.5}$.

Outcome	Exposure	Lag	RR (95% CI) adjusted for EHE	Interaction with EHE		EHE Stratification	
				F-test	*p*-value	EHE Days	Non-EHE Days
Mortality	Wildfire Smoke Plume	Lag0	1.02 (0.98, 1.06)	F(0.12)	0.73	0.99 (0.84, 1.16)	1.02 (0.98, 1.06)
		Lag1	1.03 (0.99, 1.07)	F(14.9)	**<0.01**	**1.47 (1.27, 1.71)**	1.01 (0.97, 1.05)
	Wildfire-related $PM_{2.5}$	Lag0	**1.02 (1.00, 1.04)**	F(3.92)	**<0.05**	0.96 (0.89, 1.03)	**1.03 (1.01, 1.05)**
		Lag1	1.01 (0.99, 1.03)	F(6.49)	**<0.05**	**1.11 (1.03, 1.20)**	1.00 (0.98, 1.02)
Hospitaliz-ation	Wildfire Smoke Plume	Lag0	1.02 (0.99, 1.04)	F(0.33)	0.56	1.05 (0.94, 1.16)	1.01 (0.99, 1.04)
		Lag1	**1.04 (1.01, 1.06)**	F(0.01)	0.93	1.04 (0.94, 1.16)	**1.04 (1.01, 1.06)**
	Wildfire-related $PM_{2.5}$	Lag0	**1.01 (1.00, 1.03)**	F(1.43)	0.23	**1.03 (1.00, 1.07)**	1.01 (0.99, 1.03)
		Lag1	**1.01 (1.00, 1.03)**	F(1.10)	0.29	1.00 (0.96, 1.03)	**1.02 (1.00, 1.04)**

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Appendices 2. Inclement weather and risk of missing scheduled hemodialysis appointments among kidney failure patients

Remigio RV, Song H, Raimann JG, Kotanko P, Maddux FW, Lasky RA, He X, Sapkota A. Inclement Weather and Risk of Missing Scheduled Hemodialysis Appointments among Patients with Kidney Failure. Clin J Am Soc Nephrol. 2023 Apr 18;18(7):904–12. doi: 10.2215/CJN.0000000000000174. Epub ahead of print. PMID: 37071662; PMCID: PMC10356145.

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Abstract

Background: Nonadherence to hemodialysis appointments could potentially result in health complications that can influence morbidity and mortality. We examined the association between different types of inclement weather and hemodialysis appointment adherence.

Methods: We analyzed health records of 60,135 patients with kidney failure who received in-center hemodialysis treatment at Fresenius Kidney Care clinics across the Northeastern US counties during 2001-2019. County-level daily meteorological data on rainfall, hurricane and tropical storm events, snowfall, snow depth, and wind speed were extracted using National Oceanic and Atmosphere Agency data sources. A time-stratified case-crossover study design with conditional Poisson regression was used to estimate the effect of inclement weather exposures within the Northeastern US region. We applied a distributed lag nonlinear model framework to evaluate the delayed effect of inclement weather for up to 1 week.

Results: We observed positive associations between inclement weather and missed appointment (rainfall, hurricane and tropical storm, snowfall, snow depth, and wind advisory) when compared with non-inclement weather days. The risk of missed appointments was most pronounced during the day of inclement weather (lag 0) for rainfall (incidence rate ratio [RR], 1.03 per 10-mm rainfall; 95% confidence interval [Cl], 1.02 to 1.03) and snowfall (RR, 1.02; 95% Cl, 1.01 to 1.02). Over 7 days (lag 0-6), hurricane and tropical storm exposures were associated with a 55% higher risk of missed appointments (RR, 1.55; 95% Cl, 1.22 to 1.98). Similarly, 7-day cumulative exposure to sustained wind advisories was associated with 29% higher risk (RR, 1.29; 95% Cl, 1.25 to 1.31), while wind gusts advisories showed a 34% higher risk (RR, 1.34; 95% Cl, 1.29 to 1.39) of missed appointment.

Conclusions: Inclement weather was associated with higher risk of missed hemodialysis appointments within the Northeastern United States. Furthermore, the association between inclement weather and missed hemodialysis appointments persisted for several days, depending on the inclement weather type.

Introduction

Missing scheduled hemodialysis appointments can result in higher risk of morbidity, hospitalization, and mortality.[1] Nonadherence to scheduled hemodialysis can vary across age groups, race/ethnicity, and educational status. Previous studies have reported a higher prevalence of missed treatments among Black, Hispanic, and Native American patients within the United States.[2] In addition, male patients and patients with lower attained education status (a high school education or below), on average, were less likely to adhere to scheduled appointments.[3] Other factors such as short hemodialysis duration, unreliable transportation, holidays, gastrointestinal upset, chronic pain, and psychiatric illness were also barriers to hemodialysis adherence.[4] Patient autonomy and comfort may also influence nonadherence among US in-center hemodialysis patients.[5]

Although multiple studies have explored determinants for nonadherence,[1-5] thus far, very few studies have investigated weather as a predictor for missed hemodialysis treatments.[4] One such study considered same-day snowfall above or below 1 inch (25.4 mm) as a representation of inclement weather but did not investigate other severe weather types that could potentially influence treatment nonadherence.[4] Inclement weather can interrupt electrical power, damage infrastructure, and overwhelm health care systems, hindering dialysis treatment.[6,7] A 2009 study reported increased missed appointments and hospital admissions among dialysis patients in New Orleans after Hurricane Katrina.[7] Such disturbances can lead to unintended complications, morbidities, and premature death from missed treatments.[8-10] Others have reported higher hospitalization risk among patients with endocrine disorders and genitourinary diseases residing in counties the week after a hurricane event was observed.[11] In light of this, here is a need to characterize how inclement weather affects dialysis treatment adherence. Such data can enhance preparedness for severe weather events, especially with ongoing climate change.

In this observational study, we examined the association between different types of inclement weather (rainfall, snowfall, snow depth, wind advisory, and hurricane and tropical storm) and hemodialysis appointment adherence among patients with kidney failure in the Northeastern United States. We hypothesized that the short-term risk of missed hemodialysis appointments would be higher after inclement weather events compared with non-inclement weather days.

Methods

Study Population

We obtained deidentified electronic health records of patients with kidney failure 19 years or older and receiving in-center hemodialysis treatment at Fresenius Kidney Care facilities across the Northeastern United States between 2001 and 2019. The eligible study participants included patients with kidney failure (19 years or older) who had hemodialysis treatment during the study period. There were a total of 60,717 patients with kidney failure from 99 clinics within 27 counties (**Figure 1**), of which of 60,135 met the inclusion criteria and were included in the analysis. We used clinic ZIP codes where patients received treatment as a proxy for a residence to assign county-specific exposures. We defined missed appointments as events when a patient failed to show up for a scheduled treatment without an excuse. These exclude missed treatment due to prearranged travel or hospitalizations. Counts of missed appointments were aggregated for each day and by county. This study was considered exempt from human subjects review by the University of Maryland Institutional Review Board.

Exposure

On the basis of the ZIP codes of the Fresenius Kidney Care clinics, we verified the county of each clinic by using ZIP Code Tabulation Areas.[13] Subsequently, we selected the nearest weather station from each county's centroid (longitude and latitude) through the Global Historical Climatology Network (GHCN) database maintained by National Oceanic and Atmospheric Administration. Using the rnoaa R package, we extracted the following data elements for each patient from the GHCN database: total daily precipitation (amount of all types of precipitation, including melted and frozen) from April to October, total daily snowfall (amount of snowfall since the previous 24 hours observation) of November-March, total daily snow depth (depth of the new and old snow remaining on the ground at 24 hours observation time) of November-March, sustained wind speed (the fastest speed for the day that is sustained for at least 2 minutes), and peak wind speed (the fastest speed for the day that is sustained for at least 5 seconds) from 2001 to 2019.[14-16] Rainfall-related analyses were restricted to warmer months (April-October) since the total daily precipitation combined melted and frozen types of rainfall, while snowfall- and snow depth-related analyses were restricted to colder months (November-March). Owing to the limited availability for snow-related data, we restricted the study area to

13 counties for snowfall-related and snow depth-related analysis (Supplemental Table 1). Missing values for each inclement weather data were <9%, and we used all available data in our analysis.

Daily rainfall, snowfall, and snow depth were analyzed as continuous variables. We applied formalized wind categories using the National Weather Service definitions for wind advisory on the basis of sustained wind speed >31 mph or 26.9 knots (13.86 m/s) and peak wind speed >46 mph or 40 knots (20.56 m/s).[17] We used the hurricaneexposuredata R package to identify hurricane and tropical storm events from May to October that affected our study area from 2001 to 2018.[18] The package includes processed hazards-related data on county-level Atlantic basin tropical storms along the Eastern portion of the United States for counties within at least 250 km from the storm track. For our main analysis, we defined a county as exposed to a hurricane and tropical storm event when gale force sustained wind speeds reach 34 knots (17.49 m/s) or above brought on by a hurricane storm event.[11,18,19] As part of a sensitivity analysis, we explored distance-based thresholds in defining tropical storm-related exposures by including hurricane storms between a county's population-weighted center and storm track distances of 150 and 200 km.

Statistical Analysis

We used a time-stratified case-crossover study design to investigate the association between inclement weather events and missed hemodialysis appointments. Case crossover methods are consistently used in epidemiological analyses involving acute exposures and clearly defined event-based outcomes. In our case-crossover design, exposure immediately preceding the missed appointments (case period) was compared with exposure during multiple control periods that included 7,14,21, or 28 days before or after the case period. The use of time-stratified referents helped us avoid overlap biases often associated with control periods adjacent to case periods. Inclement weather exposures for case and control periods were compared using stratum indicators. Self-matching is a unique feature of the case crossover design that eliminates the need to adjust for individual-level time-invariant confounders, including age, sex, race, and socioeconomic status.[20] For these reasons, case-crossover design is ideal for investigating acute outcomes related to short-term exposure. Stratum indicators were based on year, month, day of the week, and county.[21,22] We used conditional Poisson regression with aggregated daily missed appointments as the outcome and inclement weather type as the main exposure.[23] We included the day of the week as the covariate and an offset variable equaling the natural log of the monthly average number of scheduled appointments for each county to account for varying populations[23] We adopted a case crossover analysis within a distributed lag nonlinear model (DLNM) framework to characterize lag effects for up to 7 days. DLNM provides the flexibility to simultaneously model potential nonlinear associations between inclement weather and missed appointments, and how this association changes over time, that is, time elapsed since exposure onset. As such, we used DLNM to obtain risk for individual lag days (e.g., risk at lag 0 referring to the risk of missing scheduled hemodialysis appointment during the day of inclement weather exposure, and lag 7 referring to the risk of missing scheduled hemodialysis appointment 7 days after the inclement weather exposure) and cumulative effect up to 7 days (lag 0-6), which is computed by factoring all the contributions across lags.[24] We also conducted stratified analyses by sex (female and male) and race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White, Asian, and other) to investigate whether risk associated with inclement weather varied by sex and race/ethnicity.

All analyses were conducted using R statistical software version 3.6.1 with *dlnm*, *gum*, and *dplyr* packages.[25-28] All statistical tests were two-tailed and based on a significance level of 0.05.

Results

A total of 60,135 patients with kidney failure visited 99 Fresenius Kidney Care facilities in the Northeastern United States from 2001 to 2019 (T**able 1, Supplemental Tables 2 and 3**). Most patients were male (57%) and were either non-Hispanic Black (40%) or non-Hispanic White (40%). The study population's total visits and missed appointments were 16,612,373 and 454,932, respectively. Overall, 28,495 (47%) patients reported missing at least one hemodialysis session, and 29% reported missing three or more sessions (**Table 1**).

Summary statistics for inclement weather types across focused counties within the Northeastern United States from 2001 to 2019 are presented in **Table 2**. Regionally, we observed averaged daily rainfall of 3.1 mm and a maximum daily measure of 221.2 mm. During the colder months (November to March), daily average snowfall and snow depth recorded were 6.6 and 22.5 mm, respectively. Similarly, the average daily sustained wind speed was 8.4 m/s and ranged from 1.3 to 28.6 m/s. The daily peak wind speed ranged from 1.3 to 61.7 m/s, with an average wind speed of

11.0 m/s. Both wind advisories on the basis of sustained wind and peak wind were the most frequent during the winter (7% and 3%, respectively). In 2001, 2002, 2009, 2010, 2015, and 2016, none of the 27 counties experienced hurricanes and tropical storms with gale force wind speed >34 knots (17.49 m/s). We observed that 2012 had the highest number of counties affected by hurricanes and tropical storm events (n=15).

The percentage of missed appointments by inclement weather type is presented in **Table 3**. Overall, the average rates were higher on the exposure days compared with non-exposure days for all the inclement weather types. The 27 counties recorded 35,858 county days with rainfall >0 mm between 2001 and 2019. The average percentage of missed hemodialysis appointments during those days was 2.5% and was not different from days with no rainfall. There were 67 county days with hurricane and tropical storm events, and the average percentage of missed appointments during such days was 7.8% compared with 2.4% for the non-hurricane and tropical storm days. During the cold season (November to March), there were a total of 3,634 county days with snowfall >0 mm. The average percentage of missed appointments during these days was 4.9% compared with 3.4% for the non-snowfall days. Similarly, the percentage of missed appointments was higher for days with snow depth >0 mm. Similarly, the average rate of missed appointments was higher on wind advisory days, regardless of the wind speed expression (sustained wind speed or peak wind speed).

The time-dependent association between inclement weather types and missed hemodialysis appointments is shown in **Figure 2**. In general, the risk of missing scheduled appointments tended to be highest during the day of inclement weather. A 10-mm higher rainfall was associated with a 2.6% higher risk of missed appointments the same day (lag 0 rate ratio [RR], 1.02; 95% confidence interval [Cl], 1.02 to 1.03), and the risk declined over the subsequent 7 days (**Figure 2**). For every 10-mm greater snowfall and snow depth, the RR of same day (lag 0) missed appointments was 1.02 (95% Cl, 1.01 to 1.02) and 1.02 (95% Cl, 1.01 to 1.02), respectively. The presence of wind advisory on the basis of sustained wind speed (>13.86 m/s) was associated with a 5.3% higher risk of (lag 0) missed appointments (RR, 1.05; 95% Cl, 1.03 to 1.07). Similarly, days with wind advisory on the basis of wind gusts of >20.56 m/s was associated with a 9.6% higher rate of missed appointments (RR, 1.10; 95% Cl, 1.07 to 1.12). Higher hurricane and tropical storm-related risk of missed appointments was seen at lag 0 (RR, 1.38; 95% Cl, 1.17 to 1.63). The snowfall-related risk persisted for up to 7 days, while snow depth-related risk lasted for up to 2 days. Significant wind advisory-related risks persisted for up to at least 2 days for peak and sustained wind speeds (**Figure 2**).

For the continuous inclement weather types, we observed positive exposure-response linear trends when considering associations between 7-day cumulative rainfall, snowfall, snow depth, and missed hemodialysis appointments (**Figure 3**). A ten-unit higher rainfall, snowfall, and snow depth was associated with 3.8%, 5.2%, and 2.7% higher risk of missed appointments, respectively.

Table 4 presents the association between 7-day cumulative exposure (lag 0-6) to hurricane and tropical storm, sustained wind advisory, and wind gust advisory (as categorical variables) on missed hemodialysis appointment. In this analysis, hurricane and tropical storm event was associated with a higher risk of missed appointment (RR, 1.55; 95% Cl, 1.22 to 1.98). Both wind advisories on the basis of sustained winds and wind gusts were associated with a significantly higher risk of a missed appointment. Wind advisory on the basis of sustained wind speed showed overall cumulative risk of 1.29 (95% Cl, 1.25 to 1.31), while wind advisory on the basis of wind gusts was associated with a 34% higher risk (RR, 1.34; 95% Cl, 1.29 to 1.39). When stratified by sex (female and male) and race/ethnicity (Hispanic, non-Hispanic Black, non-Hispanic White, Asian, and other), we did not observe notable effect modification (**Supplemental Figures 1-7** and **Supplemental Table 4**). When redefining tropical storm-related exposures in a sensitivity analysis, we observed a significant positive association with same-day (lag 0) hurricane and tropical storm within 150 km (RR, 1.20; 95% Cl, 1.07 to 1.36) and with 5-day lag (RR, 1.27; 95% Cl, 1.09 to 1.47). Hurricanes and tropical storms within 200 km and within 250 km showed attenuated risk at lag 0 but higher risks at lag 5 (RR, 1.27; 95% Cl, 1.09 to 1.47) and lag 2 (RR, 1.17; 95% Cl, 1.05 to 1.30), respectively (**Supplemental Figure 8**).

Discussion

This study investigated the effect of inclement weather on missed hemodialysis appointments in the 27 counties in the Northeastern United States from 2001 to 2019. Overall, the rate of missed appointments was higher during inclement weather (rainfall, hurricane and tropical storms, snowfall, snow depth, and wind advisory) compared with non-inclement weather days. We observed that the risk of missed appointments was highest at lag 0 and associated with rainfall, hurricane and tropical storm, snowfall, snow depth, and wind advisories on the basis of sustained winds and wind gusts. In addition, the risks of missed appointments associated with rainfall, hurricane and tropical storm, snowfall, snow depth, and wind advisory were substantial when considering a week-long cumulative lag structure (lag 0-6). Overall, we observed rainfall-related risk of missed appointments dissipating after 1 day, whereas the risk associated with snowfall, snow depth, and wind advisories persisted for several days. This is not surprising given that snow tends to remain on the ground several days after snowfall, assuming temperatures stay below freezing. At the same time, wind advisories may cause potential physical infrastructure damage leading to sustained disruption, such as road closures, building damage, and electrical outages. Hurricane and tropical storm-related risk of missed appointment was not significant after a hurricane and tropical storm event (lag 1-4). This might be explained by potential prescheduling ahead of the predicted severe storm. According to a Fresenius Kidney Care Disaster Response representative, missed appointments after a storm are primarily due to safety concerns, transportation barriers from impassable roads, displacement after an evacuation, or a preference not to visit a backup facility (B. Loeper, Disaster Response Specialist at Fresenius Kidney Care, personal communication, September 22, 2022).

Inclement weather conditions can become a major barrier to accessing necessary health care services. In particular, patients with kidney failure who regularly receive outpatient dialysis treatments are more vulnerable to potential complications from missing their regularly scheduled treatments.[5] Previous studies have shown that missing scheduled hemodialysis appointments can result in adverse outcomes, including hyperkalemia, hyperphosphatemia, pulmonary edema, metabolic disorders, and higher risk of hospitalization and mortality.[1,3] Weather disturbances can act as a hindrance to timely dialysis treatments. Missing a single appointment may not immediately cause a life-threatening problem for some patients with kidney failure. However, multiple consecutive missed appointments because of protracted clinic closures caused by power outages, unsafe road conditions, and the shortage of available transportation can cause difficulties for patients to travel to seek treatment and for clinicians to deliver quality life-saving care. These hindrances can pose life-threatening burdens to both patients and clinicians. This challenge has been well documented in regions struck by Hurricanes Katrina, Sandy, and Maria and Winter Storm Uri.[7,8,29-31] After Hurricane Katrina in August 2005, 94 dialysis clinics closed for at least 1 week in the Gulf Coast states, including Louisiana, Mississippi, and Alabama.[29] A study investigated the factors associated with missed dialysis sessions after Hurricane Katrina and reported that the probability of missing three or more sessions was greater among those who lived alone before the hurricane's landfall, who did not evacuate before the storm, or who were placed in storm shelters.[7] Similarly, patients with kidney failure in Sandy-affected areas in 2012 had more frequent emergency department visits, hospitalizations, and 30-day mortality compared with patients with kidney failure in unaffected areas.[8] In Puerto Rico, the landfall region of Hurricanes Irma and Maria in September 2017 experienced catastrophic damage to most medical infrastructure and paralyzed dialysis operations that resulted in mandatory patient evacuations.[30] Winter storm Uri in 2021 caused mass power outages throughout Texas and affected approximately 54,000 dialysis patients.[31]

The Intergovernmental Panel on Climate Change report suggests imminent and increased extreme weather magnitudes, duration, and frequencies with substantial alterations in regional patterns of extreme weather[32] Our findings suggest that such increases in extreme event will have a considerable effect on patients with kidney failure by disrupting their dialysis care due to unfavorable transportation conditions and/or damaged infrastructure. Clinical and public health resources are crucial to ensure continuity in delivering life-saving health care to medically susceptible communities, such as patients with kidney failure. Specifically, coordination between health care providers and dialysis centers can reinforce medical care preparedness and delivery during extreme weather events.[33,34] Future studies should consider whether peritoneal dialysis may offer benefits, particularly in areas characterized by higher frequency of extreme events.

This study has several strengths. To the best of our knowledge, this is the first study that examined the association between various inclement weather types and hemodialysis appointments among patients with kidney failure. Previous studies have focused on single hazards, such as snowfall[4] or hurricane,[7,8,35] on hospitalization and mortality. As part of a more robust study on inclement weather exposures, we included different types of hazards, such as rainfall, hurricane and tropical storms, snow depth, wind advisories, and high wind advisories. In addition, this study included a relatively large sample of patients with kidney failure in the Northeastern United States. The dialysis treatment records were maintained by a global health care company that provides hemodialysis services. We applied a time-stratified case-crossover design, which is practical for estimating the acute effect of short-term exposure to inclement weather events[36] Finally, the DLNM framework enabled us to estimate the delayed effect of exposures due to inclement weather events.

This study also has several limitations. We used each hemodialysis clinic's ZIP code as a proxy of patients' residential location. For the measurement of inclement weather, spatial heterogeneity may exist within the counties. However, potential exposure misclassification errors resulting from the use of weather stations for each county were likely to be nondifferential as the stations did not change between the case period and the control periods.[37] The nondifferential exposure misclassification, if existed, likely attenuated the risk estimates.[38] Finally, future work needs to consider the localized role of inclement weather events caused by tropical storm events, extreme precipitation, snowstorms, and severe winds and quantify its effects on health complications associated with missed appointments.

Our data suggest that inclement weather events can be a major impediment to seeking scheduled hemodialysis appointments. This study showcased the effect of inclement weather conditions at finely configured temporal scales within Eastern United States. Our findings point to the need for enhanced adaptation strategies informed by robust early warning systems to minimize treatment disruption of patients with highly vulnerable kidney failure.

Table

Table 1. Characteristics of adults receiving in-center hemodialysis treatment at Fresenius Kidney Care facilities across the Northeastern U.S. between 2001 and 2019

Characteristics	
Counties, n	27
Clinics, n	99
Patients, n	60,135
Total number of visits to dialysis clinics, n	16,612,373
Average number of visits per patient	274 (385)
Average number of visits per patient per year (SD)	94 (61)
Total number of missed dialysis clinic appointments, n	454,932
Number of missed appointments per patient, n (%)	
0	31,640 (53)
1	7,081 (12)
2	3,752 (6)
≥3	17,662 (29)
Age at initial treatment, n (%)	
<40	5,224 (9)
40-49	8,123 (14)
50-59	13,272 (22)
60-69	14,929 (25)
70-79	12,146 (20)
≥80	6,441 (10)
Sex, n (%)	
Female	25,158 (42)
Male	34,598 (57)
Not Reported	379 (0.6)
Race/ethnicity, n (%)	
Hispanic	4,666 (8)
Non-Hispanic Black	23,810 (40)
Non-Hispanic White	23,813 (40)
Asian American	935 (2)
Other	465 (0.8)
Not Reported	6,446 (10)

Table 2. Daily measures of inclement weather in 27 counties in the Northeastern U.S. (2001-2019)

	Min	Median	Mean (SD)	Max
Rainfall [a] (mm)	0.0	0.0	3.1 (9.2)	221.2
Snowfall [b] (mm)	0.0	0.0	6.6 (29.5)	769.6
Snow depth [c] (mm)	0.0	0.0	22.5 (66.1)	863.6
Sustained wind speed [d] (m/s)	1.3	7.6	8.4 (2.8)	28.6
Peak wind speed [e] (m/s)	1.3	10.3	11.0 (3.8)	61.7

	Frequency by Season (%)	
	Wind advisory (Sustained wind >13.86m/s)	**Wind advisory (Peak wind >20.56m/s)**
Spring (Mar-May)	5% (1,835/36,887)	2% (724/36,887)
Summer (Jun-Aug)	2% (617/37,102)	0.8% (283/37,102)
Fall (Sept-Nov)	3% (1,116/36,983)	1% (443/36,983)
Winter (Dec-Feb)	7% (2,385/36,105)	3% (931/36,105)

Number of Hurricane and Tropical Storm -affected [f] Counties by Year

01’	**02’**	**03’**	**04’**	**05’**	**06’**
0	0	2	2	3	6
07’	**08’**	**09’**	**10’**	**11’**	**12’**
6	11	0	0	4	15
13’	**14’**	**15’**	**16’**	**17’**	**18’**
12	1	0	0	4	1

[a] **Rainfall**: daily amount of precipitation for the day from Apr to Oct[16]

[b] **Snowfall**: daily amount of snowfall from Nov to Mar. Record of the snowfall (snow, ice pellets) since the previous snowfall observation (24 hours) [16]

[c] **Snow depth**: daily reading of snow on the ground from Nov to Mar. Depth of the new and old snow remaining on the ground at observation time (24 hours) [16]

[d] **Sustained wind speed**: the fastest speed for the day that is sustained for at least 2 minutes[16]

[e] **Peak wind speed**: the fastest speed for the day that is sustained for at least 5 seconds[16]

[f] **Hurricane and tropical storm:** storms with wind speed ≥34 knots (from May to Oct) [18]

Table 3. Average percentages of daily missed hemodialysis appointments by inclement weather for 27 counties in the Northeastern U.S.

	County-days	Average % of missed appointments (SD)	
Rainfall > 0mm	35,858	2.5%	(6.1)
Rainfall = 0mm	62,880	2.5%	(6.5)
Hurricane and tropical storm	67	7.8%	(19.2)
No hurricane and tropical storm	69,832	2.4%	(6.4)
Snowfall > 0mm	3,634	4.9%	(10.4)
Snowfall = 0mm	21,858	3.4%	(8.3)
Snow depth > 0mm	4,720	4.3%	(9.2)
Snow depth = 0mm	20,126	3.5%	(8.6)
Wind advisory sustained	5,953	3.6%	(6.5)
No wind advisory sustained	140,987	2.6%	(9.0)
Wind advisory gusts	2,381	4.0%	(6.5)
No wind advisory gusts	143,509	2.6%	(9.9)

Table 4. Overall 7-day cumulative effects on missed hemodialysis appointment in incidence rate ratios (RR) and 95% confidence intervals (CI) for each type of inclement weather over 7 days of lag

Inclement Weather Type	RR (95% CI)
Hurricane and Tropical Storm	1.55 (1.22, 1.98)
Wind Advisory (sustained winds)	1.29 (1.25, 1.31)
Wind Advisory (wind gusts)	1.34 (1.29, 1.39)

Figure

Figure 1. Map of focused counties within Northeastern United States.[12] A total of 99 Fresenius Kidney Care clinics within 27 counties.

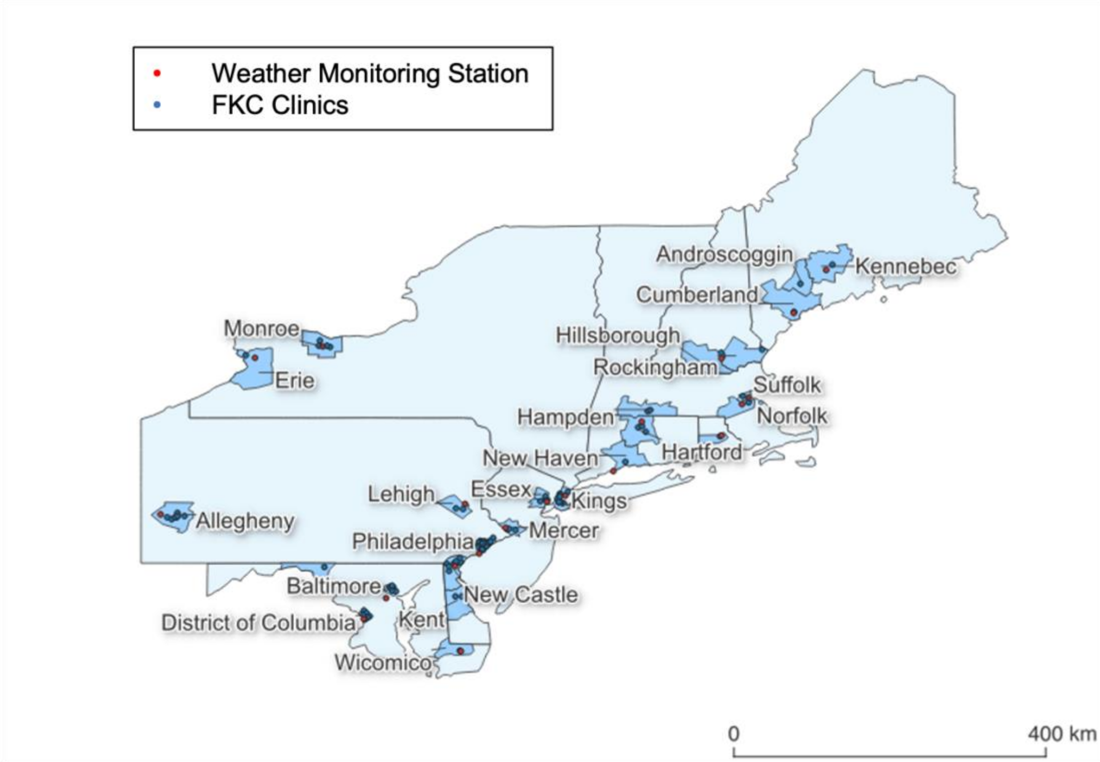


Figure 2. Lag-specific association between exposure to inclement weather type and risk of missed hemodialysis. Regression models included the day of the week as the covariate and an offset variable equaling the natural log of the monthly average number of scheduled appointments for each county. Cl, confidence interval; RR, rate ratio.

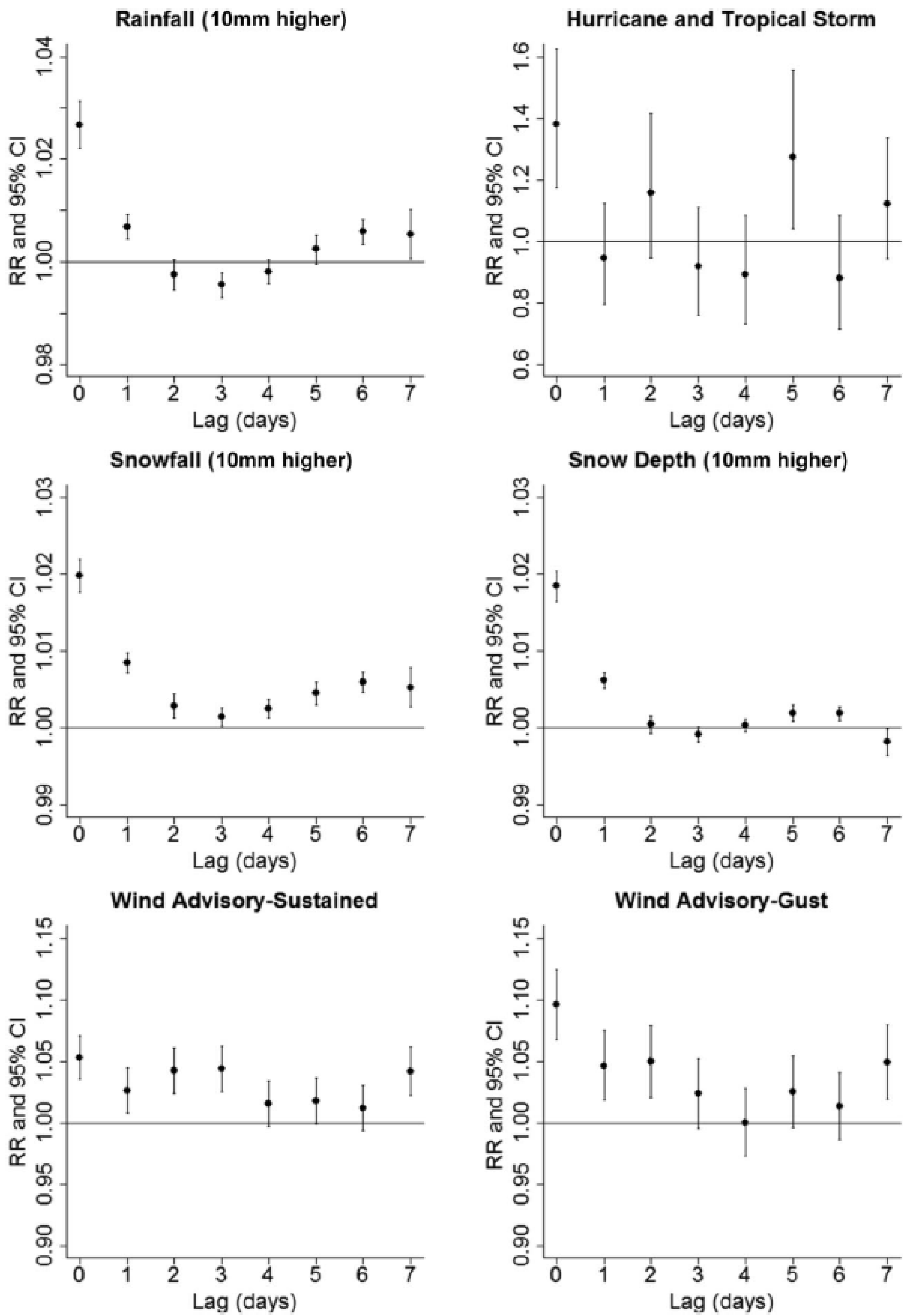
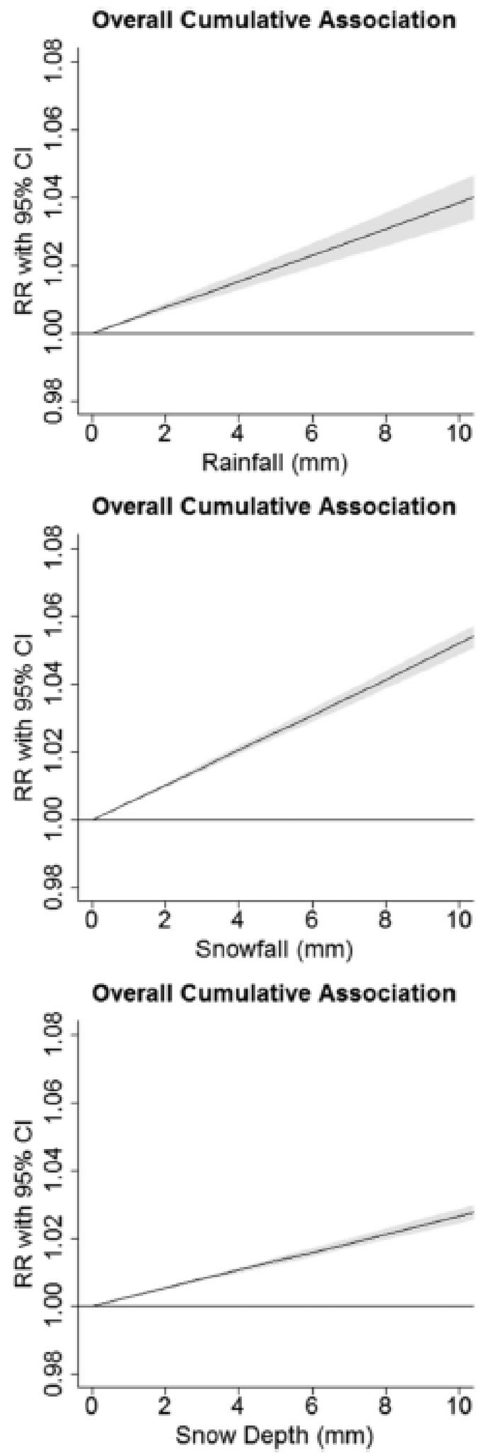


Figure 3. Association between 7-day cumulative (lag 0-6) exposure to inclement weather type and risk of missed hemodialysis appointment. Inclement weather types were analyzed as a continuous variable. Incidence RRs are presented as black lines with 95% Cl as gray region.



Supplementary Material

Supplemental Table 1. Number of county-days and missingness for each inclement weather

Inclement weather type	Number of counties and study period	Number of county-days (A)	Number of missing values (B)	% of Missingness (A/B)
Rainfall	27 counties, Warmer months (Apr to Oct), 2001-2019	98,755	17	0.0%
Hurricane and tropical storm	27 counties, Warmer months (May to Oct), 2001-2019	69,899	0	0.0%
Snowfall	13 counties, Colder months (Nov to Mar), 2001-2019	27,083	1,591	5.9%
Snow depth	13 counties, Colder months (Nov to Mar), 2001-2019	27,083	2,237	8.3%
Sustained wind speed	27 counties, All months, 2001-2019	147,077	137	0.1%
Peak wind speed	27 counties, All months, 2001-2019	147,077	1,187	0.8%

Supplemental Table 2. Summary of the follow-up periods of the 60,135 kidney failure patients during 2001-2019

	Follow-up period (days per person)
Min	0
1st quartile	42
Median	384
Mean (SD)	793 (1,041)
3rd quartile	1,157
Max	6,938
Total	48,044,318

Supplemental Table 3. Number of kidney failure patients per year

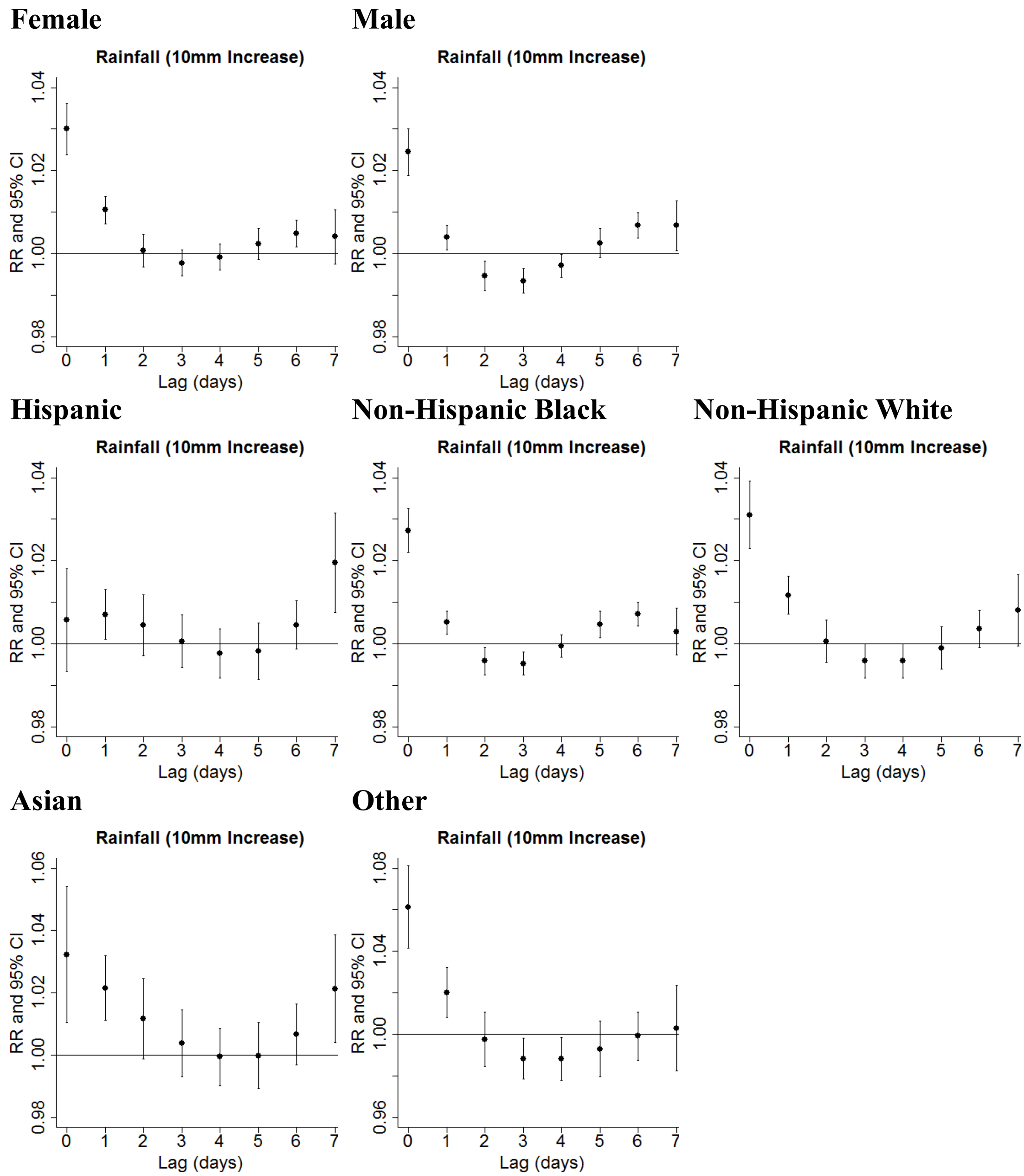
Year	Number of Kidney failure patients
2001	4,368
2002	4,953
2003	5,418
2004	6,426
2005	6,398
2006	6,973
2007	7,298
2008	7,783
2009	8,484
2010	9,172
2011	9,824
2012	10,182
2013	11,432
2014	11,962
2015	12,428
2016	12,812
2017	13,410
2018	13,752
2019	13,983

Supplemental Table 4. Overall 7-day cumulative effects on missed hemodialysis appointment in incidence rate ratios (RR) and 95% confidence intervals (CI) for each type of inclement weather over 7 days of lag stratified by sex and race/ethnicity

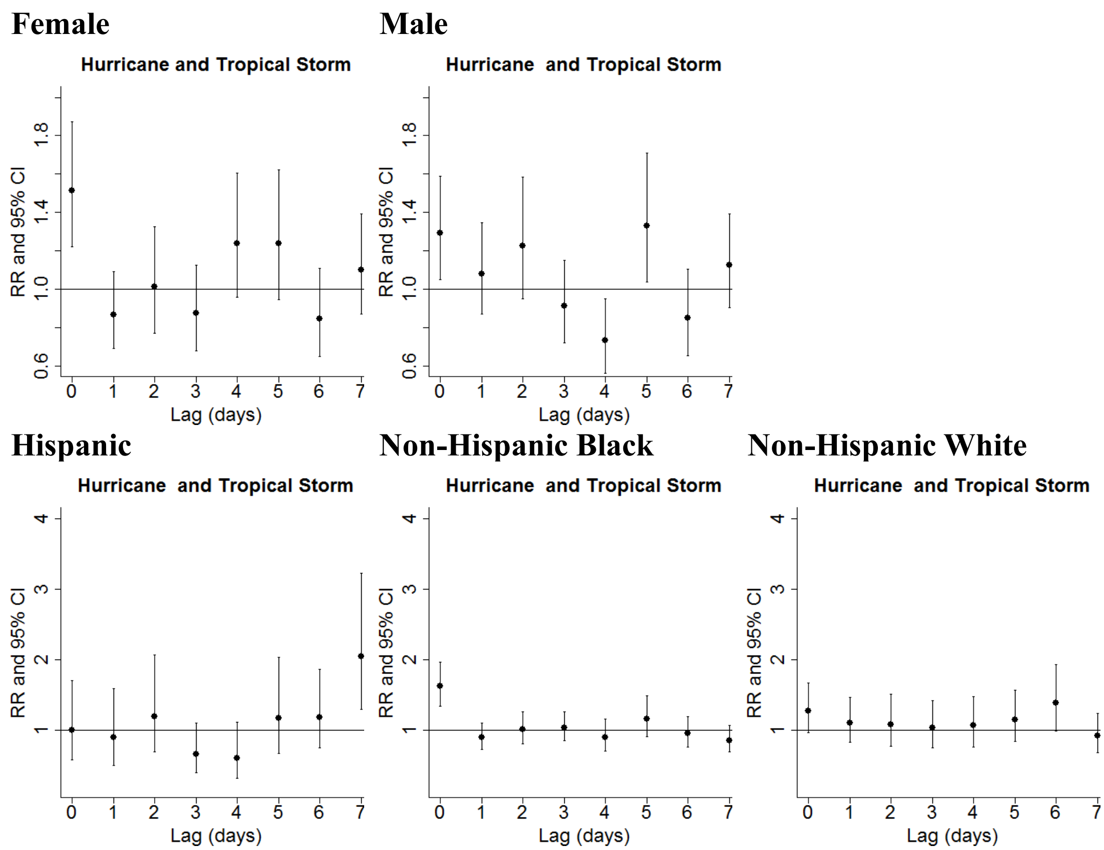
	RR (95% CI)		
	Hurricane and Tropical Storm	**Wind Advisory (sustained winds)**	**Wind Advisory (wind gusts)**
Female	1.65 (1.20, 2.28)	1.30 (1.26, 1.35)	1.37 (1.30, 1.44)
Male	1.44 (1.05, 1.97)	1.26 (1.23, 1.30)	1.32 (1.26, 1.39)
Hispanic	1.21 (0.68, 2.15)	1.34 (1.27, 1.41)	1.44 (1.32, 1.57)
Non-Hispanic Black	1.30 (0.96, 1.75)	1.26 (1.23, 1.30)	1.30 (1.25, 1.36)
Non-Hispanic White	2.43 (1.63, 2.43)	1.33 (1.27, 1.39)	1.42 (1.33, 1.52)
Asian	-	1.89 (1.73, 2.07)	1.98 (1.72, 2.28)
Other	-	1.66 (1.45, 1.90)	2.80 (2.18, 3.59)

* We were not able to do subgroup analysis for Asian and Other due to small sample size

Supplemental Figure 1. Lag-specific effects on missed hemodialysis appointments in incidence rate ratios (RR) and 95% confidence intervals (CI) for rainfall over 7 days of lag stratified by sex and race/ethnicity. Regression models included the day of the week as the covariate and an offset variable equaling the natural log of the monthly average number of scheduled appointments for each county.

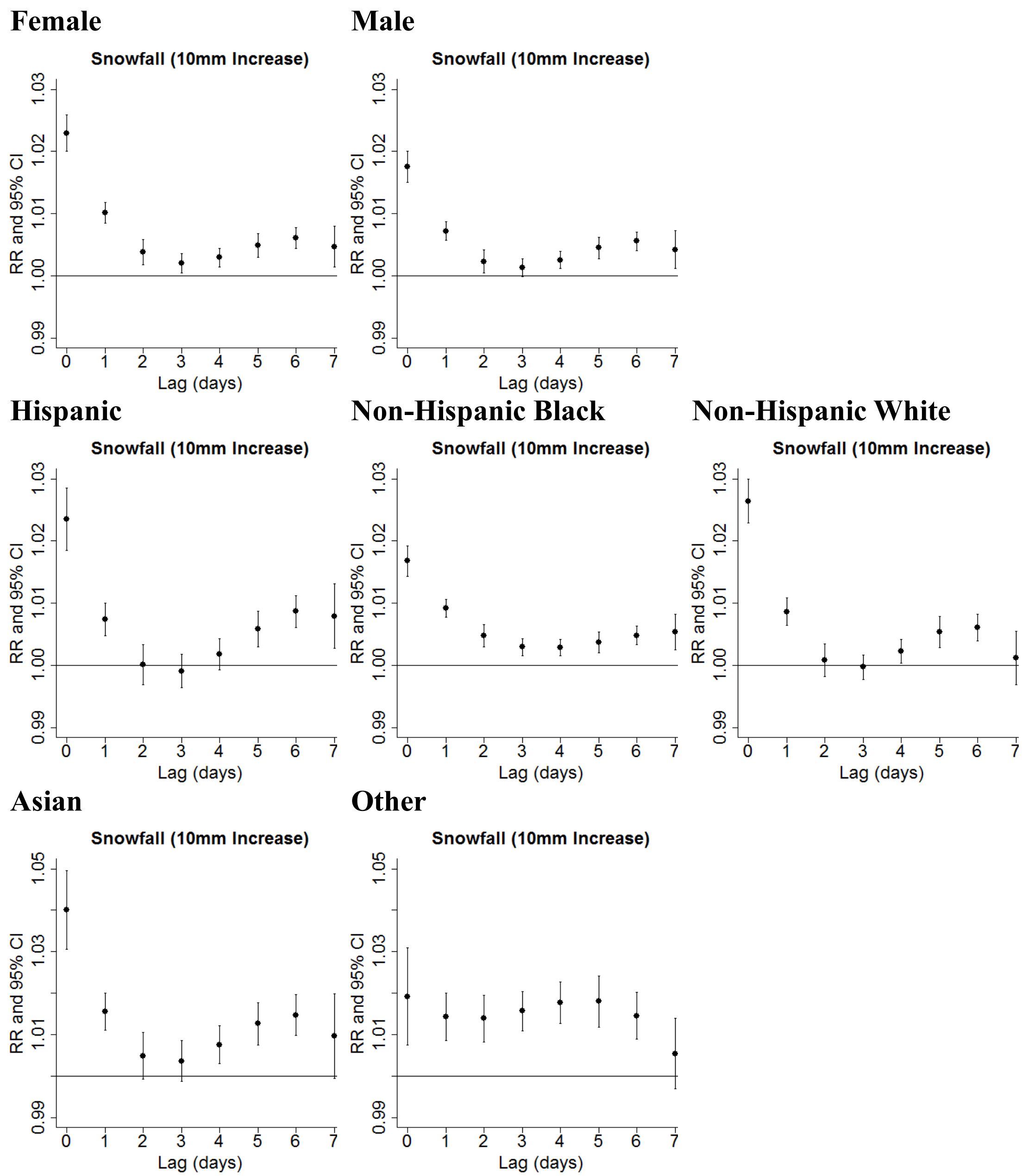


Supplemental Figure 2. Lag-specific effects on missed hemodialysis appointments in incidence rate ratios (RR) and 95% confidence intervals (CI) for hurricane and tropical storm over 7 days of lag stratified by sex and race/ethnicity. Regression models included the day of the week as the covariate and an offset variable equaling the natural log of the monthly average number of scheduled appointments for each county.

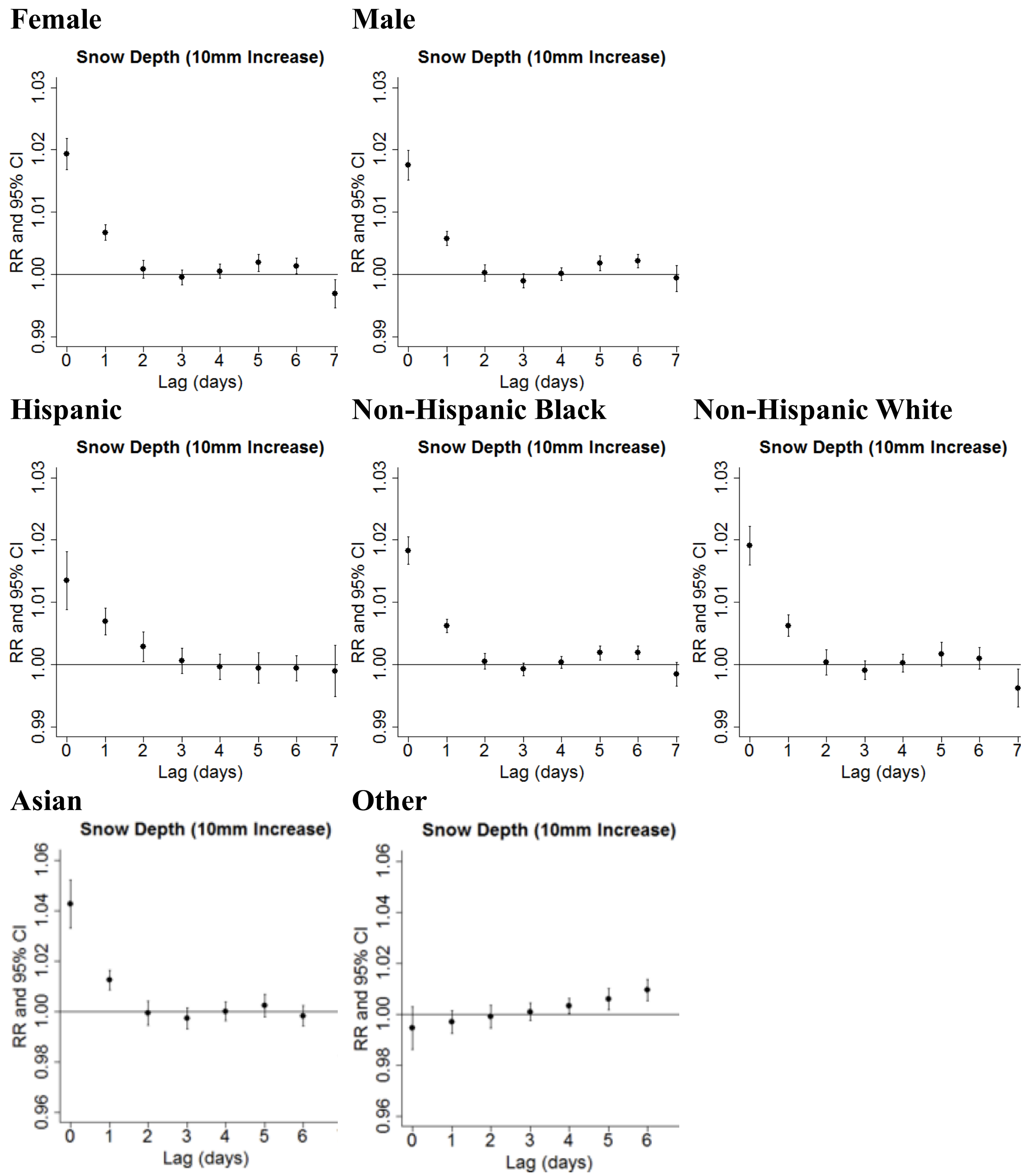


* We were not able to do subgroup analysis for Asian and Other due to small sample size

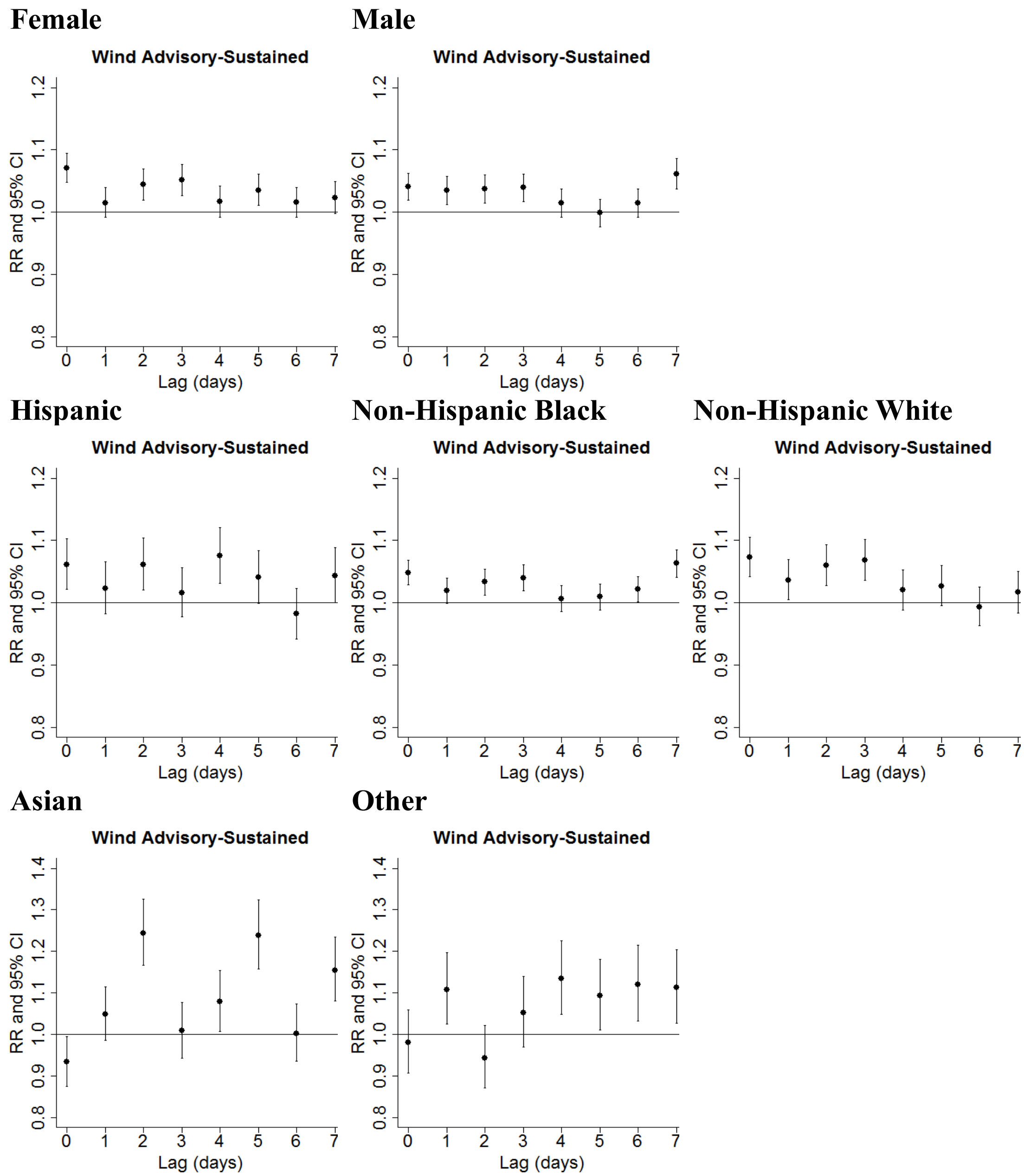
Supplemental Figure 3. Lag-specific effects on missed hemodialysis appointments in incidence rate ratios (RR) and 95% confidence intervals (CI) for snowfall over 7 days of lag stratified by sex and race/ethnicity. Regression models included the day of the week as the covariate and an offset variable equaling the natural log of the monthly average number of scheduled appointments for each county.



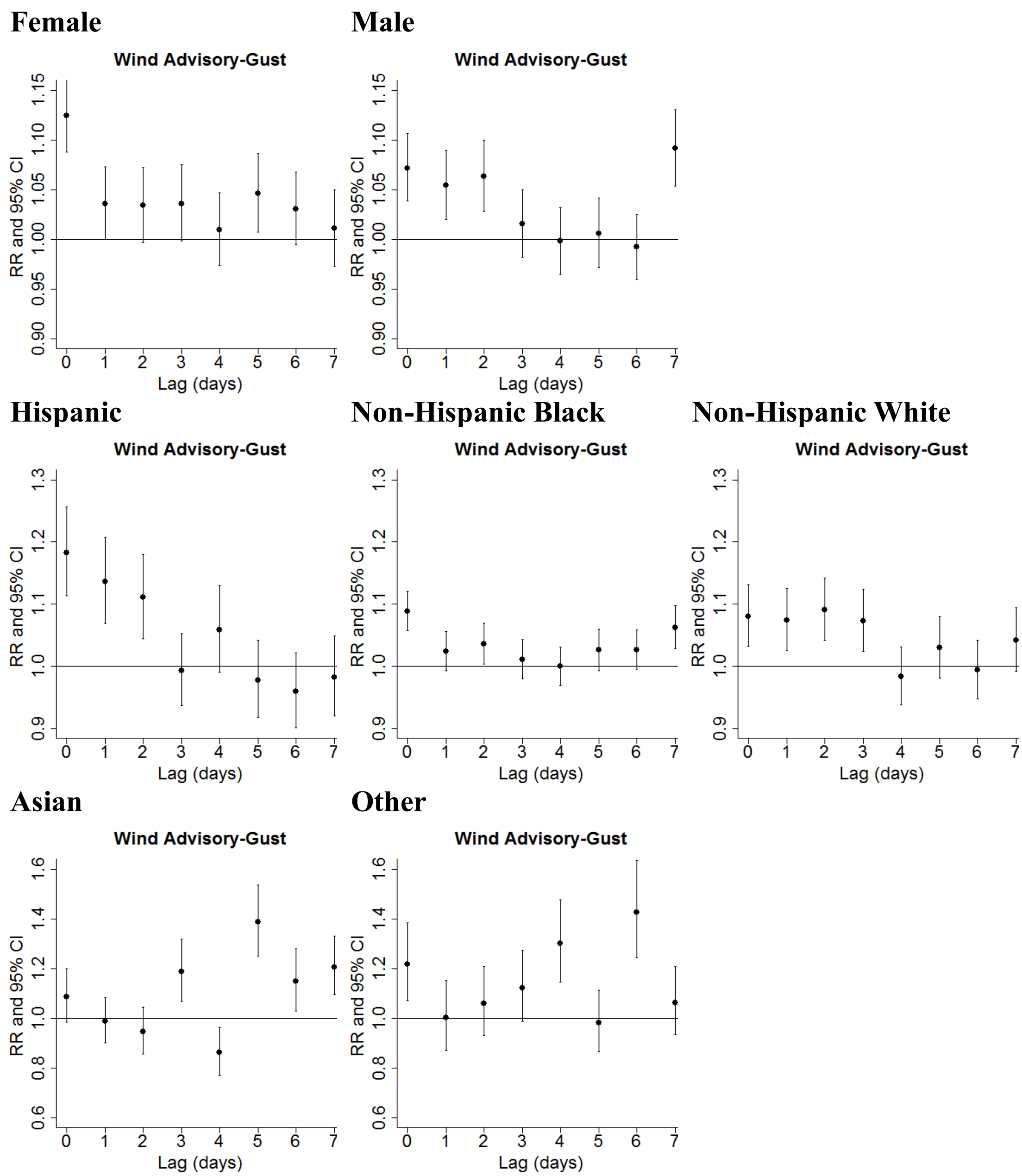
Supplemental Figure 4. Lag-specific effects on missed hemodialysis appointments in incidence rate ratios (RR) and 95% confidence intervals (CI) for snow depth over 7 days of lag stratified by sex and race/ethnicity. Regression models included the day of the week as the covariate and an offset variable equaling the natural log of the monthly average number of scheduled appointments for each county.



Supplemental Figure 5. Lag-specific effects on missed hemodialysis appointments in incidence rate ratios (RR) and 95% confidence intervals (CI) for wind advisory (sustained winds) over 7 days of lag stratified by sex and race/ethnicity. Regression models included the day of the week as the covariate and an offset variable equaling the natural log of the monthly average number of scheduled appointments for each county.

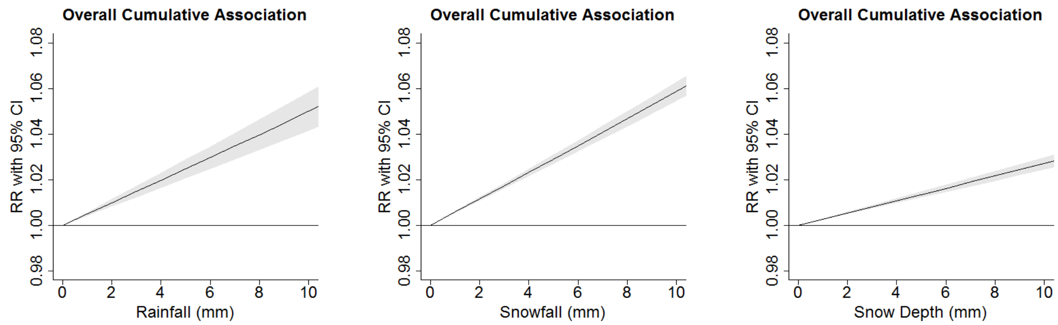


Supplemental Figure 6. Lag-specific effects on missed hemodialysis appointments in incidence rate ratios (RR) and 95% confidence intervals (CI) for wind advisory (wind gusts) over 7 days of lag stratified by sex and race/ethnicity. Regression models included the day of the week as the covariate and an offset variable equaling the natural log of the monthly average number of scheduled appointments for each county.

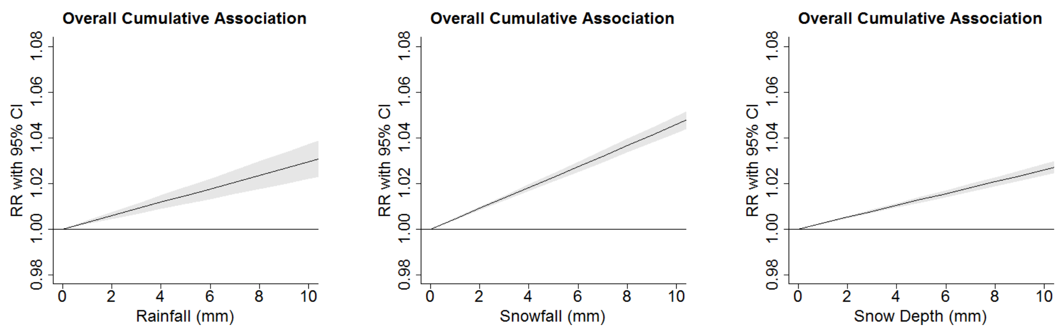


Supplemental Figure 7. Overall cumulative effects on missed hemodialysis appointment in incidence rate ratios (RR) and 95% confidence intervals (CI) for each type of inclement weather over 7 days of lag stratified by sex and race/ethnicity. Inclement weather types were analyzed as a continuous variable. Incidence RRs are presented as black lines with 95% CI as grey region.

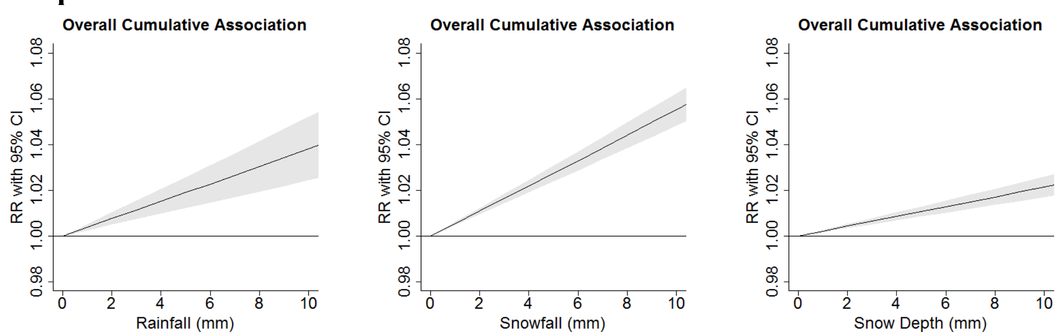
Female



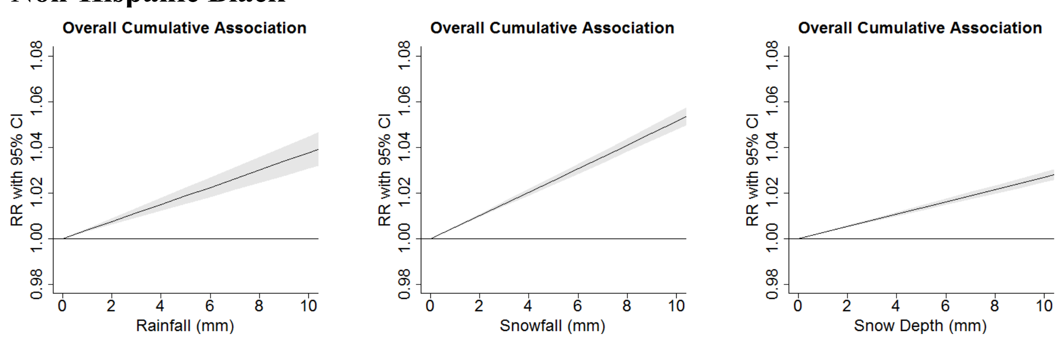
Male



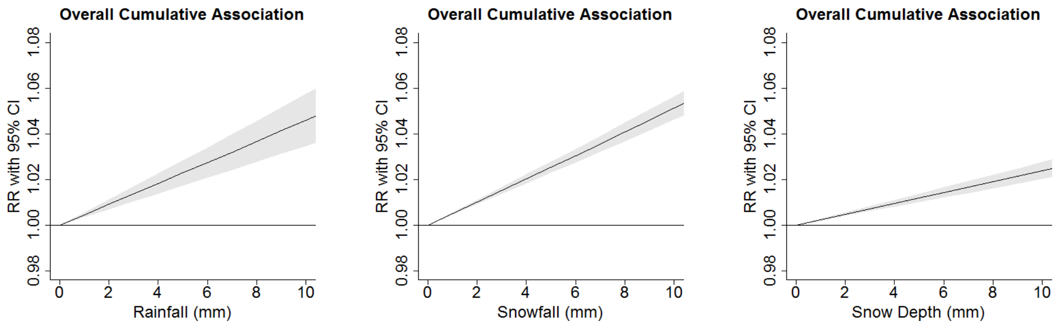
Hispanic



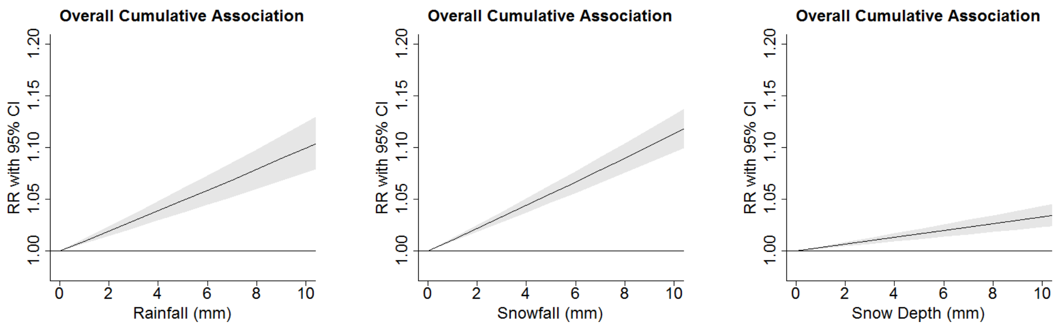
Non-Hispanic Black



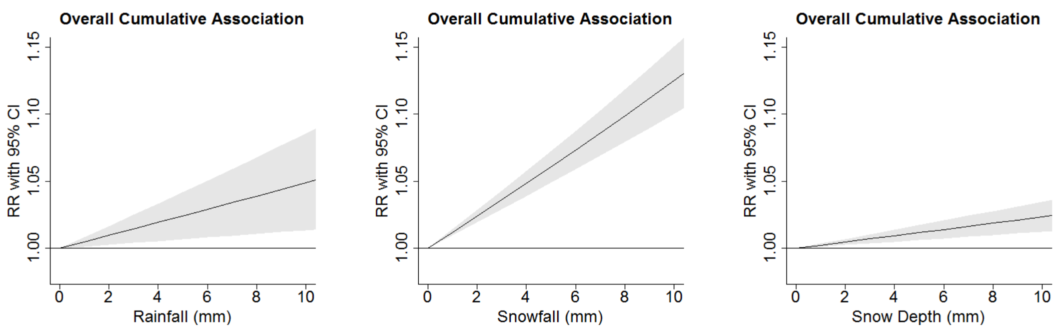
Non-Hispanic White



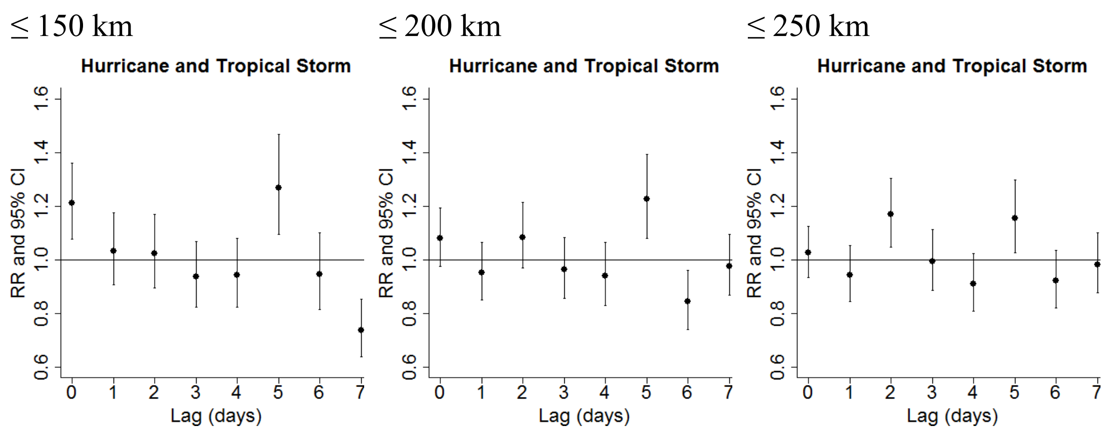
Asian



Other



Supplemental Figure 8. Lag-specific effects on missed hemodialysis appointments in incidence rate ratios (RR) and 95% confidence intervals (CI) for hurricane and tropical storm over 7 days of lag based on alternative hurricane and tropical storm exposure definitions (distance to storm track at 150 km or less, distance to storm track at 200 km or less, and distance to storm track at 250 km or less). Regression models included the day of the week as the covariate and an offset variable equaling the natural log of the monthly average number of scheduled appointments for each county.



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