ABSTRACT

Title of Dissertation:	UNMASKING RISK VARIABILITY IN A CHANGING CLIMATE: ACUTE EFFECTS FROM EXPOSURE TO OUTDOOR HEAT AND AIR POLLUTION AMONG PATIENTS WITH END-STAGE RENAL DISEASE
	Richard Vico Remigio, Doctor of Philosophy, 2021
Dissertation directed by:	Professor Amir Sapkota, Department of Epidemiology and Biostatistics, Maryland Institute for Applied Environmental Health

End-stage renal disease (ESRD) is a chronic condition that disproportionately affects communities of color and diabetics. Hallmark burdens include the lack of essential renal functions and routine life-saving dialysis treatments to filter and remove toxic wastes from the body. Given their compromised survival advantage, the ESRD population is vulnerable to adverse complications associated with acute environmental exposures. However, little is known about the effect of extreme heat events (EHE), air pollution, and ambient temperature on this targeted population. This dissertation focused on ESRD patients receiving hemodialysis treatments at Fresenius Medical Care facilities within the Northeastern United States region (n=60,717). Using longitudinal study design methods, we investigated the association between

acute environmental exposures and the risk of all-cause mortality (ACM) and all-cause hospital admissions (ACHA).

We applied case-crossover methods to estimate acute EHE effects on mortality and hospital admissions stratified by latitude, race/ethnicity, and comorbidities. Overall, risks varied, but same-day ACM and ACHA risks were most pronounced. ESRD patients with cardiovascular disease (rate ratio [RR], 2.14; 95% CI:1.91-2.40) and cerebrovascular disease (RR, 1.47; 95% CI:1.26-1.71) had notably increased risks of same-day EHE-related mortality. We furthered our investigation by studying $PM_{2.5}$ and O_3 effects using a similar study design but considered the role of EHE as a modifier and incorporated distributed lag nonlinear modeling to account for cumulative lag structures. Pooled same-day EHE-adjusted models estimated an 8% ACM rate increase when O_3 concentrations exceeded air quality standards during warmer months. Our data suggest that EHE can act as a modifier between O_3 and ACM. Though, no effect modification by EHE was observed for acute air pollutant exposures and ACHA. Lastly, this dissertation explored the mediating role of selected thermoregulatory responses to increased temperature on ACM or ACHA outcomes using traditional mediation analyses. Systolic blood pressure before dialysis treatment (preSBP) and interdialytic weight gain change (IDWG) were identified as significant pathways. However, we observed inconsistent mediation in the IDWG pathway for ACM (-6.26%) and ACHA (-2.67%). Concomitant physiological changes in preSBP and IDWG may have little intermediary effect in combined pathway models.

Overall, this research provided additional lines of evidence for enhancing patient response protocols and early warning systems to improve healthcare delivery in an era of a changing climate specific to subpopulations living with ESRD.

UNMASKING RISK VARIABILITY IN A CHANGING CLIMATE: ACUTE EFFECTS FROM EXPOSURE TO OUTDOOR HEAT AND AIR POLLUTION AMONG PATIENTS WITH END-STAGE RENAL DISEASE

by

Richard V. Remigio

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
2021

Advisory Committee:
Professor Amir Sapkota, Chair
Professor Xin He
Dr. Peter Kotanko
Professor Xin-Zhong Liang (Dean's Representative)
Professor Robin Puett
Professor Amy Sapkota

Dedication

For Mom and Dad.

Your unconditional love and sacrifices got me here.

This is for you.

Acknowledgments

The dissertation was a *long and winding road*. And like any long journeys, I met many characters along the way: fellow travelers, friendly strangers, locals, legends, good trouble-makers, and well-wishers. I want to take this opportunity to thank them.

First and foremost, I am utterly indebted to my advisor, Dr. Amir Sapkota, for taking me on as a mentee and for guiding me to realizing my doctoral endeavors. Your high expectations for scientific rigor and excellence, combined with your tough love, encouragement, and commitment to addressing climate change's impacts on human health, are inspiring. Thank you for being my mentor.

This dissertation work would not have been possible without the collaboration and support of the Renal Research Institute. I would especially like to recognize Drs. Peter Kotanko and Jochen Raimann. Besides facilitating access to Fresenius Medical Care health data, I would like to thank them for generously sharing their clinical expertise, networks, and time. I want to give Dr. Raimann additional acknowledgment as a thoughtful collaborator and whose curiosity helped me think of the implications beyond this dissertation work. I would also like to thank Dr. Patrick Kinney at Boston University for helping me initiate this project and for his support.

I would like to express my great appreciation to my other committee members: Drs. Xin He, Xin-Zhou Liang, Robin Puett, and Amy Sapkota. Dr. He trained me in applying longitudinal methods and provided invaluable statistical insight and

feedback. My most tremendous appreciation for taking the time and bandwidth to engage me with statistical and study design queries. Thank you to Dr. Liang for his insightful perspectives and facilitating access to critical air quality exposure data used in my work. My appreciation to Dr. Robin Puett for her mentorship during my lab rotation. Also, I much appreciate her sharp epidemiological insights and her collegiality. And my great gratitude to Dr. Amy Sapkota for her encouragement and support during my graduate studies at UMD and as a Global STEWARDS fellow.

I would also like to recognize additional research scholars that enhanced my doctoral training. My appreciation to Dr. Chengsheng Jiang for exposing me to large data set analysis and for his involvement in generating extreme heat data sets. Thank you to Linze Li for his friendship, enthusiasm in our climate & health work, and for introducing me to his remote sensing work. My great appreciation to Dr. Hao He for his collaboration and assistance in processing the CWRF-CMAQ data sets. And my immeasurable gratitude to Dr. Rodman Turpin for his tutelage on mediation analysis and his over-and-beyond engagement.

I would also like to express my thanks to MIAEH's leadership and staff. Thank you to Drs. Steve Roth and Paul Turner for their programmatic leadership and for fostering community within MIAEH. A special thank you to Meredith Pettit for her administrative support and kindness. And a resounding thanks to Maurice Rocque for being MIAEH's (un)official consigliere. Thank you for looking out and for keeping tabs on me. You are the core of MIAEH.

Many thanks to the Agency for Healthcare Research and Quality (AHRQ) for grant support from the R36 Dissertation Award (R36HS027716). I would also like to acknowledge support from the University of Maryland Global STEM Training at the Nexus of Energy, Water Reuse, and Food Systems fellowship. A National Science Foundation National Research Traineeship Program awarded to the University of Maryland School of Public Health. I would also like to express thanks to the Graduate School, MIAEH, the Wait Family Endowed Environmental Graduate Scholarship, and the CareFirst BlueCross BlueShield Endowed Graduate Scholarship for providing financial support.

Thank you to the SPH Solution Center and Mary Shelley for fielding my numerous computer-related fire drills: from VPN connection issues to computer crashes. I owe a boisterous thank you to Rafel Rosier and Rose Hoffman within the Office of the Dean for their administrative assistance in submitting my R36 in a flawlessly accelerated manner. Thank you to Dr. Linda Macri at the Graduate School Writing Center for the invaluable resources and space she provides to the graduate student community.

I had the great fortune to work closely with Dr. Gina Lovasi before my doctoral studies. I owe her a heartfelt thank you to her for taking me under her wing at Drexel University. While at the Urban Health Collaborative, she took it upon herself to show me “the academic ropes” during my rehabilitation. I will always treasure her mentorship and encouragement. She inspires me. And above all, she’s a great friend. Also, I would be remiss if I didn’t thank Dr. Andrea Baccarelli for his sincere warmth and unabashed support after my time at Columbia. I would

also like to acknowledge Dr. Jane Clougherty for her collaboration and friendship. I gained a lot from our spirited, in-depth discussions on our research and the world around us.

I would also like to thank Drs. Typhanye Dyer, Natalie Slopen, Quynh Nguyen, and Lesliam Quirós-Alcalá for their informal mentoring and thoughtful advice throughout my UMD tenure. Thank you to the SPH Dungeon Fam and MIAEH peers for creating community and friendship. I will miss you all and look forward to celebrating your eventual achievements. And to all the friends, current and past, for reminding me that there is life outside academic walls.

Lastly, I could not have completed this program without a small handful of individuals that are near and dear to my heart. To John Christopher Healey, who had been intimately there with me since the start, I cannot even begin to express my most profound appreciation to you. You, too, experienced the sacrifices and the struggles of my quest. Like fellow travelers that weathered terrible storms, we also experienced wondrous joys, triumphant, laughter, and passion. Here's to our continued country roads journey together- summits and all. I truly love you. To the California Alliance for Minority Participation (CAMP), Kika Friend, Dr. Juan Francisco Lara, and Dr. Brandon Brown, the shoulders of any giant do not compare to the heights in opportunities you have given me to stand on. And to my family, thank you for your unwavering and undying faith in me. I felt your thoughts, prayers, and encouragement. This achievement is all of ours. I would not be where I am without you.

Table of Contents

List of Tables

Chapter 3 Supplemental Tables

Chapter 4 Supplemental Tables

Chapter 5 Supplemental Tables

List of Figures

Chapter 3 Supplemental Figures

Chapter 4 Supplemental Figures

Chapter 5 Supplemental Figures

List of Abbreviations

°C	degree Celsius
95% CI	95% Confidence Interval
ACHA	All-Cause Hospital Admissions
ACM	All-Cause Mortality
ACR	Albumin to Creatinine Ratio
AG	Andersen-Gill
AHRQ	Agency for Healthcare Research and Quality
AQS	Air Quality System
BOS	Boston
BP	Blood Pressure
CDC	Centers for Disease Control and Prevention
CHF	Congestive Heart Failure
CKD	Chronic Kidney Disease
CMS	Centers for Medicare & Medicaid
CONUS	Contiguous United States
COPD	Chronic Obstructive Pulmonary Disease
CPR	Conditional Poisson Regression
CVD	Cardiovascular Disease
CWRF-CMAQ	Climate-Weather Research and Foresting and Community Multiscale Air Quality
DLNM	Distributed Nonlinear Modeling
eGFR	Estimated Glomerular Filtration Rate
EHE	Extreme Heat Events
ESRD	End-Stage Renal Disease
FIPS	Federal Information Process Standards
FKC	Fresenius Kidney Care
FMC-NA	Fresenius Medical Care- North American
HD	Hemodialysis
HR	Hazards Ratio
IDWG	Inter-Dialytic Weight Gain
IHF	Ischemic Heart Failure
IQR	Interquartile Range
Lag 0	Same-day
Lag 0-1	Two-day cumulative Lag
Lag 0-2	Three-day cumulative Lag
Lag 0-3	Four-day cumulative Lag
Lag 1	One-day Lag
Lag 2	Two-day Lag
Lag 3	Three-day Lag
MI	Myocardial Infarction

MICE	Multivariate Imputation by Chain Equations
MJJAS	May, June, July, August, September
mmHg	Millimeter of Mercury
NAAQS	National Ambient Air Quality Standards
NCEI	National Center for Environmental Information
NH	Non-Hispanic
NIHHIS	National Integrated Heat Health Information System
NOAA	National Oceanic and Atmospheric Agency
NWS	National Weather Service
NYC	New York City
O_3	Ground-Level Ozone
PHL	Philadelphia
$PM_{2.5}$	Particulate Matter with Less than 2.5 Microns in Aerodynamic Diameter
ppbv	Parts Per Billion by Volume
preSBP	Systolic Blood Pressure prior to dialysis treatment
r	Pearson correlation coefficient
RR	Rate Ratio
RRI	Renal Research Institute
SBP	Systolic Blood Pressure
SD	Standard Deviation
SE	Standard Error
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TMAX	Maximum daily air temperature
US	United States
USD	United States Dollar
USEPA	United States Environmental Protection Agency
USRDS	United States Renal Data System

Chapter 1: Introduction

1.1 Climate change, extreme weather, and health

Human civilization is currently experiencing the negative consequences of anthropogenic climate change. [1-4] Regions worldwide have observed record-setting extreme weather-related disasters from heatwaves [5], droughts [6], wildfires [7], and hurricanes [8, 9]. As such, irreversible environmental changes and harmful impacts on coupled human-natural systems and, consequently, on human health are rising. [10, 11] Over the last several decades, mounting studies have demonstrated the inextricable connection between ongoing climate change and human health. [12]

Linkages between heat exposures and all-cause morbidity and mortality outcomes are well recorded within the general population. [13, 14] Cause-specific outcomes include cardiopulmonary [15], cardiovascular [16-18], respiratory [19, 20], pathogenic [21], and renal [22, 23] diseases to name a few. Interestingly, more prominent causes for hospital admissions due to heatwaves are associated with fluid and electrolyte disorders, renal failure, urinary tract infection, and, most notoriously, heatstroke within the general population.[24] Such symptoms are frequent sequelae of heat stress and dehydration during periods of extreme heat that can decrease blood flow to the kidneys.[25, 26] In all, passive heat stress is a major risk factor for populations living with vascular-related chronic illnesses that regulate body temperature and offset overheating. An established metric for representing extreme heat events (EHE) related to climate change has been used to represent location-level

heat exposures at the population level. [19, 21, 27] Projected increases in the frequency of EHEs due to climate change can potentially pose a substantive public health threat to individuals living with compromised renal function, including end-stage renal disease (ESRD).

1.2 ESRD population characteristics

ESRD is the most critical stage of chronic kidney disease (CKD) characterized by lowered estimated glomerular filtration rate (eGFR; <15 ml/min/1.73m^2) and elevated protein in urine (albumin to creatinine ratio [ACR]; >300 mg/g). These clinical diagnostic tests are hallmark metrics for the accumulation of harmful levels of toxic by-products and fluid. [28, 29] Individuals with diabetes, hypertension, obesity, and pre-existing compromised kidney function (e.g., glomerulonephritis, cystic kidney) are at higher risk of developing ESRD.[28, 30] In 2020, prevalent ESRD cases within the United States are estimated at 746,557 cases with a notable declining incident standardized rate since its peak in 2006 (340.7 per million in 2017).[31] The lack of necessary modalities to supplement necessary filtration and excretion functions, such as dialysis or a kidney transplant, can ultimately result in death. In the United States, the most commonly administered form of renal replacement therapy is thrice-weekly hemodialysis (HD) treatment.[32] Recent data suggest that care and treatment for persons with ESRD in the US has an annual total Medicare-related expenditure cost of 49.2 billion USD.[30]

1.3 Potential environmental risks to the ESRD population

ESRD patients are susceptible to life-threatening complications resulting from fluctuations in weight and blood pressure.[33-35] Maintaining blood pressure (BP) stability is critical to improving survival advantage, irrespective of initial levels.[36] Generally, the relationship between blood pressure and mortality among HD patients is U-shaped with increasing risks observed along lower and higher tails.[37] However, concerning ESRD individuals, a sudden change in blood pressure has repeatedly been shown to increase the risk of premature deaths. [33-35] Also, increased changes in inter-dialytic weight gain (IDWG), a clinical anthropometric measure for fluid-related weight gain between HD treatments, is also associated with mortality. [38, 39] As such, concomitant decreases in IDWG change and BP might have possible influences in extreme heat-related associations in mortality and hospitalization. Lowered blood pressure is a typical physiological response to increasing ambient temperature among individuals irrespective of health status.[40, 41] Thus, changes in climate regimes that promote elevated temperatures and frequent extreme heat events are likely to be a significant driver in exacerbating risks. Interestingly, limited studies have described global seasonal variation as a predictor for several health endpoints among aggregated ESRD patients.[42, 43] Seasonal changes can influence physiological responses and mortality, particularly in more temperate regions where climatic fluctuations are most pronounced.[44]

1.4 Air quality as an environmental determinant

Air pollution is a known risk factor for renal function decline.[45] More recent findings have confirmed that exposure to elevated air pollution is associated with CKD development and CKD progression to ESRD. [46, 47] Furthermore, exposure to harmful air pollution levels, namely particulate matter, can increase blood pressure. [46, 48, 49] Inhaling airborne pollutants can promote vascular response changes that could decrease renal blood flow and, in turn, decrease estimated glomerular flow rates (eGFR).[47] These toxicological responses can also result in endothelial injury and inflammation that can hinder renal blood flow, and as a consequence, predispose susceptible individuals to adverse cardiovascular outcomes. [50] Long-term exposure to fine particulate matter and nitrogen dioxide can also decrease eGFR and likely increase CKD incidence. [47] Also, *in vitro* studies have shown that traffic-related $PM_{2.5}$ can induce nephrotoxicity and acute kidney injury in rodent models. [51] Ultimately, these responses can result in impaired renal function and increased severity of renal tubular necrosis.[51, 52] Degraded regional air quality from increased electrical demand for air conditioning [48] and more frequent wildfires [53] during warmer months can exacerbate health risks. Increased ozone production during an extreme heat event within urbanized regions- also known as extreme air pollution meteorological events- has severe health implications for cardiovascular and respiratory-related health complications. [54, 55] However, there is limited data regarding the potential risks from joint effects of air pollution and extreme heat events among ESRD patients.

1.5 Pilot work

In a piloted retrospective cohort study, we characterized the impact of extreme heat events (EHE) on HD patients treated at Fresenius Medical Center in North America (FMC-NA) in selected Northeastern US cities (Boston MA; New York, NY; and Philadelphia, PA) (**Chapter 2**). [56]

We found that exposure to EHE increased the risk of same-day hospitalization (rate ratio [RR], 1.27; 95% CI, 1.13-1.43) and same-day mortality (RR, 1.31; 95% CI, 1.01-1.70) among ESRD patients. In the same pilot work, we found that extreme heat events can, on average, reduce systolic blood pressure (-1.6 mmHg; 95% CI: -1.8- -1.4) and inter-dialytic weight gain (IDWG) percentage changes (-0.14%; 95% CI: -0.21- -0.18) when compared to non-extreme heat events. [57]. These observations present an interesting paradox for ESRD patients where both reduced blood pressure and weight changes can co-occur during extreme heat days. [38, 39] Our preliminary findings did not account for the modifying effect of air pollution. Although the study had a limited geographic scope, heterogeneity across cities, race/ethnicity, and co-morbidities were strongly observed. The work highlighted the need for a more robust and scaled assessment to better understand risk disparities and to further investigate the combined impact of air pollution and EHE on mortality and hospitalization risk.

1.6 Extreme Heat Event (EHE) Metric

A climate-based exposure surrogate was used to identify daily extreme heat events in the pilot study. The development and the application of this method are described in further detail elsewhere.[19, 27]

In summary, maximum daily air temperature (TMAX) data were extracted from the Global Historical Climate Database (GHCD) through the National Center for Environmental Information at the National Oceanic and Atmosphere Agency (NOAA). We used location-specific daily measures to generate county-level 30-year baselines from 1960-1989 and county-level extreme temperature thresholds. The thresholds for counties of focus were determined by calculating 95th percentiles of $TMAX_{95}$ based on a 31 day-moving window centered for any calendar day during all baseline years for a respective county. This approach was repeated for each calendar day during the study period within each studied county. And lastly, we compared the $TMAX_{95}$ derived EHE thresholds to observed TMAX daily measures to identify EHEs. We note that this method had an added advantage in capturing long-term changes in climate variability and in estimating acute heat effects on population health.

1.7 Outline of Dissertation

In general, we sought to follow-up with our preliminary work by expanding the geographic coverage and the study population within the Northeastern United States region to investigate the role of acute environmental exposures from extreme heat, air pollution, and its combination on ESRD patients. Our central hypothesis is that EHEs will increase mortality and hospitalization risk among ESRD patients with pre-existing co-morbidities. Still, effects will vary by location and by race/ethnicity. We also hypothesize that elevated air pollutants as modifiers will exacerbate mortality and hospitalization risks during EHE periods. Lastly, we hypothesize that reduced blood pressure from increased ambient temperature may have a substantive indirect

effect on increasing mortality and hospitalization risks. The specific aims for this dissertation are to:

1. **Quantify extreme heat events (EHE)-related risk of mortality and hospitalization among ESRD patients undergoing hemodialysis in the northeastern United States by location, race/ethnicity, and pre-existing co-morbidity.**
2. **Investigate the cumulative joint effects of extreme heat events and air pollution among ESRD patients.**
3. **Identify probable mechanistic pathways between air temperature and mortality and hospitalization risks through physiological measurements using mediation analysis**

These research aims have been expanded into three manuscripts, preceded by published piloted work that showcased adopted methods and preliminary results on three highly-urbanized northeastern locations, followed by an overall dissertation conclusion and public health implications chapter. Aim 1 examines the acute effects of extreme heat events and apparent temperature on ESRD patients within the United States' northeastern region using study design methods consistent with piloted work. Stratification analyses based on location, race/ethnicity, and pre-existing co-morbidities are featured in this work. Aim 2 characterizes the interaction between air quality and extreme heat events on mortality and hospitalization outcomes. Air quality data for $PM_{2.5}$ and ozone are based on highly-resolved spatio-temporal data from coupled environmental models. Distributed lag nonlinear modeling is used to estimate cumulative lag exposures for up to three days. Aim 3 examined mechanistic

pathways between acute temperature exposure and mortality and hospitalization risks through selected clinical measurements taken before hemodialysis treatments. We applied mediation analyses based on survival outcomes to assess potential competing pathways mediated by systolic blood pressure before treatment (preSBP) and IDWG. Proportion mediated estimates for preSBP, IDWG, and preSBP+IDWG pathways in individual and combined pathway models were quantified. And finally, the dissertation ends with overall conclusions followed by public health/clinical implications and next steps for advancing the research.

Chapter 2: Association of Extreme Heat Events With Hospital Admission or Mortality Among Patients With End-Stage Renal Disease

Remigio, R.V., Jiang, C., Raimann, J., Kotanko, P., Usvyat, L., Maddux, F.W., Kinney, P. and Sapkota, A., 2019. Association of Extreme Heat Events with Hospital Admission or mortality among patients with end-stage renal disease. *JAMA network* open, 2(8), pp.e198904-e198904.

2.1 Abstract

Importance. Extreme heat events (EHEs) are increasing in frequency, duration, and intensity, and this trend is projected to continue as part of ongoing climate change. There is a paucity of data regarding how EHEs may affect highly vulnerable populations, such as patients with end-stage renal disease (ESRD). Such data are needed to inform ESRD patient management guidelines in a changing climate.

Objectives. To investigate the association between EHEs and the risk of hospital admission or mortality among patients with ESRD and further characterize how this risk may vary among races/ethnicities or patients with preexisting comorbidities.

Design, Setting, and Participants. This study used hospital admission and mortality records of patients with ESRD who underwent hemodialysis treatment at Fresenius Kidney Care clinics in Boston, Massachusetts; Philadelphia, Pennsylvania; or New York, New York, from January 1, 2001, to December 31, 2012. Data were analyzed using a time-stratified case-crossover design with conditional Poisson regression to investigate associations between EHEs and risk of hospital admission or mortality

among patients with ESRD. Data were analyzed from July 1, 2017, to March 31, 2019.

Exposures. Calendar day– and location-specific 95th-percentile maximum temperature thresholds were calculated using daily meteorological data from 1960 to 1989. These thresholds were used to identify EHEs in each of the 3 cities during the study.

Main Outcomes and Measures. Daily all-cause hospital admission and all-cause mortality among patients with ESRD.

Results. The study included 7445 patients with ESRD (mean [SD] age, 61.1 [14.1] years; 4283 [57.5%] men), among whom 2953 deaths (39.7%) and 44 941 hospital admissions (mean [SD], 6.0 [7.5] per patient) were recorded. Extreme heat events were associated with increased risk of same-day hospital admission (rate ratio [RR], 1.27; 95% CI, 1.13-1.43) and same-day mortality (RR, 1.31; 95% CI, 1.01-1.70) among patients with ESRD. There was some heterogeneity in risk, with patients in Boston showing statistically significant increased risk for hospital admission (RR, 1.15; 95% CI, 1.00-1.31) and mortality (RR, 1.45; 95% CI, 1.04-2.02) associated with cumulative exposure to EHEs, while such risk was absent among patients with ESRD in Philadelphia. While increases in risks were similar among non-Hispanic black and non-Hispanic white patients, findings among Hispanic and Asian patients were less clear. After stratifying by preexisting comorbidities, cumulative lag exposure to EHEs was associated with increased risk of mortality among patients with ESRD living with congestive heart failure (RR, 1.55; 95% CI, 1.27-1.89), chronic obstructive

pulmonary disease (RR, 1.60; 95% CI, 1.24-2.06), or diabetes (RR, 1.83; 95% CI, 1.51-2.21).

Conclusions and Relevance. In this study, extreme heat events were associated with increased risk of hospital admission or mortality among patients with ESRD, and the association was potentially affected by geographic region and race/ethnicity. Future studies with larger populations and broader geographic coverage are needed to better characterize this variability in risk and inform ESRD management guidelines and differential risk variables, given the projected increases in the frequency, duration, and intensity of EHEs.

2.2 Introduction

The evidence that climate and human health are inextricably connected has been mounting over the last decade.[58, 59] To our knowledge, most studies have focused on exposure to extreme heat events (EHEs), as they are projected to increase in frequency, intensity, and duration with a changing climate[60]. Prior studies on the effects of extreme heat have consistently shown an increased risk of hospital admission and mortality among the general population, particularly within urban areas.[61-65] Urban communities may be disproportionately affected by extreme heat because of higher rates of poverty and more intense heat exposure due to the urban heat island effect [64-68], contributing to higher risk of hospital admissions and mortality.[24, 69-75] However, to our knowledge, few studies have investigated how EHEs may affect highly vulnerable populations, such as individuals living with end-stage renal diseases (ESRD) patients, within these urban centers.

End-stage renal disease is the final stage of chronic kidney disease which causes gradual decrease in renal function. Patients with ESRD require some form of renal replacement therapy, such as hemodialysis or kidney transplantation, to survive. In the United States, the most commonly administered form of renal replacement therapy is thrice-weekly hemodialysis treatment.[32] Patients with ESRD must also adhere to dietary modifications, such as restricting the consumption of water and foods containing high levels of sodium, potassium, and phosphorus, to manage excess fluid accumulation.[76] Data from 2017 suggest that there were 500,000 ESRD patients in the United States undergoing routine hemodialysis treatment in 2015, with an annual Medicare treatment and management cost of $34 billion.[77]

Previous studies have reported seasonal, as well as regional patterns of mortality among patients undergoing hemodialysis, with higher rates observed in the tropical regions of the world.[43, 44] Other studies [24, 25] have hypothesized renal-related diagnoses, such as kidney failure, and electrolyte imbalances are the underlying causes of hospital admissions and mortality risk among elderly populations exposed to high temperatures. Such diagnosis are frequent sequelae of heat stress and dehydration during periods of extreme heat [25] and have been implicated in acute renal failure among sugarcane workers working in harsh outdoor conditions.[71, 72] A 2018 study [78] reported extended periods of exposures to extreme heat were associated with an increased risk of acute kidney injury-related emergency department visits and hospital admissions among older adults. However, to our knowledge, such associations between EHEs and hospitalization or mortality among patients with ESRD has not been characterized, and it is unclear if such

association differs by race/ethnicity or preexisting comorbidities.

We used data from the Fresenius Kidney Care (FKC) clinics to investigate the association between EHEs and risk of hospital admissions or mortality among patients with ESRD undergoing HD treatment in 3 northeastern cities: Boston, Massachusetts (BOS); New York City, New York (NYC); Philadelphia, Pennsylvania (PHL). Our objectives were to (1) quantify risk of hospital admission or mortality among patients with ESRD associated with EHEs; (2) investigate whether this risk varied by race/ethnicity or preexisting comorbidities, including congestive heart failure (CHF), diabetes, and chronic obstructive pulmonary disease (COPD); and (3) characterize the time course of mortality and hospital admission risk associated with EHEs using time-varying (lagged) exposures.

2.3 Methods

2.3.1 Health Data

The period for this analysis is from January 2001 to December 31, 2012, focusing on warmer months of the year (May to September). We obtained deidentified data on patients with ESRD who were treated at 23 FKC clinics (Figure 1) located in Boston, NYC, and Philadelphia from electronic health records.[79] Eligible patients were selected based on clinic zip codes where hemodialysis treatment was received. Our study population can be considered a representative sample of patients with ESRD, who typically receive fully or nearly fully managed care for hemodialysis treatments.[80] We used all-cause hospital admission and all-cause mortality as the primary outcomes. Counts of hospital admissions and mortality

events were aggregated for each day by location. We obtained information on self-reported race/ethnicity and categorized patients as Hispanic, NH (NH) black, NH white, Asian, or other (e.g., American Indian, Native Hawaiian, other). We also obtained information on other preexisting comorbidities, including CHF, COPD, and diabetes. Patients who had received fewer than 30 hemodialysis treatments at a given clinic were excluded to ensure location membership during the study. This study was determined exempt by the Western Institutional Review Board and the University of Maryland Institutional Review Board, which waived the need for informed consent because it used deidentified data. Our study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guideline for case-control studies. Data were analyzed from July 1, 2017, to March 31, 2019.

2.3.2 Extreme Heat Events

Extreme heat events were identified using previously described methods[19, 27]. In brief, we used 30 years (1960-1989) of daily maximum temperature obtained from the National Center for Environmental Information (NCEI) through the National Oceanic and Atmosphere Agency (NOAA) to calculate unique calendar day- and location-specific 95^{th}-percentile thresholds. Following this, daily maximum temperature for targeted study locations during 2001-2012 were compared with their respective calendar day- and location-specific thresholds and assigned a value of *1* if they exceeded the upper 95^{th} -percentile threshold and *0* if they did not. Days exceeding the thresholds were identified as EHEs.

2.3.2 Statistical Analysis

We applied a time-stratified case-crossover study design with conditional Poisson regression to estimate location-specific associations between EHE exposures and hospitalization & mortality risk among ESRD patients using the *gnm* package in R version 3.5.0 [81, 82]. In a case-crossover study design, each individual serves as his or her own control. This unique feature of the case-crossover design eliminates the need to adjust for individual level time-invariant confounders, including age, sex, race, and socioeconomic status.[83-86] This study design with conditional Poisson model accounts for varying population changes during a study and allows adjustments for autocorrelation and overdispersion, which is not possible with conditional logistic regression methods.[87] Furthermore, when adjustment for autocorrelation and over-dispersion is not necessary, results obtained from conditional Poisson model is identical to that obtained with conditional logistic regression.[87] Stratum indicators are based on the combination of year, month, and the day of week. This approach is consistent with other studies that have used case-crossover designs to measure acute health effects associated with short term environmental exposures. [62, 88-91] We checked for autocorrelation and overdispersion and found that the assumption that variance is proportional to its mean was violated. Thus, a quasi-Poisson method was adopted into the conditional Poisson regression.

We used unconstrained same-day (lag 0), one-day lag (lag1), and cumulative same-day and one-day lag (lag 0-1) exposures to EHE during warm months (May-September) for the northeastern cities and the northeast region combined. The combined data from the 3 cities were also used to conduct stratified analyses by

race/ethnicity and comorbidity status to investigate if risk associated with EHEs varied by race/ethnicity (i.e., Asian, non-Hispanic black, non-Hispanic white, and Hispanic) and by preexisting comorbidities (i.e., CHF, COPD, and diabetes). We further tested for effect modification by location, race/ethnicity, and comorbidities using previously described methods used in similar case-crossover analyses stratified by time-invariant demographic characteristics[92, 93] We used a Wald χ^2 test to determine statistical significance for EHE exposure at an α level of 0.05.

2.4 Results

This study included 7445 patients with ESRD from 3 cities (**Table 1**). The participants tended to be older (mean [SD] age, 61.1 [14.6] years) and men (4283 [57.5%]). Owing to data restrictions, NYC patients' data were not available from 2001 to 2003. Philadelphia and NYC had the most NH black patients (Philadelphia, 2558 patients [68.0%]; NYC, 1418 patients [63.3%]), whereas NH white patients were overrepresented in Boston (1083 patients [75.2%]). Overall, the prevalence of diabetes (1710 [23.0%]) was higher compared with CHF (939 [12.6%]) and COPD (289 [3.9%]). We observed the highest 12-year mortality rate in Boston (700 deaths [48.6%]), followed by Philadelphia (1433 deaths [38.1%]), then NYC (820 deaths [36.6%]). Hospital admission can be a recurrent event among patients undergoing hemodialysis. As such, patients in this study had a mean (SD) of 6.0 (7.5) hospital admissions during the warmer months (**Table 1**). The expected number of annual EHEs based on the 95th-percentile threshold is 18.25 (365 × 0.05). During the study, the annual mean (SD) number of EHEs was higher in Boston (37.4 [23.0] days) but

lower in NYC (14.2 [10.1] days) or Philadelphia (11.9 [6.5] days) (**Table 1**; **Figure S2-1**).

In the combined regional analysis, cumulative exposure to EHEs was associated with higher risk of hospital admission among patients with ESRD (rate ratio [RR], 1.36; 95% CI, 1.23-1.50) (Figure 2A). City-specific risks of hospital admission were statistically significant for Boston (RR, 1.15; 95% CI, 1.00-1.31) and NYC (RR, 1.17; 95% CI, 1.03-1.34) but not for Philadelphia (RR, 1.05; 95% CI, 0.97-1.13). Findings regarding same-day exposure and 1-day lagged exposure were robust for the combined analysis, but the city specific estimates were statistically significant for NYC only (RR, 1.21; 95% CI, 1.03-1.42). Likewise, cumulative exposure to EHEs was associated with increased risk of mortality among patients with ESRD in the regional analysis (RR, 1.32; 95% CI, 1.06-1.65) as well as in Boston (RR, 1.45; 95% CI, 1.04-2.02) but not in NYC (RR, 1.11; 95% CI, 0.76-1.63) or Philadelphia (RR, 1.05; 95% CI, 0.78-1.39). Findings for Boston remained statistically significant for same-day (RR, 1.50; 95% CI, 1.03-2.19) and 1-day lag (RR, 1.78; 95% CI, 1.21-2.61) exposures (Figure 2B).

Cumulative exposure to EHEs was associated with increased risk of mortality among non-Hispanic black patients (RR, 1.57; 95% CI, 1.25-1.97) and non-Hispanic white patients (RR, 1.38; 95% CI, 1.16-1.64) but not among Hispanic patients (RR, 1.27; 95% CI, 0.94-1.70). The increases in risk of mortality observed among non-Hispanic black and non-Hispanic white patients remained elevated for both same-day and 1-day lag exposures. For Hispanic patients, same-day exposure to extreme heat was associated with increased risk of mortality (RR, 1.58; 95% CI, 1.16-2.14), but

exposure from the previous day was associated with decreased risk of mortality, although the decrease was not statistically significant (RR, 0.82; 95% CI, 0.55-1.22) (Figure 4A). Because there were too few deaths among Asian patients with ESRD (<5 deaths) during EHEs, we removed them from the analysis owing to model instability. The increases in risk of mortality associated with EHEs were statistically significant among patients with ESRD and living with COPD (RR, 1.60; 95% CI, 1.24-2.06), CHF (RR, 1.55; 95% CI, 1.27-1.89), or diabetes (RR, 1.83; 95% CI: 1.51-2.21) (Figure 4B). Findings for same-day and previous-day EHE exposures were similar to those for the cumulative exposure. We found some evidence of effect modification by race/ethnicity and location. These findings were higher than the overall increases in mortality observed for the combined population (RR, 1.32; 95% CI, 1.06-1.65), indicating potential effect modification (Figure 2B).

2.5 Discussion

The projected increases in the duration, frequency, and intensity of EHEs associated with climate change are a significant public health concern, as they can negatively affect vulnerable populations, such as patients with ESRD. The geographic heterogeneity in EHEs observed among BOS, NYC, and PHL during the study is in agreement with previous studies [94, 95] that have noted such variability in the influence of climate change on local weather events. Our results suggest that EHEs are associated with increased risk of hospital admission and mortality among patients with ESRD. While the risk estimates for hospital admission and mortality were consistent for the regional combined analysis, city-specific risk estimates differed, highlighting the geographic variability. Increases in risk of hospital admission and

mortality associated with EHEs were consistently higher NH black and NH white patients, but findings among Hispanic and Asian patients were less clear. Risk of mortality associated with EHEs among patients with ESRD was consistent among patients with CHF, COPD, or diabetes as comorbidities. However, hospital admission risk differed by comorbidity status, ie, EHEs were associated with increased risk of same-day hospital admission among patients with ESRD and diabetes, but this risk was not elevated among patients with ESRD and COPD or CHF as comorbidities. These preliminary findings highlight the need for national scale assessments to quantify the underlying geographic and demographic variability in risk of hospital admission and mortality associated with EHEs to better inform ESRD management in a changing climate.

Our findings of increased hospital admissions and mortality risk associated with EHEs among patients with ESRD is consistent with previous studies[24, 72, 96, 97] that have reported similar findings among general populations. While both New York City and Philadelphia had higher proportions of non-Hispanic Black patients and similar rates of EHE, the extreme heat related risk of hospitalization and mortality was not significant in Philadelphia. The interpretation of this observation remains unclear as we did not investigate facility specific characteristics. Our finding of increased mortality associated with EHEs among patients with ESRD and CHF or COPD as comorbidities is consistent with a 2010 study[98] among elderly people with CHF and COPD. According to the United States Renal Data System[77], cardiovascular causes, including CHF, account for almost half of deaths among patients undergoing hemodialysis. Lowered blood pressure is a common

physiological response to increasing ambient temperature among individuals irrespective of cardiovascular health status.[40, 41] However, with respect to people with ESRD, low blood pressure has been shown to increase the risk of premature deaths. [33-35] The underlying mechanism for heat related mortality among patients with ESRD living with COPD and diabetes remains unclear and needs further investigation. [99, 100]

Individual-level determinants, such as education level, socioeconomic status, and race/ethnicity, have been shown to increase vulnerability and can potentially modify the association between heat exposure and mortality. [101-103] While we excluded Asian patients from the mortality analysis owing to model instability attributed to a small number of events (<5 deaths) during an EHE, others have suggested this particular group may be less vulnerable to EHE exposures.[104, 105] For example, a 2015 study[106] reported that Asian laborers in the United States exhibited a lower rate of mortality associated with occupational heat exposure during 2000 to 2010. Interestingly, among Medicare enrollees in the United States, older Asian adults appear to experience significantly reduced rates of health care visits associated with hyperthermia.[107] We observed some evidence of effect modification by location, race/ethnicity, and comorbidities, but results were not statistically significant because of limited sample size. This is consistent with a previous study that reported higher risk of mortality among individuals with CHF, diabetes, or COPD during the summer season.[102]

2.5.1 Strengths and Limitations

This study consisted of a relatively large sample size of patients with ESRD, a previously understudied vulnerable population in the context of climate change. Hospital admission and mortality records for the study population were maintained by FKC, a globally known hemodialysis care enterprise. We also computed a robust exposure metric using location- and calendar day–specific thresholds that incorporated local climatological measures. This enabled us to use EHE frequency as an exposure metric, which may be more relevant than daily mean temperature in the context of climate change.[27] We used a time-stratified case-crossover design with conditional Poisson analysis, as it is more flexible in estimating acute effects associated with short-term exposures. Through self-matching, this study design negated the need to control for individual-level measured and unmeasured time-invariant confounders.[84, 85]

The study had limitations as well. We used a single-day exposure metric; therefore, we did not account for alternative definitions for EHEs, including heat wave, as seen in other work.[24, 74] The consideration of multiple-day heat waves could represent a more severe exposure experience for patients with ESRD, especially given the frequent occurrence of heat waves in the United States. Our exposure metric was dichotomous (ie, presence or absence); thus, it did not account for the intensity of exposure on a continuous scale. In addition, a limitation of this study is the lack of data verifying indoor conditions for patients in our study population. Prior studies have reported that outdoor temperatures correlate well with indoor temperatures, especially during warmer months, in Boston[10] and New York.[67, 68, 108] This suggests that extreme heat measured outdoors can serve as a surrogate for indoor

environments. Another limitation is the spatial heterogeneity in exposure that may exist among the patient's residence, the treating clinic, and the nearest weather station. Built-environment features, such as green[61, 109] and blue spaces[110], and impervious cover[89, 111] can influence local surface temperatures. However, potential exposure misclassification errors that resulted from the use of central weather stations were likely nondifferential in nature, as monitoring stations did not change between the case period and the control periods.[112] This non-differential measurement error, if present, likely attenuated the risk estimates.[113] In this analysis, we did not adjust for time-varying confounders, such as air quality. Another limitation relates to the lack of specific causes for hospital admission and mortality for the study population. Future studies with larger sample sizes are needed to investigate how cause-specific mortality and hospital admission associated with EHEs among patients with ESRD varies by geographic locations, race/ethnicity, socioeconomic status, and comorbidities while accounting for time-varying confounders, such as air pollution.

2.6 Conclusions

Our results showed that EHEs were associated with increased risk of hospital admission or mortality among patients with ESRD and that such risks may vary by city, race/ethnicity, and comorbidity. With the projected increases in frequency, duration, and intensity of extreme weather events, future ESRD management guideline need to incorporate EHEs as part of the adaptation measures to minimize morbidity and mortality among patients with ESRD in a changing climate.

2.7 Tables

Table. Summary Statistics for Patients With End-Stage Renal Disease From 2001 to 2012

Characteristic	No. (%)			
	Boston, Massachusetts	New York, New York	Philadelphia, Pennsylvania	Total
Clinics, No.	4	5	14	23
Patients, No.	1439	2241	3763	7445
Men	868 (60.3)	1260 (56.2)	2155 (57.3)	4283 (57.5)
Age, mean (SD), y	66.5 (14.7)	60.5 (14.2)	59.4 (14.4)	61.1 (14.6)
Race/ethnicity				
Hispanic	61 (4.2)	420 (18.7)	426 (11.3)	907 (12.2)
Non-Hispanic black	220 (16.0)	1418 (63.3)	2558 (68.0)	4196 (56.4)
Non-Hispanic white	1083 (75.2)	208 (9.28)	717 (19.1)	2108 (28.3)
Asian	50 (3.5)	84 (3.7)	50 (1.3)	184 (2.5)
Other	15 (1.0)	18 (0.8)	38 (1.0)	71 (1.0)
Comorbidities				
Congestive heart failure	369 (25.6)	206 (9.2)	364 (9.7)	939 (12.6)
Chronic obstructive pulmonary disease	90 (6.4)	63 (2.8)	134 (3.6)	289 (3.9)
Diabetes	448 (31.1)	635 (28.3)	627 (16.7)	1710 (23.0)
Health outcomes				
Mortality, No. (%)	700 (48.6)	820 (36.6)	1433 (38.1)	2953 (39.7)
Total hospital admissions, No.	8041	11 424	25 476	44 941
Hospital admissions per patient, mean (SD)	5.6 (6.8)	5.1 (6.7)	6.8 (8.2)	6.0 (7.5)
Daily maximum temperature, mean (SD) [range], °C[a]	29.3 (5.7) [7.2-38.9]	25.8 (4.7) [9.0-39.4]	27.6 (4.8) [11.1-40.0]	25.9 (5.6) [7.2-40.0]
Extreme heat events/y, mean (SD)[a]	37.4 (23.1)	14.2 (10.1)	11.9 (6.5)	21.2 (35.6)

[a] May through September.

Table 1. Summary statistics for patients with end-stage renal disease from 2001 to 2012

2.6 Figures

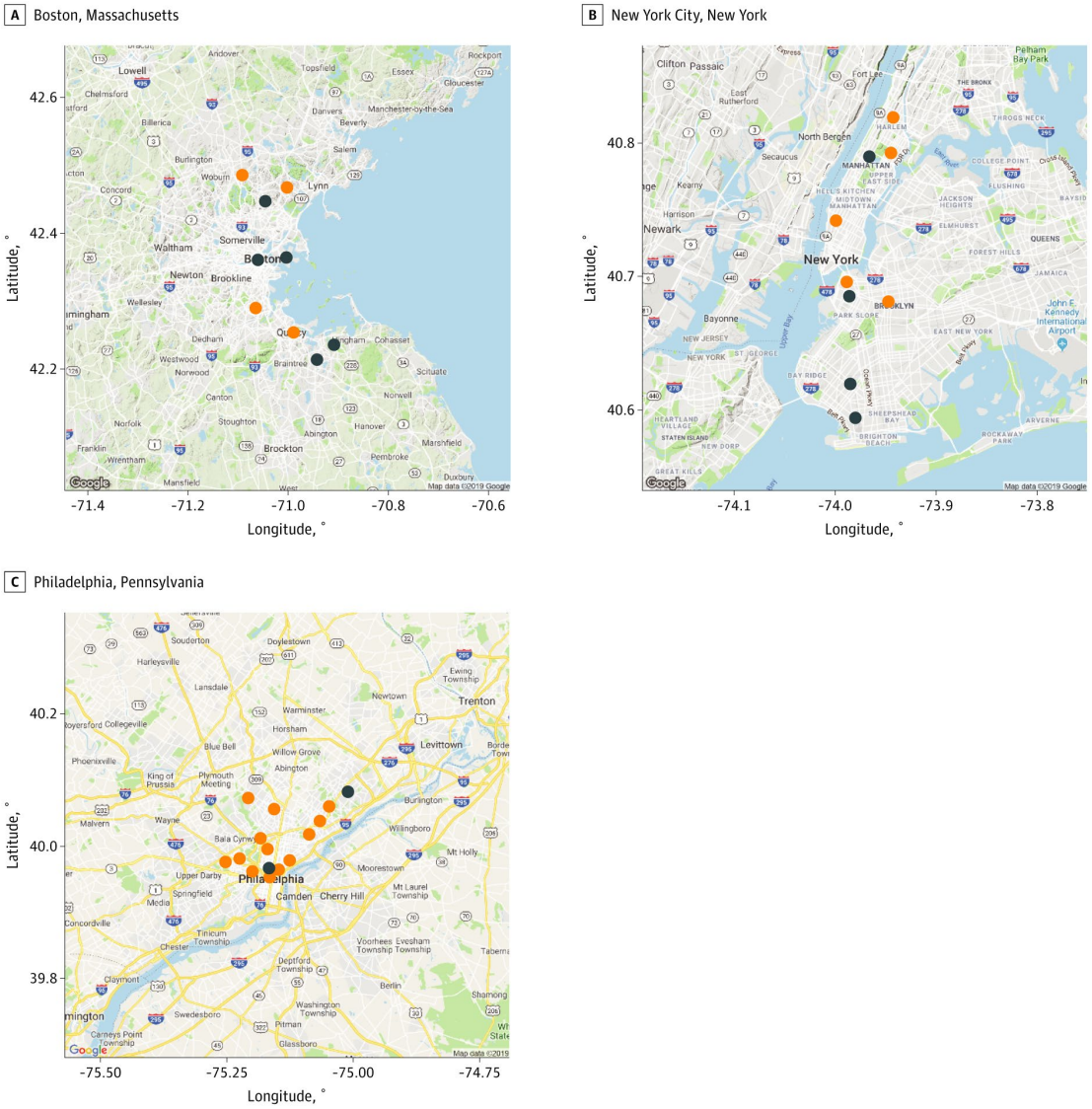
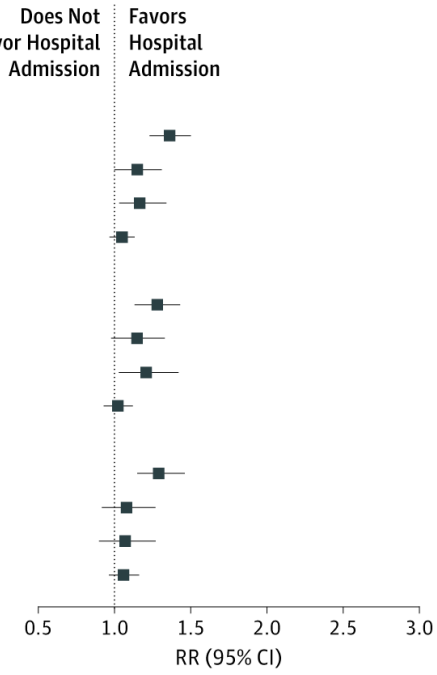


Figure 1. Map of Fresenius Kidney Care hemodialysis clinics and weather stations in Boston, Massachusetts; New York City, New York; and Philadelphia, Pennsylvania

A Hospital admission

City	RR (95% CI)
Cumulative	
All	1.36 (1.23-1.50)
Boston	1.15 (1.00-1.31)
NYC	1.17 (1.03-1.34)
Philadelphia	1.05 (0.97-1.13)
Same day	
All	1.27 (1.13-1.43)
Boston	1.14 (0.98-1.33)
NYC	1.21 (1.03-1.42)
Philadelphia	1.02 (0.93-1.12)
1-Day lag	
All	1.29 (1.15-1.46)
Boston	1.08 (0.92-1.27)
NYC	1.07 (0.90-1.27)
Philadelphia	1.06 (0.96-1.16)



B Mortality

City	RR (95% CI)
Cumulative	
All	1.32 (1.06-1.65)
Boston	1.45 (1.04-2.02)
NYC	1.11 (0.76-1.63)
Philadelphia	1.05 (0.78-1.39)
Same day	
All	1.31 (1.01-1.70)
Boston	1.50 (1.03-2.19)
NYC	1.21 (0.76-1.91)
Philadelphia	1.08 (0.77-1.53)
1-Day lag	
All	1.24 (0.95-1.64)
Boston	1.78 (1.21-2.61)
NYC	1.00 (0.61-1.62)
Philadelphia	0.88 (0.62-1.26)

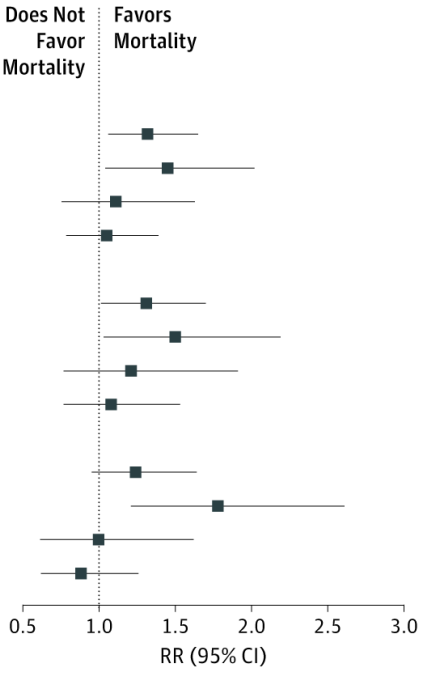
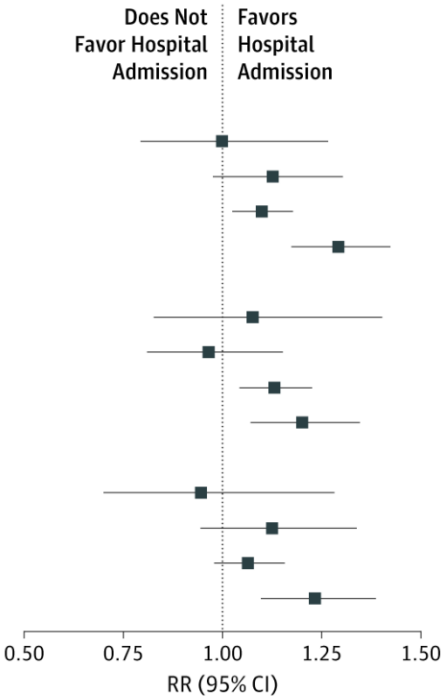


Figure 2. Risk of hospital admission and mortality associated with extreme heat events among patients with end-stage renal disease in Boston, Massachusetts; New York City, New York (NYC); and Philadelphia, Pennsylvania. RR indicates rate ratio.

A Race/ethnicity

Race/Ethnicity	RR (95% CI)
Cumulative	
Asian	1.00 (0.79-1.26)
Hispanic	1.13 (0.97-1.30)
NH white	1.10 (1.02-1.18)
NH black	1.29 (1.17-1.42)
Same day	
Asian	1.07 (0.82-1.40)
Hispanic	0.96 (0.81-1.15)
NH white	1.13 (1.04-1.23)
NH black	1.20 (1.07-1.34)
1-Day lag	
Asian	0.94 (0.70-1.28)
Hispanic	1.12 (0.94-1.34)
NH white	1.06 (0.98-1.16)
NH black	1.23 (1.09-1.39)



B Comorbidities

Comorbidity	RR (95% CI)
Cumulative	
CHF	1.04 (0.88-1.23)
COPD	0.95 (0.76-1.18)
Diabetes	1.12 (0.97-1.29)
Same day	
CHF	1.08 (0.88-1.31)
COPD	0.86 (0.65-1.14)
Diabetes	1.18 (1.00-1.40)
1-Day lag	
CHF	0.97 (0.78-1.20)
COPD	1.01 (0.77-1.32)
Diabetes	1.08 (0.90-1.29)

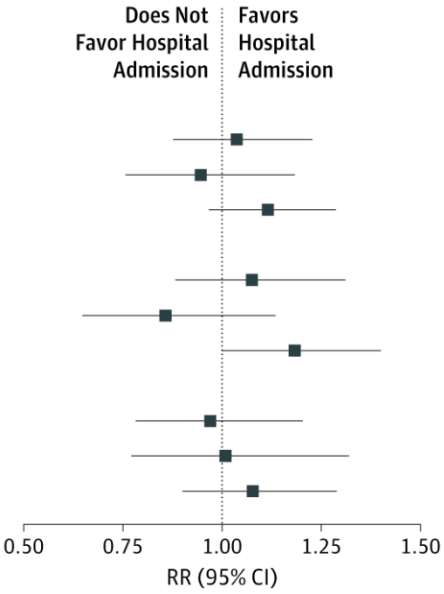


Figure 3. Risk of hospital admission associated with extreme heat events among patients with end-stage renal disease stratified by race/ethnicity and comorbidities. CHF indicates congestive heart failure; COPD, chronic obstructive pulmonary disease; NH, non-Hispanic; and RR, rate ratio.

Chapter 3: Pre-existing comorbidities among end-stage renal disease (ESRD) patients may worsen extreme heat-related risk of death

3.1 Abstract

Background: There is a scientific consensus that the frequency, duration, and intensity of extreme heat events (EHE) will continue to rise in response to ongoing climate change. Such increases in EHEs may disproportionately impact individuals living with end-stage renal disease (ESRD).

Objectives: To quantify EHE-related risk of all-cause mortality and hospital admissions among ESRD patients undergoing hemodialysis (HD) in the northeastern United States and further investigate if this relationship varies by location, race/ethnicity, and pre-existing comorbidity.

Methods: We pooled all-cause hospital admission and all-cause mortality records (2001-2019) for ESRD patients treated at the Fresenius Kidney Care (FKC) facilities from 28 selected Northeastern counties. We used time-stratified case-crossover analyses with conditional Poisson regression models to investigate the association between -term exposure to EHE and the risk of hospitalization and mortality among these patients. We further stratified our analysis by county, race/ethnicity, and comorbidity. As part of a sensitivity analysis, we replicated the work using apparent temperature.

Results: Among 60,717 ESRD patients, we observed 15,711 deaths (25.9%) and 99,464 hospital admissions (mean [SD], 2.95 [3.21] per patient) during the study period. We found increased region-wide mortality risks (rate ratio [RR], 1.07; 95% CI, 1.00-1.13) from extreme heat exposure, which tended to vary by latitude.,

race/ethnicity, and comorbidity. Interquartile range (IQR) cumulative lag (0-1) risk estimates ranged between 0.84-1.23 for mortality and 0.95-1.04 for hospital admission county-level risks. Same-day (Lag 0) mortality was higher among Hispanics (RR, 1.39; 95% CI, 1.28-1.51 and non-Hispanic Black (RR, 1.12; 95% CI, 1.04-1.21) groups. Likewise, ESRD patients with cardiovascular disease (RR, 2.14; 95% CI:1.91-2.40), Diabetes (RR, 1.07; 95% CI:1.00-1.15), and cerebrovascular disease (RR, 1.47; 95% CI:1.26-1.71) as comorbidities had higher risks of EHE related same-day mortality. Risks mostly dampened after 1 day except for ESRD patients with cerebrovascular diseases. Hospital admission risk by latitude and race/ethnicity displayed mostly non-significant null associations. A sensitivity analysis using apparent temperature did not change the overall findings.

Conclusion: Our results presented evidence of modification by location, race/ethnicity, and comorbidity with short-term EHE and all-cause mortality. This occurrence was most evident during same-day EHE exposures and particularly among ESRD patients with pre-existing comorbidities. Heterogeneity in magnitude and precision were commonplace. Future heat management and adaptation protocols for ESRD patients need to consider geographic and socio-demographic differences and the enhanced susceptibilities from living with additional comorbidities.

3.2 Introduction

Exposure to extreme heat events (EHE) has been linked with increased mortality and hospitalization risks.[61-63, 114, 115] Based on empirical evidence, other studies have suggested that projected increases in EHE frequency related to climate change will pose a substantive public health threat. [116] Such threats may vary considerably across geographic regions and population subgroups. For example, urban communities are often disproportionately exposed to extreme heat due to increased surface temperature related to urban heat island effects.[117] A recent observation found a higher mean number of National Weather Services (NWS) heat alerts per year among sampled United States (US) cities in the northeastern region compared to other US regions. [118]

Additionally, social determinants of health rooted in underlying income inequality, healthcare access, age, and racial composition can also enhance vulnerability to extreme heat exposure.[61, 101, 104, 117] Others have shown that lower-income, older adults, and communities of color often experience higher risk despite the availability of localized heat action plans. [119] These lines of evidence suggest that, in addition to spatial heterogeneity in exposure, heat-related health impacts may be influenced by individual-level characteristics that can also include pre-existing chronic health conditions.

End-stage renal disease (ESRD) patients undergoing hemodialysis represent a medically-fragile population that is highly vulnerable to extreme heat. ESRD is the

most critical stage of chronic kidney disease (CKD) characterized by lowered estimated glomerular filtration rate (eGFR; <15 ml/min/1.73m^2) and elevated protein in the urine (albumin to creatinine ratio [ACR]; >300 mg/g).[28, 29] ESRD patients must undergo renal replacement therapy due to their lack of renal function to filter and remove toxic wastes from the body. Hemodialysis is a typical modality treatment, provided 2-3 times/week, and requires in-person clinical visits. Prior epidemiological studies have shown an increased risk of hospitalization and mortality among older adults from renal-related symptoms such as kidney failure and fluid and electrolyte imbalances due to increased temperatures.[24, 25]. As such, projected increases in the frequency of extreme heat related to climate change can disproportionately impact ESRD patients. [42, 43] Despite this, there is a lack of data regarding whether EHE-related risk of hospitalization and mortality may vary across individual-level characteristics and geographic areas or how other concomitant environmental exposures may modify such risk.

Using data from three cities, we have previously documented how heat-related mortality and hospital admission rates among the ESRD population may vary by race/ethnicity or pre-existing comorbidities.[56] In this follow-up study, we build on our previous findings by expanding the catchment area to include multiple locations within the United States' northeastern region where heat hazards are projected to worsen. [120-122]

3.3 Methods

3.3.1 Study Population

Using electronic health records, we generated an open cohort of ESRD patients receiving hemodialysis treatment at Fresenius Kidney Care (FKC) facilities between 2001 and 2019. The Renal Research Institute (RRI), a wholly-owned subsidiary of FKC, provided access to patients' limited, longitudinal health records. The study sampled FKC clinics serving northeastern US counties and their patients from the District of Columbia to Maine (**Supplemental Figure 1**). As part of the study's exclusion criteria, patients with less than 20 treatment visits at any given location were restricted. In total, 60,717 FMC patients from 115 clinics were considered eligible for analysis. Relevant patient information included limited time-invariant data related to medical history, socio-demographics, and ZIP codes of home HD clinics. As the study entailed using de-identified information, it was deemed exempt by the University of Maryland Institutional Review Board (IRB).

3.3.2 Outcomes Assessment

Our analysis focused on all-cause mortality and all-cause hospital admissions. Health endpoints were aggregated into daily and county-level events. Several studies, including prior work, have reliably used *all-cause* as a broad outcome category to maintain a sufficient sample size for analysis. [56, 123, 124] Its use also curbs concerns for outcome misclassification biases stemming from inaccurate reporting commonly found with cause-specific diagnostic codes.[125] Overall, mortality and hospital admission events are tracked through billing and payment operations and

Centers for Medicare & Medicaid (CMS) reporting. For billing purposes, hospitalization documentation is considered to be accurate. Like hospitalization, data on deaths occurring outside of FMC clinics (e.g., unaffiliated hospitals. emergency rooms, at home) are required for billing requirements and entered into the patient's FMC electronic health records. All-cause mortality records are considered accurate for CMS reporting as well.

3.3.3 Exposure Assessment

We used county-level daily extreme heat events as an exposure metric. Details for computing extreme heat events have been previously described elsewhere.[19, 27] In brief, we used 30 years (1960-1989) of daily meteorological data on maximum temperatures obtained from the National Oceanic and Atmosphere Agency (NOAA) to calculate single calendar-days and location-specific 95th percentile thresholds. [126] The daily maximum temperature for each county and study period were compared to their respective calendar day– and country-specific thresholds and categorized as an 'extreme heat event' if the value exceeded the upper 95th percentile threshold. County-level EHE data were matched to the health outcome dataset based on patient clinic ZIP code. Consistent with previous work, unconstrained same-day (lag 0), 1-day lag (lag 1), and cumulative same-day and 1-day lag (lag 0-1) exposures were used to capture inter-dialytic EHE effects between dialysis treatments.

3.3.4 Statistical Analyses

We applied a time-stratified case-crossover study design to investigate the association between exposure to EHE and mortality/hospital admission outcomes

among ESRD patients. Case-crossover methods are consistently used in epidemiological analyses involving acute exposure and defined event-based outcomes. [127] The study design is an advanced case-control design that compares cases through self-matching. [113] Each case serves as its own control during 'hazardous' and 'referent' periods. Typically, risk exposures during a hazardous period are compared to risk exposures during a referent period. Conditional Poisson regression (CPR) is employed to determine the health effects of acute environmental exposures.[87] CPR is conditioned on the number of outcome events in stratum indictors. [87, 127] Depending on the data structure, strata indicators are based on the combination of year, month, and day of the week. [56, 87] For each sampled county, we considered unconstrainted same-day (Lag 0), one-day lag (Lag 1), and cumulative exposures (Lag 0-1) during warmer calendar months (May-September [MJJAS]) to assess the effect of acute EHE exposure. We pooled all county-level data and applied strata indicators that include specific counties into CPR models for the region-wide analysis. We used a Wald χ^2 test to determine statistical significance for EHE exposure at a significance level of 0.05.

To further investigate the heterogeneity in risk across socio-demographic factors, we stratified our analysis by extracting race/ethnicity (Asian, Hispanic, non-Hispanic Black, non-Hispanic White, and Other/Not Reported) and pre-existing comorbidities (cerebrovascular, congestive heart failure (CHF), chronic obstructive pulmonary disease (COPD), diabetes, ischemic heart disease, and myocardial infarction) information from FKC medical records. The International Classification of Diseases (ICD) codes used to categorize selected comorbidities are based on in-house

standardized guidance for data extraction. We estimated extreme heat effects using strata related to year, month, day of the week, and county. All analyses were conducted using R statistical software version 3.6.1 [128] with the *gnm* [129] and *dplyr* [130] packages.

3.3.5 Sensitivity Analysis

To simultaneously account for temperature and humidity, we performed a sensitivity analysis using observed daily apparent temperature measurements. Heat perception can be exacerbated due to higher relative humidity at warmer temperatures. Therefore, including a hybridized measure like apparent temperature is considered a useful predictor of heat stress for environmental health and epidemiology research. [131, 132] We calculated daily apparent temperature based on a widely adopted algorithm from the US National Weather Service [133, 134] using the R package *weathermetrics* [135]. Replicating a similar EHE-metric approach for apparent temperature is not achievable since daily historic data from 1960-1989 for relative humidity and dew point were not readily available. These analyses are presented in detail in **Supplemental Figures S3-1 and S3-2, and Tables S3-2 to S3-8**.

3.4 Results

Demographic characteristics of the study population, along with mortality and hospital admissions summaries stratified by EHE, are depicted in **Table 1**. Of the 60,717 sampled patients (39.5% non-Hispanic Black and 39.9% non-Hispanic White), the crude mortality rate during MJJAS months of the observation period was

1744 deaths per 100,000 population with ESRD. On average, FKC patients experienced approximately three hospital admissions. The majority of our study population reported having diabetes (60.0%), followed by CVD (1.3%), and CHF (0.8%). On average, we observed 10.3 EHEs per annual season (MJJAS) across sampled counties during the study period. Total annual EHEs varied across counties, as seen in **Supplemental Figure 2,** with 2010 as the highest peak for several counties. Interestingly, Wicomico (10.8%), New Haven (8.7%), and Erie (8.4%) counties exhibited the highest mean monthly EHE rates shown in **Supplemental Table S1**. The daily mean apparent temperature ranged from 5.5 °C to 45.0 °C across counties. Overall daily mean apparent temperature for EHE-only days was 28.9 C.

Pooled regional estimates from all counties (**Table 3**) suggest increased risk of mortality for same-day (rate ratio [RR], 1.07; 95% CI, 1.00-1.13) and cumulative lag (RR, 1.02; 95% CI, 0.94-1.09) EHE exposures. Overall hospitalization suggested a weaker association with the same-day EHE exposure (RR, 1.01, 95% CI: 0.98-1.03). The county-specific analysis for mortality and hospitalization is depicted **in Figures 1 & 2**, respectively, arranged by decreasing latitude. Mortality (**Figure 1**) and hospital admissions (**Figure 2**) varied in direction and effect size from north to south. County-level cumulative lag (0-1) risk estimates, based on interquartile range from county estimates, ranged between 0.84-1.23 for mortality and 0.95-1.04 for hospital admission risks. Approximately 57% and 41% of studied counties exhibited positive associations based on cumulative EHE exposures for mortality and hospital admission outcomes, respectively. Due to data sparseness from tabulating mortality events occurring during EHEs, Caledonia, Erie, Kennebec, and Union counties were

not included for EHE-mortality analyses resulting in 23 studied counties. Sensitivity analyses performed using apparent temperature did not substantially change the overall findings for the pooled analysis (**Table S3-2**) as well as county-specific analysis for mortality (**Table S3-3)** and hospitalization (**Table S3-4)**.

When we stratified the analysis by race/ethnicity (**Figure 3**), we observed associations between EHE and same-day (Lag 0) mortality among Hispanics (RR, 1.40; 95% CI, 1.29-1.51) and non-Hispanic Blacks (RR, 1.12; 95% CI, 1.04-1.21). Though, EHE exposure from the prior day (Lag 1) appeared to have a protective effect among Hispanic patients (RR, 0.65; 95% CI, 0.59-0.71). Asian subgroup was not included in mortality analyses due to under-sampled cases (< 5) during Lag 0 and Lag 1 EHE events. With hospital admissions (**Figure 4**), Lag 0 exposure to EHE was associated with increased risk among Asian patients. However, prior day exposure was associated with decreased risk among Asians and Hispanics. Our sensitivity analysis (**Table S3-5**) showed that a 5°C increase in apparent temperature increased same-day mortality risk among Asian (RR, 1.42; 95% CI, 1.36-1.49) and Hispanic (RR, 1.46; 95% CI, 1.41-1.52) subgroups. Consistent with EHE effects, the increase in apparent temperature was not significantly associated with hospital admissions (**Table S3-6**).

To further investigate the effect of extreme heat exposure on ESRD patients with pre-existing comorbidities, we stratified our analysis by comorbidity status (Diabetes, congestive heart failure (CHF), Cerebrovascular, ischemic heart disease (IHD), Any CVD, and Any comorbidity). Exposure to EHE was associated with a higher risk of same-day mortality among groups living with IHD (RR, 2.33; 95% CI,

2.08-2.62), CHF (RR, 2.46; 95% CI, 2.14-2.83), cerebrovascular (RR, 1.86; 95% CI, 1.57-2.20), and Any CVD (RR, 2.14; 95% CI, 1.91-2.40) (**Figure 6**). These risks appeared to be attenuated or even protective when considering Lag 1 exposures, with a noted exception for cerebrovascular diseases. Patients living with IHD (RR, 1.15; 95% CI, 1.05-1.27) and cerebrovascular disease (RR, 1.27; 95% CI, 1.12-1.46) diseases shown higher hospitalization risks associated with cumulative lag EHEs. Sensitivity analysis performed using apparent temperature agreed with overall findings for mortality (**Table S3-7**) and hospital admissions (**Table S3-8**) in terms of directionality and precision except for Lag 1 EHE effects for cerebrovascular mortality.

3.5 Discussion

Prior studies have linked exposure to extreme heat events with a range of adverse health outcomes within the general population. Still, only a few studies have investigated how it may impact populations that live with chronic kidney diseases, especially end-stage renal disease. Clinically, people living with ESRD must adhere to restrictive lifestyles and receive, on average, thrice-weekly life-saving dialysis treatments. This highly regimented quality of life (e.g., limited water volume consumption) poses unique coping challenges and health risks with extreme heat, unlike relatively healthier individuals. Our findings showed that same-day and two-day cumulative EHE exposures might increase mortality risk among this vulnerable population in the NE region. Region-wide risk estimates observed in this study were reduced compared to prior work, which focused on three cities from the same region (Boston, MA; Philadelphia, PA; and New York City, NY). [56] In the same previous

EHE-ESRD study, city-specific findings demonstrated significantly increased mortality and hospitalization risks at Boston and New York clinics. The inclusion of additional counties from lower latitude and its extended study period (2001-2019) may partially explain this attenuation. It is important to note that mortality risks in studied Boston (Suffolk and Norfolk), New York City (Bronx, Kings, and New York), and Philadelphia counties displayed some agreement from our earlier work. Also, we note that our catchment region was not exclusive to major metropolitan hubs. Peri-urban and suburban locations were included in our regional analysis. Visually, we observed a varied risk gradient across latitudes. As expected, we did observe location-specific variability in EHE responses, as observed in other studies when using the EHE metric and heat index.[27, 118, 136, 137] Most northern counties in Vermont, Maine, and New Hampshire exhibited significantly higher mortality magnitudes from 5°C increases in apparent temperature.

Subgroup analyses for race/ethnicity EHE effects suggested increased mortality and hospitalization risks for same-day EHE exposures but attenuation after one-day EHE events. Hispanic and NH-Black patients appear to have the highest risk of death, and evidence from our prior study corroborates this observation. Unfortunately, similar to our previous study, Asian patients were excluded from mortality analysis due to sample size-limited deaths during lag0 and lag1 EHEs. However, risk detection in hospital admissions indicates null rate changes, except for Asian patients, from same-day EHE. This lack of effect on hospital admission risk requires further investigation. The higher frequency in scheduled clinical visits for HD treatments and more dedicated medical attention may have to do with staving off

potential complications associated with elevated medical care mitigated during dialysis.

Overall, we found heterogeneity in risk, particularly among patients with pre-existing comorbidities. All comorbidity categories showed increased mortality risks from EHEs among ESRD patients. According to the United States Renal Disease Data System (USRDS), among sampled Medicare patients over 65 years of age, 6.7% of patients living with a chronic renal disease also live with at least one comorbidity. [138] Whereas 5.0% of sampled Medicare patients with chronic renal conditions also lived with at least two comorbidities. [138] Our study found that virtually all comorbidities potentiated the EHE related same day mortality risks among ESRD patients. The same observation applied to cumulative lag 0-1 EHE exposures associated with all-cause mortality. Notably, cardiovascular and cerebrovascular comorbidities yielded the largest observed effect sizes for all-cause mortality and all-cause hospital admissions. This may be related to a lower blood pressure, which is a typical physiological response to increasing ambient temperature among individuals irrespective of cardiovascular health status.[40, 41] Prior studies have suggested that sudden changes in blood pressure and lowered blood pressure can compromise survival advantage and increase the risk of premature deaths among ESRD patients. [33-35] We found that same-day heat effects could exacerbate death risk among ESRD patients living with any CVD. Secondly, the connection between cerebrovascular and ESRD to heat-related effects seem highly plausible, given that common heat-related illness such as heat stroke and heat exhaustion involve cerebral ischemia.[139, 140] This is consistent with a recent study from China demonstrating

consistent increased cerebrovascular-related mortality risk across five major cities when considering a cumulative lag period from 0-2 days. [141] In all, our results point to higher vulnerability for populations living with chronic renal conditions and additional comorbidities.

National Weather Service (NWS) heat advisories and alerts typically involve apparent temperature (heat index) and not climate-based extreme heat metrics. [142] Using apparent temperature as a continuous parameter instead of categorized EHE exposures in our sensitivity analysis revealed some general consistency with our main analysis. Discretized exposure data like the dichotomized EHE metric can encounter data sparseness and result in subgroup exclusions as seen with all-cause mortality models (e.g., Caledonia and Kennebec Counties, COPD, and Asian subgroups). Thus, a modified EHE metric based on a continuous apparent temperature scale would help contextualize findings to NWS heat advisories and alerts in future work.

3.5.1 Strengths and Limitations

This study enjoyed some notable strengths. Health endpoint data were highly accurate and thorough. Another major strength was the use of the case-crossover design as part of our analytic approach. As many studies have highlighted, this method has added advantages in eliminating measured and unmeasured time-invariant individual-level confounders since individuals provide their own exposure and control periods through self-matching. [83-85] Furthermore, the inclusion of additional comorbidities gave us an enhanced appreciation of the composition of the ESRD population and the increased vulnerability of ESRD patients living with other

vascular-related comorbidities. Finally, our sensitivity analysis suggests relative agreement regarding consistency and directionality between the EHE metric and apparent temperature as heat exposures.

Our study also had several limitations. We applied county-level aggregations for exposure-response models. Clinic ZIP codes were only provided as location-based identifiers. Therefore, we assumed that patients resided within, or near, the same county of their HD clinic. For the EHE metric, despite considered delayed effects, we exclusively studied single-day exposures. Heat waves that last beyond a single day is a primary contributor to heat-related illnesses and mortality. Also, it is crucial to consider moderate heat exposures, not just extreme measures. In recent work from Weinberger and colleagues, the burden of disease from moderate heat was greater than extreme heat. [94] This could be remedied by considering decreased upper percentiles thresholds for baselines when using the EHE metric. Next, our work did not use cause-specific outcomes due to concerns with drastically reduced sample size after subsetting for more-defined causes. Studying specified causes would be an essential follow-up extension in a more extensively scaled study similar to studies using Medicare-Medicaid medical records. [24, 123] Finally, we should note that these results may not be generalizable to the target population in other counties or regions within the United States. As an example, we observed a lower prevalence of ESRD patients with CVD within the study population (1.6%). According to the most recent United States Renal Data System (USRDS) Annual Report [30], the prevalence of CVD in 2018 was estimated at 76.5% in patients receiving hemodialysis. This

discrepancy might be attributed to potential reporting and misclassification errors from data pulling.

3.6 Conclusions

In a regional study consisting of 28 counties, we found increased mortality and hospitalization risks from extreme heat exposure among ESRD patients. Though, risks between locations did vary across latitudes, even among neighboring counties. ESRD patients diagnosed with additional comorbidities appear to have increased risk from EHE exposures. A sensitivity analysis using heat index for heat advisories and alert confirms EHE effects. This information will help develop future heat management protocols using a multi-hazard framework that incorporate location-specific and individual-specific characteristics among ESRD patients. Though, comorbidity as an individual-level determinant is a critical characteristic for protection from EHEs.

3.7 Tables

Characteristics	
Counties, n	28
Clinics, n	115
Patients, n	60,717
Race/Ethnicity, n (%)	
Hispanic	4,719 (7.8)
non-Hispanic Black	24,006 (39.5)
non-Hispanic White	24,211 (39.9)
Asian	934 (1.5)
Other/Not Reported	577 (1.0)
Comorbidities, n (%)	
Any	36,932 (60.8)
Any CVD	763 (1.3)
Cerebrovascular	154 (0.3)
CHF	502 (0.8)
COPD	112 (0.2)
Diabetes	36,446 (60.0)
IHD	433 (0.7)
Sex	
Men, n (%)	35,152 (57.9)
Environmental exposures, mean (SD)	
Mean daily maximum temperature, °C	25.6 (5.3)
EHE annual rate by county, EHE/year/county	9.8 (6.3)
Mean daily apparent temperature, °C	20.7 (5.5)

Table 1. Summary statistics for ESRD study population and exposure data from 2001 to 2019

	All	EHE	non-EHE
Mortality, n (%)	15,711 (25.9)	1,059 (1.7)	14,652 (24.1)
Hospital admissions, n	99,464	6,428	93,036
Hospital admission rate, #/person, mean (SD)	2.95 (3.21)	1.19 (0.51)	3.29 (3.39)
Mean air temperature, mean (SD) [range], °C	25.6 (5.3) [4.4-42.2]	32.5 (3.1) [16.1-42.2]	25.1 (5.1) [4.4-40.0]
Mean daily apparent temperature, mean (SD) [range], °C	20.7 (5.5) [3-45]	27.9 (4.5) [10-45]	20.2 (5.2) [3-38]

Table 2. Summary for health outcomes and exposure data from 2001 to 2019 stratified by extreme heat events during May to September (MJJAS) months

	All-cause mortality		All-cause hospital admissions	
	RR	95% CI	RR	95% CI
Lag 0	1.07	1.00-1.13	1.01	0.98-1.03
Lag 1	0.96	0.90-1.02	0.98	0.96-1.01
Cumulative Lag 0-1	1.02	0.94-1.09	0.99	0.96-1.02

Table 3. Pooled rate ratio (RR) and 95% confidence interval of mortality and hospital admissions across the northeastern region comparing EHE events to non-EHE events

3.8 Figures

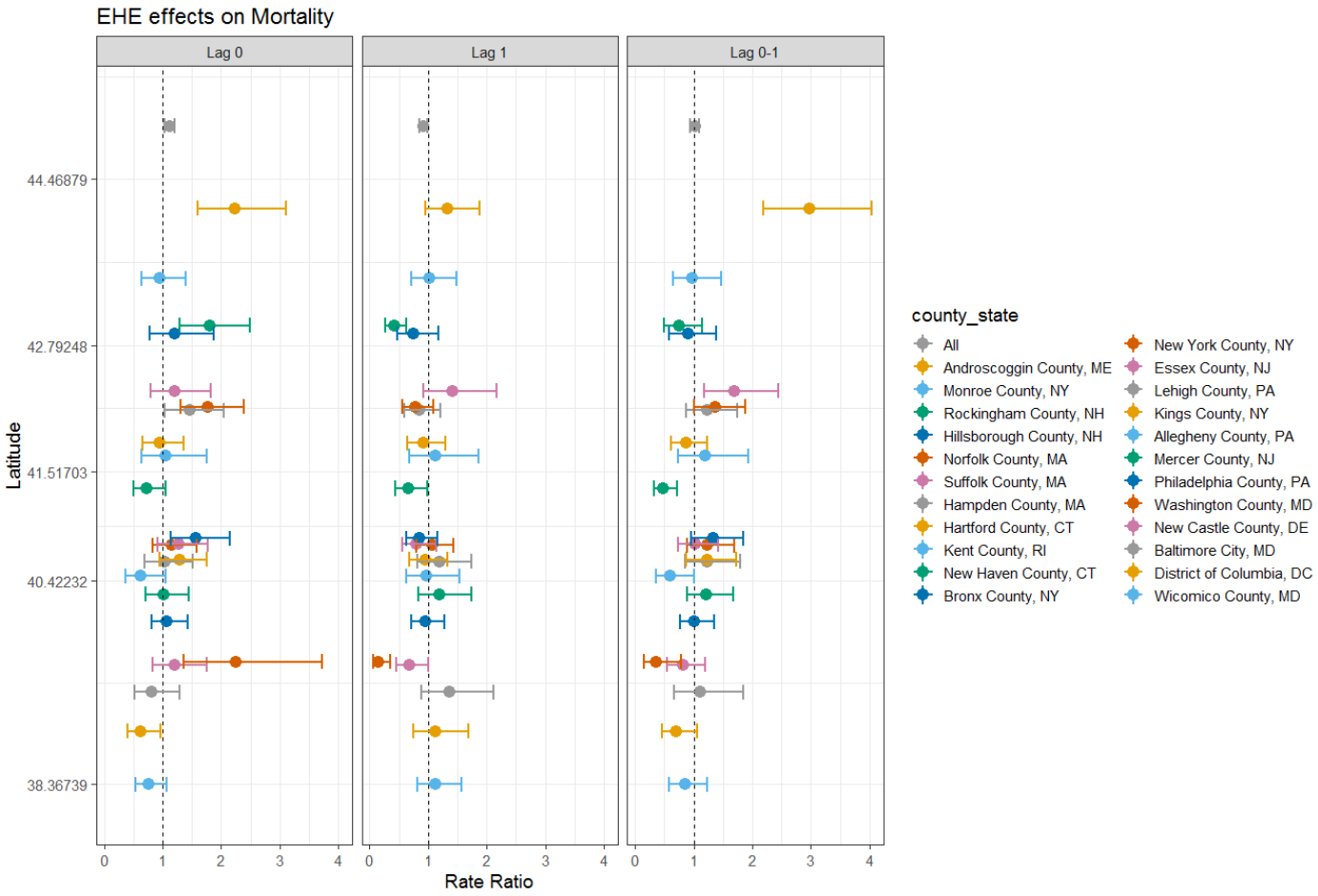


Figure 1. Forest plot of mortality risks across counties and lagged EHE exposures; Lag 0 (same-day), Lag 1 (one-day lag), and cumulative lag (Lag 0-1)

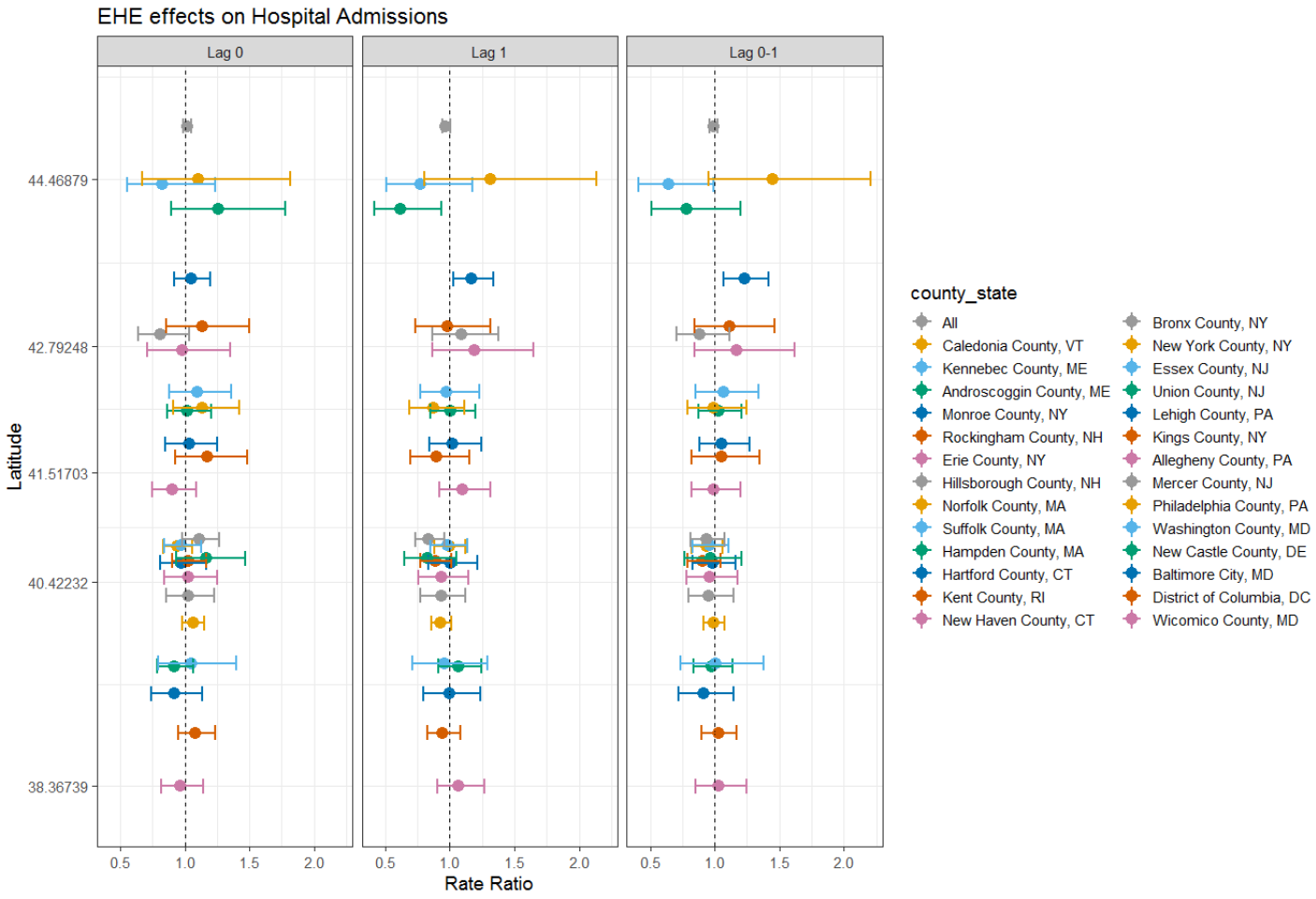


Figure 2. Forest plot of hospital admission risks across counties and lagged EHE; Lag 0 (same-day), Lag 1 (one-day lag), and cumulative lag (Lag 0-1)

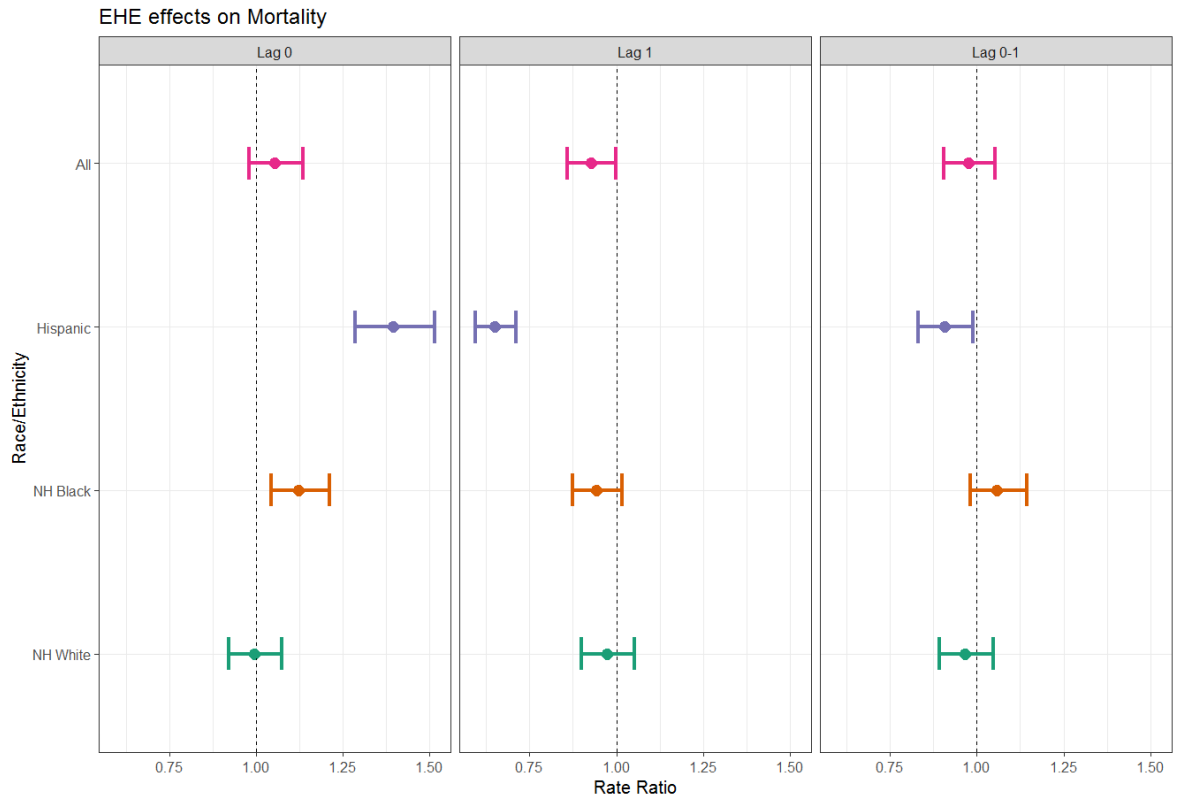


Figure 3. Forest plot of mortality risks for race/ethnicity groups and lagged EHE; Lag 0 (same-day) , Lag 1 (one-day lag), and cumulative lag (Lag 0-1)

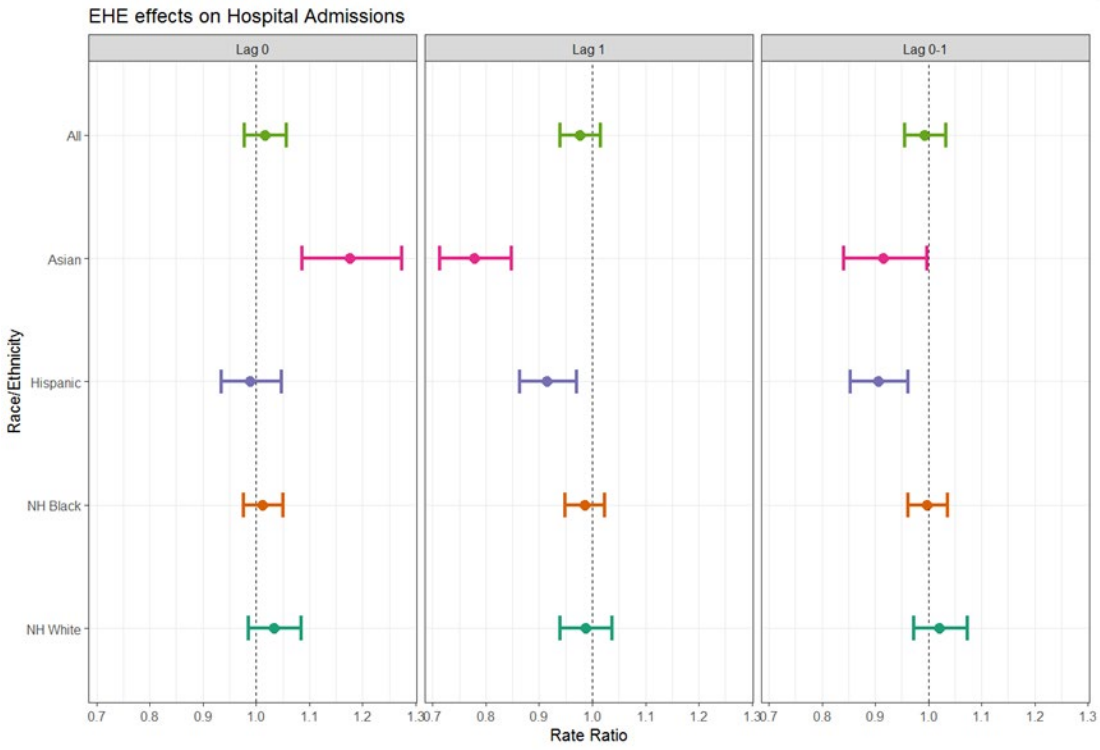


Figure 4. Forest plot of hospital admission risks for race/ethnicity groups and lagged EHE exposures; Lag 0 (same-day), Lag 1 (one-day lag), and cumulative lag (Lag 0-1)

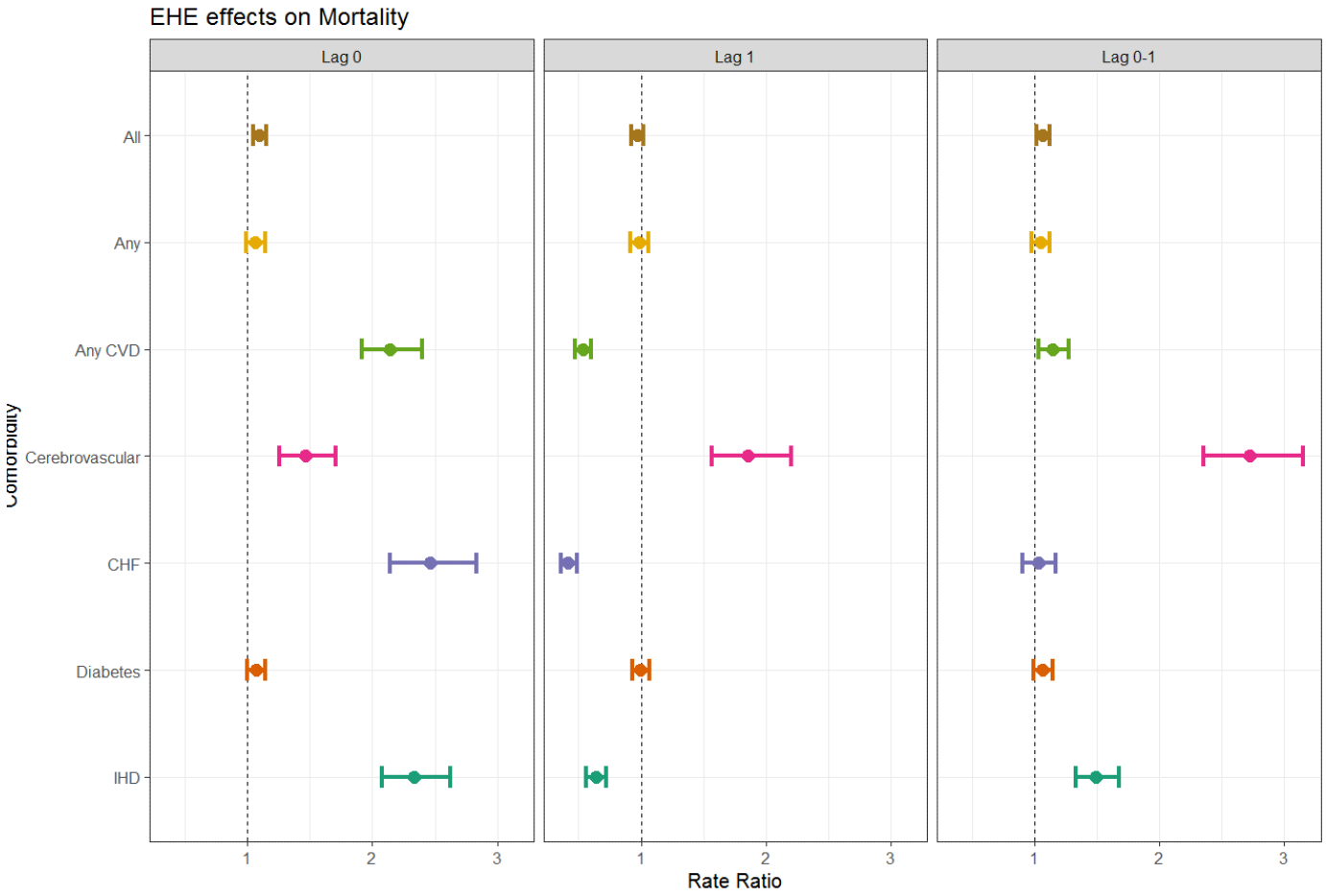


Figure 5. Forest plot of mortality risks for comorbidity groups and lagged EHE exposures; Lag 0 (same-day), Lag 1 (one-day lag), and cumulative lag (Lag 0-1). All category represents all patients within the sample population; Any category represents patients with any studied comorbidity; and Any CVD represents patients with any cardiovascular-related comorbidities like CHF, IHD, and MI.

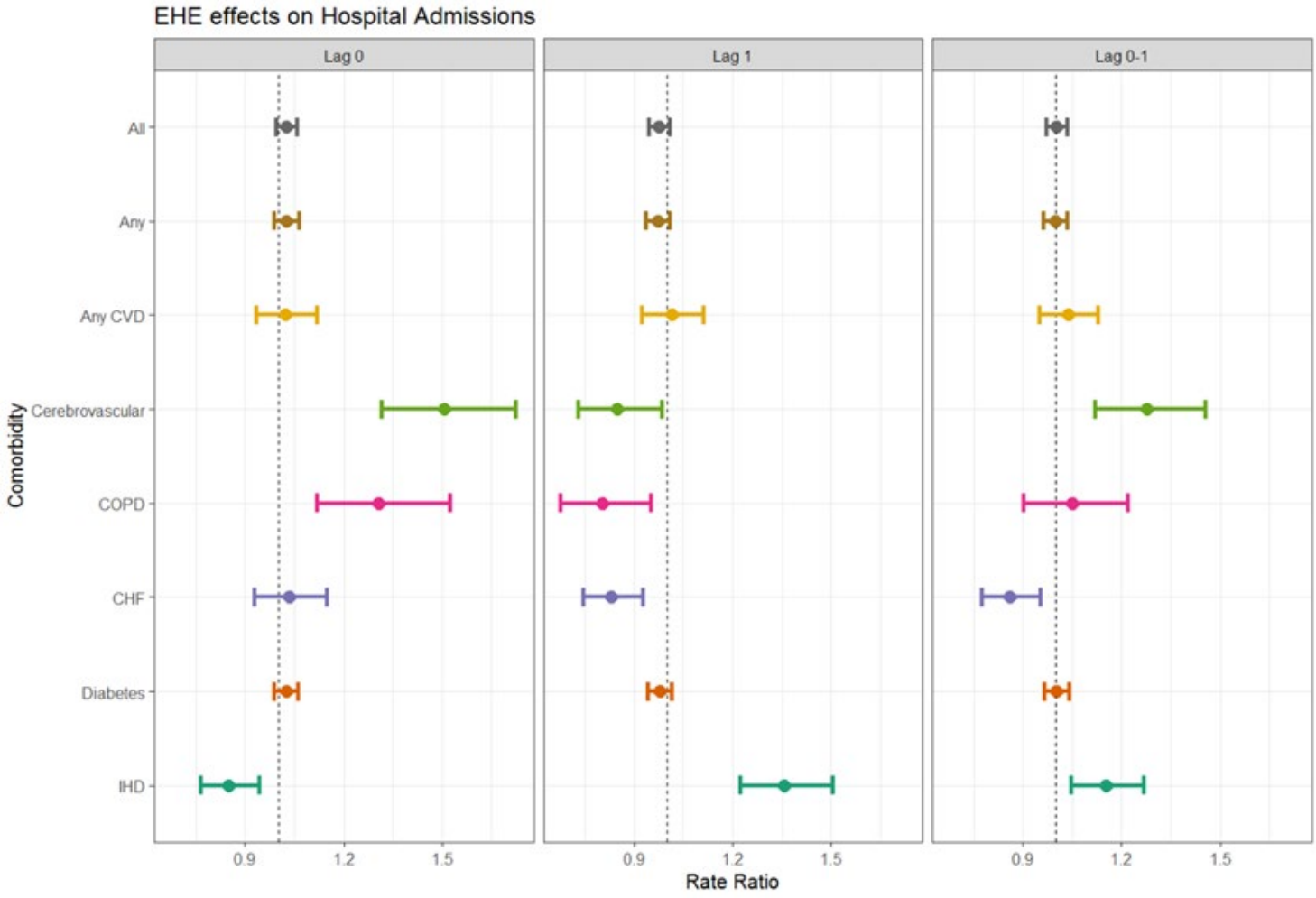


Figure 6. Forest plot of hospital admission risks for comorbidity groups and lagged EHE exposures; Lag 0 (same-day), Lag 1 (one-day lag), and cumulative lag (Lag 0-1). All category represents all patients within the sample population; Any category represents patients with any studied comorbidity; and Any CVD represents patients with any cardiovascular-related comorbidities like CHF, IHD, and MI.

Chapter 4: Cumulative joint effects of air pollution and extreme heat events among ESRD patients

4.1 Abstract

Background: Increasing number of studies have linked air pollution exposure with renal function decline and disease. However, there is a paucity of data on its impact among end-stage renal disease (ESRD) patients, and how extreme heat events may modify the exposure-outcome relationship.

Objectives: To investigate the main effects of daily $PM_{2.5}$ and O_3 after adjusting for extreme heat events (EHE) on all-cause mortality (ACM) and all-cause hospital admissions (ACH) outcomes among ESRD patients undergoing hemodialysis (HD) in the northeastern United States region. Also, to investigate the modifying effects of EHE on the association between air pollutants and ACM or ACHA.

Methods: Fresenius Kidney Care (FKC) records from 28 selected northeastern counties were used to pool daily ACM and ACHA counts. Daily ambient $PM_{2.5}$ and ozone were estimated for selected northeastern counties using a high-resolution spatiotemporal coupled model. We used time-stratified case-crossover analyses to characterize acute EHE exposures using individual and cumulative lag structures for up to 3 days (Lag 0-3). A distributed lag non-linear model (DLNM) framework was applied in non-stratified and EHE-stratified analyses. We used a nested model comparison test to assess the goodness-of-fit of models by including interaction terms to evaluate for interaction effects.

Results: From 2001 to 2016, the sample population consisted of 43,338 ESRD patients and yielded 5,217 deaths (10.8%) and 78,433 hospital admissions (mean [SD], 2.89 [3.08] per patient). A 10-unit increase in $PM_{2.5}$ concentration was associated with a 5% increase in ACM (rate ratio [RR_{Lag0-3}], 1.05; 95% CI, 1.00-1.10) and same-day (Lag0) O_3 (RR_{Lag0}, 1.02; 95% CI, 1.01-1.03) after adjusting for extreme heat exposures. Our data suggest that EHE modifies the association between ground-level ozone exposures and mortality. Exceedance of ozone national ambient air quality standard (NAAQS) in the prior 3 days (Lag 0-3) was associated with a 29% increase in ACM (RR_{Lag0-3}, 1.29; 95% CI, 1.00-1.66) during EHE days. Alternatively, O_3 NAAQS exceedance-related risk was attenuated in non-EHE days (RR_{Lag0-3}, 1.04; 95% CI, 0.97-1.12). Statistical model improvements from including interaction terms between cumulative effects of air pollutants and EHE were observed for Lag 0-3 $PM_{2.5}$ ($p=0.004$) and Lag 0-3 ozone ($p=0.004$) ACM models. No effect modification by EHE was observed for acute air pollutant exposures and ACHA.

Conclusion: Our study shows that short-term exposure to $PM_{2.5}$ and O_3 for up to 3 days is associated with increased ACM risk and negligible risk of ACHA among ESRD patients. Also, preliminary evidence points to potential effect modification from extreme heat events though further analysis is required. Public health implications could also broaden regulatory action for increased air quality mitigation and human health protections that consider the ESRD population a sensitive population.

4.2 Introduction

Prevalence of chronic kidney disease (CKD) and end-stage renal disease (ESRD), which represents the final stage of CKD, are increasing across the globe. [30, 143] The ESRD population is considered to be particularly vulnerable to environmental risk factors. [56, 123, 144] While previous studies have shown that exposure to air pollutants such as $PM_{2.5}$ (particulate matter with less than 2.5 microns in aerodynamic diameter) and ground-level ozone (O_3) can increase the risk of all-cause mortality, hospital admissions, and emergency room visits within the general population [54, 145-147], its impact on ESRD patients remains largely under-studied. Physiologically, exposure to $PM_{2.5}$ is associated with vascular changes that can increase blood pressure. [46, 48, 49] This response can trigger acute arterial vasoconstriction, decrease renal blood flow, and, ultimately, decrease estimated glomerular flow (eGFR) and increase albumin-creatine ratios. [47] Inflammatory mediators induced by airborne particulate matter and other contaminants in the lungs impact the circulatory system, resulting in systemic inflammation, oxidative stress, and damage to distal organs that include the kidneys. [50, 148-151] These responses can ultimately result in adverse renal-related vascular pathologies like impaired function and severe renal tubular necrosis.[51, 52] Such mechanisms, in addition to preexisting comorbidities and lifestyle risk factors, are linked to the development of chronic kidney disease (CKD) and end-stage renal disease (ESRD)- the most severe stage of CKD. [39] According to recent reporting by the United States Renal Data System (USRDS), the prevalence of CKD risk factors and ESRD is rising in the US. [30]

An increasing number of studies have linked exposure to air pollution with elevated CKD incidence and CKD progression to ESRD. [45, 46, 152-155] In the US, the association between air pollution and renal-related mortality was first observed within a mining population in the Appalachian region. [156] Among US veterans [152, 157], increases in particulate matter, nitrogen dioxide, and carbon monoxide, as individual exposures, were associated with eGFR decline- a precursor to developing CKD and ESRD progression. Another study from Taiwan reported a 6% increased risk of developing chronic kidney disease per 10 ug/m3 increase in $PM_{2.5}$. [155] However, there is a lack of data regarding how specific air pollutants can impact ESRD patients' health. To the best of our knowledge, only one air pollution study has focused on the ESRD population by investigating the association between wildfire-related $PM_{2.5}$ levels and all-cause mortality.[158] Though, a separate study showed that extreme heat events could increase the risk of hospitalization and mortality among ESRD patients. [56] Given the potential role of air quality as a health hazard for ESRD patients undergoing hemodialysis (HD) treatment, it is also crucial to characterize the joint effect of acute air pollution and extreme heat among ESRD patients. Recent human health and climate assessment reports suggest that the frequency, duration, and intensity of extreme heat events are increasing and will continue to do so due to a changing climate.[59, 159] In addition to increased tropospheric ozone production during extreme heat events [160], the warmer temperature can contribute to more frequent wildfires driven largely from prolonged drought conditions [53, 161], resulting in degraded regional air quality and adverse health implications.[54]

While there has been a considerable body of work on the interactive effects of air pollution and weather on health, studies on $PM_{2.5}$ and O_3 effects among ESRD patients are scant compared to an already smaller body of work specific for air pollution and renal health. To address this, we investigated the combined role of short-term air pollution ($PM_{2.5}$ and O_3) exposure and extreme heat on all-cause mortality risks (ACM) and all-cause hospital admissions (ACHA) among ESRD patients undergoing hemodialysis at FKC facilities located within the Northeast United States.

4.3 Methods

4.3.1 Study population and outcome measures

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

4.3.2 Exposure assessment

The main exposures of interest are county-level daily average $PM_{2.5}$ concentration, daily 8-hour average O_3 concentrations, and presence/absence of extreme heat events (EHE). We obtained air quality data using model outputs from coupled Climate-Weather Research and Foresting and Community Multiscale Air Quality (CWRF-CMAQ) simulations.[162, 163] Briefly, regional weather-air quality was simulated through regional climate downscaling and chemical-transport atmospheric modeling. Detailed information on the modeling can be found elsewhere. [35,36] The CWRF-CMAQ model simulated hourly concentrations of O_3 and $PM_{2.5}$ at a 30x30 km grid for the Contiguous United States (CONUS). A county map was developed to link modeled grids to CONUS counties. Then, we calculated daily mean $PM_{2.5}$ and daily maximum 8-hour average (MDA8) O_3 concentrations for selected counties with FKC clinics. Averaging times for modeled $PM_{2.5}$ and O_3 estimates are consistent with USEPA National Ambient Air Quality Standards (NAAQS).[164] Additionally, we dichotomized continuous air pollution measures using NAAQS as thresholds (1= NAAQS exceedance, 0= no exceedance): 70 parts per billion by volume [ppbv] for MDA8 O_3) and 35 $\mu g/m^3$ for $PM_{2.5}$. [164]

To identify county-level EHEs, we used location and calendar day-specific 95^{th} percentile temperature thresholds derived using 30 years of baseline temperature data as previously described. [27, 56] EHE is a useful marker for extreme heat events driven by climate change and compatible with event-based health data. Metric development and methodology are described elsewhere.[27]

4.3.3 Statistical analysis

We applied a time-stratified case-crossover design to evaluate the short-term effects of intermittent environmental exposures ($PM_{2.5}$, O_3, and EHE) on event-based daily health endpoints (ACM and ACHA). [18, 19, 56, 61, 97, 165] The methodology has added advantages in eliminating measured and unmeasured time-invariant individual-level confounders, such as age, race, sex, and socioeconomic status [83-85] and temporal confounding, such as seasonality and long-term trends, by design. [85, 166]

We used the conditional Poisson model (CPM) to estimate regional-level air pollutant effects for crude and EHE-adjusted models. The regression model accounts for varying population changes during a study period and accounts for over-dispersion.[87] As part of the self-matching mechanism, strata indicators were included to match by the day of the week, month, year, and county. Air pollution exposures occurring on the day of outcome events (Lag 0) and exposures occurring in days prior to outcomes (Lag1, Lag 2, and Lag3) were examined in additional models. Natural cubic spline functions were applied to O_3 and $PM_{2.5}$ terms.

All analyses were restricted to MJJAS months to emphasize air quality at higher temperatures and adjusted for EHE. Measures of associations were reported as rate ratios (RRs) using 95% confidence intervals (95% CI). The rate ratios for $PM_{2.5}$ and O_3 as continuous variables were expressed as per 10-μg/m3 and 10-ppbv incremental increases. We considered up to a three-day lag period to capture the delayed effects of acute exposures. Overall cumulative lag effects were estimated for 0-3 lag days for continuous and NAAQS-based predictors. We also incorporated

delay effects for EHE up to three days to match temporal consistency with air pollutant exposures. For adjusted models, we matched lag structures from air pollutant parameters to EHE. All analyses were conducted using R statistical software version 3.6.1. [128] Statistical software for CPR and DLNM is available as R packages through CRAN. The *gnm* and *dlnm* packages are peer-reviewed and frequently updated.[129, 167]

4.3.4 Effect modification

This present study tested for the interaction between extreme heat events and air pollution on all-cause hospital admission and all-cause mortality for up to three days after exposure. As an initial analysis to evaluate interaction effects between cumulative lag air pollutants and EHE, we compared DLNM models without interaction terms (reduced) and with interaction terms (full) using goodness-of-fit tests in non-stratified models. Nested models were compared using *F*-tests. The addition of interaction terms between crossbasis terms that represent cumulative-based exposures over lags of 0-3 days and cumulative-based EHE exposures over lags of 0-1 days was mostly used to determine model improvement and serve as an indirect model specification test for interaction effects. [168, 169] Results from the stratification analysis mentioned above can help substantiate inferred interaction effects.

In addition to conducting crude and EHE-adjusted analyses for daily $PM_{2.5}$ and ozone exposures, we conducted EHE-stratified analysis using the same health endpoints and cumulative lagged effect to estimate risks. Prior research focusing on

acute air pollution effects has successfully used subgroup analysis (e.g., EHE vs. non-EHE) for effect modification analyses using a distributed non-linear lag model (DLNM) framework. [169-171] This approach can estimate a cumulative net effect along defined lag periods in addition to individual lags. [172, 173] In this work, we adapted the case-crossover analysis and applied DLNM to estimate cumulative lag effects in EHE-stratified models. Similar to adjusted EHE models, lag structure periods for air pollutant exposures were also applied to the EHE variable. For example, for calculating estimates based on cumulative Lag 0-2 exposure for $PM_{2.5}$, individual Lag 0, Lag 1, and Lag 2 EHEs were used for stratification. We specified natural cubic B-splines and B-splines for nonlinear air pollutant and lag models fits, respectively, to create cross-basis matrices in our exposure-lag-response models.

4.4 Results

Among 48,338 eligible FKC patients in 28 selected counties within the northeastern US region (**Figure 1**), there were 5,217 deaths and 78,433 hospital visits from 2001-2016 during MJJAS months. **Table 1** did show that 60% of the patients reported having diabetes. There were near equal proportions of non-Hispanic Black (43.4%) and non-Hispanic White (42.2%). Daily $PM_{2.5}$ and ozone concentrations were both significantly higher during EHE days compared to non EHE days ($PM_{2.5}^{EHE}$ mean (SD)= 13.08 (5.91) ug/m3 vs $PM_{2.5}^{non\text{-}EHE}$ = 8.35 (5.53) ug/m3; and O_3^{EHE} = 75.38 (19.75) ppbv vs $O_3^{non\text{-}EHE}$ = 62.63 (15.84) ppbv (**Table 2**). There was a total of 218 and 17,694 NAAQS exceedance days for CMAQ-based $PM_{2.5}$ and O_3 estimates during the 15-year period. County-level daily $PM_{2.5}$ and ozone estimates are shown in **Tables S4-1 and S4-2**. Overall, the Pearson correlation coefficients (*r*)

between CWRF-CMAQ derived $PM_{2.5}$ and O_3 concentrations varied across counties and ranged from 0.40 to 0.63 (**Figure S4-1**). The regional correlation was moderate (r=0.54, p<2.2e-16) after aggregation (**Figure S4-2**). During the study period, there was 9.7 EHEs/year/county with a standard deviation (SD) of 6.5 and a regional mean daily maximum temperature of 25.6 °C (SD=5.3) during the warmer months.

4.4.1 Main analysis

Short-term $PM_{2.5}$ and ozone effects on ACM and ACHA outcomes are presented in **Tables 3 and 4**, respectively, first as a 10 unit increase in exposure (Models 1 & 2), and for exceeding NAAQS standards for either $PM_{2.5}$ or ozone (Models 3 & 4). A 10 ug/m3 increase from 4-day cumulative $PM_{2.5}$ concentrations (Lag 0-3) was associated with a 5% increase in mortality among ESRD patients after adjusting for cumulative EHE exposures ($RR_{Lag0\text{-}3}$:1.05; 95%CI: 1.00-1.10). $PM_{2.5}$ NAAQS exceedance was associated with increased ACM risk. However, the risk increases were not statistically significant (p<0.05), irrespective of the lag structure (**Table 3**). Same-day ozone exposure (Lag 0) was significantly associated with increased ACM risk in both adjusted and unadjusted models. A 10 ppbv increase in ozone exposure was associated with a 2% increase in mortality (RR_{Lag0}:1.02; 95% CI: 1.01-1.03). At the same time, same-day NAAQS-based ozone exceedances were associated with 8% increase in mortality (RR_{Lag0}:1.08; 95% CI: 1.04-1.13). EHE appeared not to confound the association between ozone and mortality since the effect estimates for EHE-adjusted models were virtually identical (**Table 3**). Overall, averaged ACM rates from both pollutants dampened as lag periods increased. In ACHA models (**Table 4**), we observed mostly null estimates across all model fits for

each pollutant except for significant negative associations for cumulative Lag 0-3 in NAAQS-based $PM_{2.5}$ (RR_{Lag0-3}: 0.73; 95% CI: 0.57-0.93)

4.4.2 Effect modification analysis

Significant interaction effects between cumulative lag effects of air pollutants and EHE were observed for Lag 0-3 $PM_{2.5}$ (F=2.656 p=0.004) and Lag 0-3 ozone (F=3.915, p=0.00352) ACM models. EHE was also shown to be a significant modifier for Lag 0-2 O_3 (F=4.430, p=0.004). Though, for ACHA outcomes, we saw weak evidence (p>0.05) for effect modification. The same observation applied to all O_3-NAAQS exceedance models irrespective of outcome.

Table 5 presents EHE-adjusted and EHE stratified (presence vs absence of EHE) ACM risk estimates associated with a 10-unit increase in exposure across cumulative lag periods ranging from 0 to 3 days. Also included are goodness-of-fit test results (F-statistic, degrees of freedom (df), and p-value) for examining EHE as a potential modifier. Consistent positive associations with $PM_{2.5}$ across each cumulative lag period were observed in the analysis adjusted for EHE as well as the analysis restricted to non-EHE periods. We observed highly reduced risk from Lag 0-1 (RR_{Lag0-1}:0.60; 95% CI: 0.50-0.72) and Lag 0 (RR_{Lag0}:0.60; 95% CI: 0.47-0.75) in the analysis restricted to the days with the presence of EHE. A suggestive increased risk was observed for ozone exposures for most cumulative lag periods during EHE days. This result suggests a 5% increased risk from delayed ozone exposures up to four days (RR_{Lag0-3}:1.05; 95% CI: 1.00-1.10). As a comparison, **Table 6** presents a

similarly formatted **Table 5** with ACHA as our outcome. We note mostly null associations across cumulative lag periods for $PM_{2.5}$ and O_3.

Finally, we extended the analysis to NAAQS exceedance models (**Table 7**), focusing only on ozone due to limited $PM_{2.5}$ exceedances during the study period. After stratifying for EHE, all-cause mortality was considerably higher when ozone levels exceeded NAAQS thresholds during EHE days for cumulative Lag 0-3 and Lag 0-2 exposures. For instance, we observed a 29% increase in the risk of ACM when the ozone exposure (cumulative Lag 0-3) exceeded the NAAQS in the presence of EHE (RR_{Lag0-3}:1.29; 95% CI: 1.00-1.66). Such substantive risk was not observed when daily ozone measures exceeded the NAAQS during non-EHE days (RR_{Lag0-3}:1.04; 95% CI: 0.97-1.12). However, this relationship reversed when considering same-day exposure. Lag 0 ozone NAAQS exceedance was associated with decreased ACM risk during EHE days (RR_{Lag0}:0.55; 95% CI: 0.41-0.75). The same exposure was positively associated with increased ACM risk in non-EHE stratified models (RR_{Lag0}:1.08; 95% CI: 1.04-1.13). For ACHA outcomes, we observe mostly non-significant and null associations across all O_3-NAAQS exceedance models. Interestingly, unlike ACM, where overall cumulative risk appears to increase with delay effects, overall cumulative risks appear to dampen over time.

4.5 Discussion

Prior studies have reported interactive effects of air pollution and weather on health, we found that ambient temperature can modify the short-term association between particulate matter and O_3 on mortality[168, 169, 174, 175]. We built on these

findings by investigating the role of high air pollution episodes and extreme heat events on mortality risk among highly vulnerable ESRD patients. Our regional-scale analysis of 28 northeastern counties found that $PM_{2.5}$ and O_3 had a measurable impact on mortality among ESRD patients undergoing HD treatments at FKC clinics. Cumulative $PM_{2.5}$ and same-day O_3 exposures yielded significant ACM positive effects, though the relationship varied across lag periods and between EHE and non-EHE periods. We observed a 29% increased mortality rate (RR_{Lag0-3}, 1.29; 95% CI, 1.00-1.66) from 4-day cumulative lag ozone NAAQS exceedance during EHE days. Our study provided preliminary evidence that ozone and ACM are subject to effect modification across cumulative lag structures beyond Lag 0. Our findings are consistent with prior studies that have confirmed effect modification by temperature between air pollutants and mortality among the general population. [174-176] Nested model comparison tests did not suggest such effect modification for ACHA outcomes and NAAQS-based exposure models.

While a recent study has shown the independent effect of air pollution and temperature on ESRD patients [123], this work is one of the first studies to demonstrate the modifying effect of EHE between air pollution and hospital admissions or mortality among ESRD patients. Understanding the ESRD population's sensitivities from heat-air quality exposures is critical, considering projected increases in average regional temperatures and extreme heat frequencies and durations within the near-term. [177]

Unhealthy levels of ground-level O_3 and $PM_{2.5}$ are known to impair breathing, trigger asthmatic episodes, and exacerbate respiratory-related illnesses. [178-180] In

this work, we found that the cumulative effects of O_3- and $PM_{2.5}$-related exposures can increase mortality among ESRD patients. Consequently, our findings pose clinical concerns as exposure to these pollutants can exacerbate shortness of breath and result in unintended complications. This symptom among HD patients is commonly caused by fluid build-up in the lungs between dialysis treatments. [181] Confirmation of this plausible causal relationship needs to be conducted by targeting respiratory-and cardiac-related outcomes and measurements. Alternatively, restricting focus to ESRD patients diagnosed with respiratory-cardiovascular comorbidities may verify this sensitivity.

Regionally, our findings do suggest that exceeding regulatory NAAQS limits, particularly for O_3 may substantially increase mortality risk. An additional layer of importance is the consideration of ESRD patients as a priority population as defined by the Agency for Healthcare Research and Quality (AHRQ) for developing air quality standards, in addition to older adults, children, and people with asthma. Similarly, projected increases in the frequency of extreme heat related to climate change and its joint effect of air pollution can pose a substantive public health threat to ESRD patients. For example, extended drought periods attributed to climate change can unintentionally increase the frequency and intensity of wildfires, resulting in hazardous and extended air pollution episodes in surrounding communities.[2] Also, atmospheric warming, as an unintended consequence of climate change, can enhance ground-level ozone chemical production during warmer months. [2, 177]

Methodologically, our approach to assessing the effect modification of extreme heat on air pollution-health events using DLNM has been featured in other

work. [168, 169, 171] We applied a nested model comparison test between models with and without an interaction term. The interaction term represented a cross-basis matrix of a natural cubic spline for air pollutants and EHE. Then, we conducted a subgroup analysis by stratifying by EHE to estimate rate ratios for EHE and non-EHE days. We observed some perceived disagreement for evidence of effect modification between stratum-based effect estimates and *F*-test statistics in a few of the cumulative lag models. Li and colleagues explained this discrepancy by suggesting that comparing point estimate differences between EHE strata as a direct approach may have created unintended measurement error due to loss of statistical variability when using categorized variables. [169] Also, as mentioned earlier, *F*-test comparison tests suggests interaction despite model complexity. A larger sample of ACM and ACHA events and using a continuous-based EHE variable may be needed to explore both moderate and extreme heat effects while using more robust model specifications in future work.

In this study, we observed mostly negligible or null associations for hospital admissions similar to Chapter 3 work. A plausible clinical explanation for this population-level response could relate to the higher frequency of clinical visits for HD treatments. Thrice-weekly treatments may promote a survival advantage by stabilizing deleterious health responses after short-term environmental exposures. A cause-specific analysis is required to identify clinically meaningful causes for hospital admissions after acute air pollution and extreme heat exposures. This approach may also help explain the few cases of statistically negative associations with $PM_{2.5}$ and O_3 in some same day and one-day lag ACM models as seen in other work. [182]

There are several strengths of our study. To our knowledge, this is the first study to characterize extreme heat events, projected to increase in frequency over time, as a modifier on the effect of ambient air pollution exposure on mortality and hospitalization risk among a highly sensitive population. The case-crossover study design diminished concerns with individual-level confounding. Also, we factored extreme heat as a time-varying confounder. An advantage to using DLNM as our statistical model to estimate risk is the flexibility to fit both non-linear and lagged exposure-responses simultaneously.[173] Air pollution exposure measures were derived from CWRF-CMAQ data using high spatial and temporal resolutions. Lastly, high-quality mortality and hospital admission data used in this study are from FKC- a major and internationally known dialysis service provider. Patient data on mortality and hospital admission events are considered accurate since they are subject to billing requirements and tracking protocols established by Centers for Medicare & Medicaid (CMS) reporting.

Our study also has some limitations. Exposure misclassification bias from using simulated data remained a concern despite the improved data resolution. We compared county-level CWRF-CMAQ estimates against stationary USEPA Air Quality System (AQS) observations using the AQS database [183] to confirm this bias. Based on summary statistics (**Tables S4-3**) and correlations between daily CWRF-CMAQ and AQS measures (**Figures S4-2 to S4-6**), CWRF-CMAQ observations appear to overestimate O_3 at both county and regional levels. In contrast, simulated estimates seem to underestimate $PM_{2.5}$ when compared to AQS averaged measurements. This statistic discrepancy is consistently seen with spatiotemporal air

quality estimates. [184, 185] Another limitation is that we conducted single pollutant models focusing only on $PM_{2.5}$ and ozone, separately. Future studies should incorporate additional criteria air pollutants like carbon monoxide and nitrogen dioxide into more complex models. Despite the reduction of outcome misclassification biases from using all-cause morbidity and mortality endpoints, cause-specific outcomes related to cardiac and vascular systems could enhance clinical specificity for prevention and treatment. Lastly, we did not consider chronic air pollution exposures and the role of social stressors that can also modify and mediate the impact of air pollution within this population. Chronic stress due to socioeconomic position can partly influence susceptibility.[186]

4.6 Conclusions

Our study provides that short-term exposure to $PM_{2.5}$ and O_3 for up to 3 days is associated with increased ACM risk and negligible risk of ACHA among ESRD patients. Also, preliminary evidence points to potential effect modification from extreme heat events though further analysis is required. Our findings will spur enhanced public surveillance and outreach to facilitate timely medical access and assistance to the most vulnerable subpopulation by characterizing the underlying population vulnerability. Public health implications could also broaden regulatory action for increased air quality mitigation and human health protections that consider the ESRD population a sensitive population.

4.7 Tables

Characteristics	
Counties, n	28
Clinics, n	104
Patients, n	48,338
Race/Ethnicity, n (%)	
Hispanic	3,834 (7.9)
non-Hispanic Black	20,974 (43.4)
non-Hispanic White	20,398 (42.2)
Asian	756 (1.6)
Other/Not Reported	538 (1.1)
Comorbidities, n (%)	
Any	29,255 (60.5)
Any CVD	750 (1.6)
Cerebrovascular	152 (0.2)
CHF	500 (1.0)
COPD	112 (0.2)
Diabetes	28,772 (59.9)
IHD	432 (0.9)
Sex	
Men, n (%)	27,782 (57.5)

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

		EHE Stratification		
	All	**EHE**	**non-EHE**	**p-value**
Mortality, n (%)	5,217 (10.8)	344 (0.7)	4,873 (10.1)	0.198
Hospital admissions, n	78,443	5,058	73,375	0.121
Hospital admission rate, #/person, mean (SD)	2.89 (3.1)	1.2 (0.5)	3.2 (3.3)	<0.001
Air pollution exposures				
CMAQ PM2.5 [μg/m3], mean (SD)	8.6 (5.7)	13.1 (5.9)	8.4 (5.5)	<0.001
CMAQ PM2.5 NAAQS Exceedance	218 (0.3)	14 (0.02)	204 (0.2)	0.863
CMAQ O3 [ppbv], mean (SD)	63.4 (16.4)	75.4 (19.8)	62.6 (15.8)	<0.001
CMAQ O3 NAAQS Exceedance	17,694 (23.8)	2,094 (2.8)	15,600 (21.0)	<0.001

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

Pollutant Type	Lag	Mortality			
		Model 1 Crude	**Model 2 EHE-adjusted**	**Model 3 Crude**	**Model 4 EHE-adjusted**
$PM_{2.5}$	Lag 0	1.03 (0.99-1.06)	1.02 (0.98-1.06)	1.14 (0.85-1.53)	1.14 (0.85-1.53)
	Lag 1	1.02 (0.98-1.07)	1.02 (0.98-1.07)	1.01 (0.73-1.41)	1.01 (0.72-1.41)
	Lag 2	0.99 (0.95-1.03)	0.99 (0.95-1.04)	1.04 (0.72-1.51)	1.04 (0.72-1.51)
	Lag 3	1.00 (0.96-1.04)	1.01 (0.97-1.05)	0.98 (0.70-1.38)	0.98 (0.70-1.38)
	Lag 0-3	1.04 (0.99-1.08)	1.05 (1.00-1.10)	1.19 (0.74-1.92)	1.18 (0.73-1.92)
O_3	Lag 0	1.02 (1.01-1.04)	1.02 (1.01-1.03)	1.09 (1.04-1.13)	1.08 (1.04-1.13)
	Lag 1	0.97 (0.96-0.99)	0.97 (0.96-0.99)	0.97 (0.92-1.01)	0.97 (0.93-1.01)
	Lag 2	1.00 (0.99-1.02)	1.00 (0.99-1.02)	0.94 (0.98-1.02)	0.98 (0.94-1.03)
	Lag 3	1.00 (0.99-1.01)	1.00 (0.99-1.02)	1.01 (0.96-1.05)	1.01 (0.97-1.06)
	Lag 0-3	1.00 (0.98-1.01)	1.00 (0.98-1.01)	1.04 (0.97-1.11)	1.05 (0.98-1.12)

Table 3. Rate ratios and 95% confidence intervals per change in 10-unit increments (Models 1 & 2) and per NAAQS-exceedance (Models 3 & 4) for associations across selected Lag 0, Lag 1, Lag, 2, Lag 3, and 4-day average (Lag 0-3) air pollutant exposures and all-cause mortality (ACM).

Pollutant Type	Lag	Hospital Admissions			
		Model 1 Crude	**Model 2 EHE-adjusted**	**Model 3 Crude**	**Model 4 EHE-adjusted**
$PM_{2.5}$	Lag 0	0.99 (0.97-1.01)	0.99 (0.97-1.00)	0.96 (0.81-1.13)	0.96 (0.82-1.14)
	Lag 1	1.01 (0.99-1.03)	1.01 (0.99-1.03)	0.90 (0.75-1.09)	0.90 (0.75-1.08)
	Lag 2	1.00 (0.98-1.01)	1.00 (0.98-1.02)	0.97 (0.82-1.15)	0.97 (0.82-1.15)
	Lag 3	1.00 (0.98-1.02)	1.00 (0.98-1.01)	0.86 (0.74-1.01)	0.87 (0.74-1.01)
	Lag 0-3	0.99 (0.97-1.01)	0.99 (0.97-1.01)	0.73 (0.57-0.93)	0.73 (0.57-0.93)
O_3	Lag 0	1.00 (0.99-1.00)	1.00 (0.99-1.00)	1.00 (0.98-1.02)	1.00 (0.98-1.02)
	Lag 1	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.02 (1.00-1.04)	1.02 (1.00-1.04)
	Lag 2	1.00 (0.99-1.01)	1.00 (0.99-1.01)	0.99 (0.97-1.01)	0.99 (0.97-1.01)
	Lag 3	1.00 (1.00-1.01)	1.00 (1.00-1.01)	1.00 (0.98-1.02)	1.00 (0.98-1.02)
	Lag 0-3	1.00 (0.99-1.01)	1.00 (0.99-1.01)	1.01 (0.98-1.04)	1.01 (0.98-1.04)

Table 4. Rate ratios and 95% confidence intervals per change in 10-unit increments (Models 1 & 2) and per NAAQS-exceedance (Models 3 & 4) for associations across selected Lag 0, Lag 1, Lag 2, Lag 3, and 4-day average (Lag0-3) air pollutant exposures and all-cause hospital admissions (ACHA).

Lag Structure	Air Pollutant	EHE-adjusted	EHE Stratification		F-test, df	p-value
			EHE Presence	EHE Absence		
Lag 0-3	$PM_{2.5}$	1.05 (1.00-1.10)	0.93 (0.81-1.07)	1.04 (0.99-1.09)	F(2.655), 4	p=0.031
	O_3	1.00 (0.98-1.01)	1.05 (0.99-1.12)	0.99 (0.98-1.01)	F(3.915),4	p=0.004
Lag 0-2	$PM_{2.5}$	1.04 (0.99-1.09)	0.95 (0.82-1.10)	1.03 (0.99-1.08)	F(2.129), 3	p=0.094
	O_3	0.99 (0.98-1.01)	1.02 (0.97-1.08)	1.00 (0.98-1.01)	F(4.430), 3	p=0.004
Lag 0-1	PM2.5	1.05 (1.00-1.09)	0.60 (0.50-0.72)	1.04 (1.00-1.08)	F(2.694), 2	p=0.068
	O_3	0.99 (0.98-1.01)	0.96 (0.90-1.04)	0.99 (0.98-1.00)	F(3.857), 2	p=0.021
Lag 0	$PM_{2.5}$	1.02 (0.98-1.06)	0.60 (0.47-0.75)	1.04 (1.01-1.07)	F(2.261), 1	p=0.133
	O_3	1.02 (1.01-1.03)	1.02 (0.93-1.11)	1.01 (1.00-1.03)	F(0.610), 1	p=0.435

Table 5. Rate ratios and 95% confidence intervals per change in 10-unit increments for associations across selected cumulative Lag 0, Lag 0-1, Lag 0-2, and Lag 0-3 air pollutant exposures and all-cause mortality (ACM) fitted by EHE-adjusted and EHE-stratified models. Also provided are F-statistic, degrees of freedom (df), and p-value results from model comparison tests for each cumulative lag-pollutant model's interaction effects.

Lag Structure	Air Pollutant	EHE-adjusted	EHE Stratification		F-test, df	p-value
			EHE Presence	EHE Absence		
Lag 0-3	$PM_{2.5}$	0.99 (0.97-1.01)	1.00 (0.93-1.08)	0.99 (0.97-1.01)	F(1.188), 4	p=0.314
	O_3	1.00 (0.99-1.01)	0.99 (0.96-1.02)	1.00 (0.99-1.01)	F(2.134), 4	p=0.074
Lag 0-2	$PM_{2.5}$	0.99 (0.97-1.01)	0.91 (0.84-0.99)	0.99 (0.97-1.01)	F(1.364), 3	p=0.252
	O_3	1.00 (0.99-1.01)	0.97 (0.93-1.00)	1.00 (0.99-1.01)	F(2.130), 3	p=0.094
Lag 0-1	PM2.5	0.99 (0.97-1.01)	0.90 (0.81-1.01)	0.99 (0.97-1.01)	F(1.561), 2	p=0.210
	O_3	1.00 (0.99-1.01)	1.00 (0.96-1.04)	1.00 (0.99-1.01)	F(2.103), 2	p=0.122
Lag 0	$PM_{2.5}$	0.98 (0.97-1.00)	0.98 (0.87-1.11)	0.99 (0.97-1.00)	F(0.106), 1	p=0.744
	O_3	1.00 (0.99-1.00)	0.97 (0.92-1.02)	1.00 (0.99-1.01)	F(0.630), 1	p=0.428

Table 6. Rate ratios and 95% confidence intervals per change in 10-unit increments for associations across selected cumulative Lag 0, Lag 0-1, Lag 0-2, and Lag 0-3 air pollutant exposures and all-cause hospital admissions (ACHA) fitted by EHE-adjusted and EHE-stratified models. Also provided are F-statistic, degrees of freedom (df), and p-value results from model comparison tests for each cumulative lag-pollutant model's interaction effects.

Outcome	Lag Structure	EHE-adjusted	EHE Stratification		F-test, df	p-value
			EHE Presence	EHE Absence		
ACM	Lag 0-3	1.05 (0.98-1.12)	1.29 (1.00-1.66)	1.04 (0.97-1.12)	F(1.614), 4	p=0.168
ACM	Lag 0-2	1.03 (0.97-1.10)	1.45 (1.14-1.85)	1.03 (0.97-1.10)	F(0.813),3	p=0.487
ACM	Lag 0-1	1.05 (1.00-1.11)	0.82 (0.63-1.07)	1.04 (0.99-1.10)	F(1.107), 2	p=0.330
ACM	Lag 0	1.08 (1.04-1.13)	0.55 (0.41-0.75)	1.08 (1.04-1.13)	F(0.223), 1	p=0.636
ACHA	Lag 0-3	1.01 (0.98-1.04)	0.92 (0.82-1.05)	1.01 (0.98-1.04)	F(1.401), 4	p=0.231
ACHA	Lag 0-2	1.01 (0.98-1.04)	0.94 (0.82-1.07)	1.00 (0.98-1.03)	F(1.680), 3	p=0.221
ACHA	Lag 0-1	1.01 (0.99-1.03)	1.01 (0.86-1.17)	1.01 (0.98-1.03)	F(1.841), 2	p=0.159
ACHA	Lag 0	1.00 (0.98-1.02)	1.07 (0.88-1.29)	1.00 (0.98-1.02)	F(1.316), 1	p=0.251

Table 7. Rate ratios and 95% confidence intervals per change per NAAQS-exceedance for associations across selected cumulative Lag 0, Lag 0-1, Lag 0-2, and Lag 0-3 daily 8-hour mean ozone fitted by EHE-adjusted and EHE-stratified models. Also provided are F-statistic, degrees of freedom (df), and p-value results from model comparison tests for each cumulative lag-pollutant model's interaction effects.

4.8 Figures

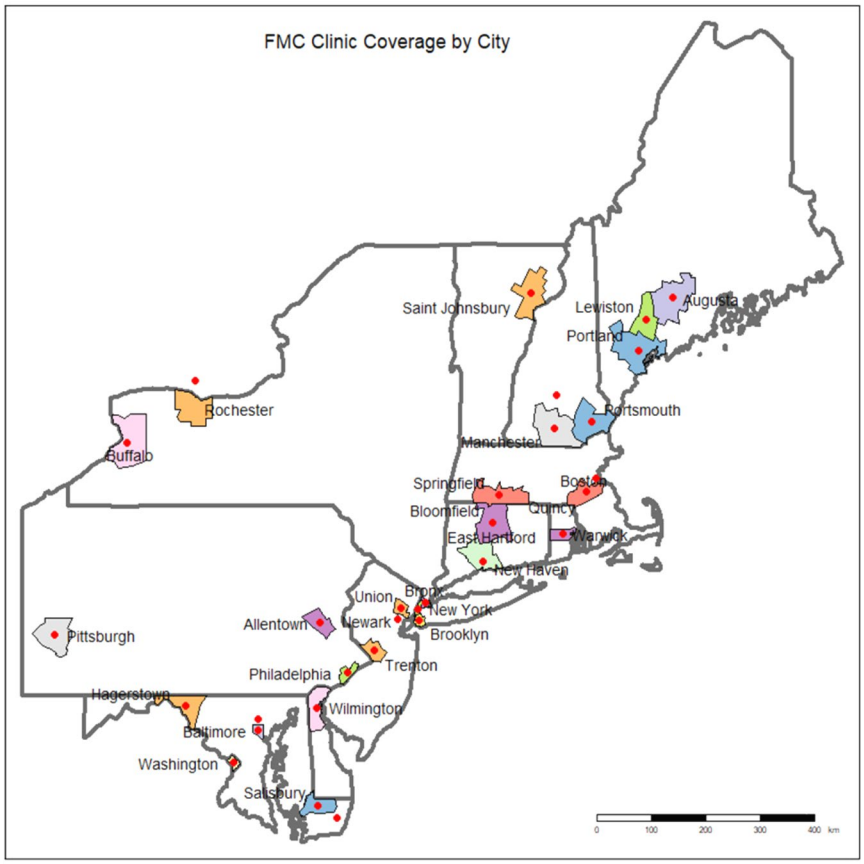


Figure 1. Map of focused counties within Northeastern study catchment

Chapter 5: Investigating the role of clinical measures before dialysis treatment as mediators between ambient temperature and mortality and hospital admissions outcomes

5.1 Abstract

Background. Typical thermoregulatory responses to elevated temperatures among healthy individuals include reduced blood pressure and perspiration. Individuals living with end-stage renal disease (ESRD) are susceptible to physiological fluctuations caused by ambient temperature changes that may increase health complications. We investigated whether systolic blood pressure (preSBP) and changes in interdialytic weight gain change (IDWG) can independently mediate the association between ambient temperature and hospital admissions and also between mortality outcomes among ESRD patients.

Methods. The study population consisted of ESRD patients receiving hemodialysis treatments at Fresenius Medical Care facilities in Philadelphia County, PA, from 2011 to 2019 (n=1981). Within a time-to-event framework, we estimated the association between daily maximum dry-bulb temperature (TMAX) and, as separate models, all-cause hospital admissions (ACHA) and all-cause mortality (ACM) outcomes during warmer calendar months. Also, mean preSBP and IDWG responses to temperature increases were estimated using linear mixed effect models. The study employed VanderWeele's difference (*c-c'*) method to decompose total effect models for ACHA and ACM using preSBP and IDWG as time-dependent mediators. Covariate adjustments for exposure-mediator and total and direct effect models include age, race/ethnicity, blood pressure medication use, treatment location,

preSBP, and IDWG. We considered lags up to two days for exposure and one-day lag for mediator variables (Lag 2-Lag 1) to assure temporality between exposure-outcome models. Sensitivity analyses for two-day (Lag 2-only) and one-day (Lag 1-only) lag structures were also conducted.

Results. Based on Lag 2- Lag 1 temporal ordering, 1°C increase in daily maximum temperature was associated with increased hazard of hospital admissions by 7.6% (adjusted hazard ratio (HR), 1.076; 95% confidence interval, 1.070-1.082) and mortality 7.5% (adjusted HR, 1.075, 1.050-1.100) after adjusting for covariates. Short-term lag exposures to 10°C increase in temperature predicted mean reductions in IDWG and blood pressure by 0.13%-0.15% and 1.68 mmHg-2.29 mmHg, respectively. Mediation analysis for hospital admission events identified significant indirect effects for all three studied pathways and significant indirect effects for IDWG and conjoined preSBP + IDWG pathways for mortality. Only 1.03% of the association between temperature and mortality path was mediated through preSBP. The mechanistic path for IDWG, independent of preSBP, demonstrated inconsistent mediation and, consequently, potential suppression effects in ACHA (-2.67%) and ACM (-6.26%) based on combined pathway models. Proportion mediated estimates from preSBP + IDWG pathways achieved near 0% in combined pathway analysis. Lag 2 discrete-time ACM mediation models exhibited consistent mediation for all three pathways suggesting that two-day lag IDWG and blood pressure can explain 2.11% and 4.41% of total effect association between temperature and mortality, respectively.

Conclusion. We confirmed evidence of the association between ambient temperature and ACHA/ACM outcomes for the ESRD population using Cox models. This work has provided a step forward to understanding potential physiological linkages that may explain or suppress temperature-driven hospital admissions and mortality risks. Concomitant physiological changes in blood pressure and IDWG may have little intermediary effect when modeled with IDWG and preSBP in combined pathway models. These findings could help discern candidate interventions to minimize the impact of outdoor temperature change among ESRD patients in future work.

5.2 Introduction

Warming ambient temperatures can influence physiological changes within the general population. More specifically, renal-related health effects, such as acute kidney failure, heatstroke, as well as fluid and electrolyte imbalances, are typical causes of hospital admissions and mortality among older adults exposed to heatwaves.[24, 25, 187] Such symptoms are frequent sequelae of heat stress and dehydration during periods of extreme heat.[25] At the proximal level, typical thermoregulatory responses to elevated temperature among healthy individuals can include reduced blood pressure and loss of extracellular fluid through perspiration and dehydration.[40] As such, projected elevated temperature and increased frequency of extreme heat related to climate change can pose a substantive public health threat to individuals with chronic renal dysfunction such as end-stage renal disease (ESRD).

Chronic renal disease management includes frequent dialysis treatments to prevent the accumulation of harmful levels of electrolytes, wastes, and fluids.[32] As an added health care safety concern, ESRD patients are susceptible to life-threatening complications resulting from fluctuations in weight and blood pressure.[33-35] Blood pressure stability is critical to improving survival advantage, irrespective of initial blood pressure levels. [188] Increased fluid-based weight gains between hemodialysis (HD) treatments, measured by inter-dialytic weight gain (IDWG), can increase fluid overflow complications resulting in hospitalization or death. [39] The accumulation of fluids between treatments is known to cause increased blood pressure. As such, more often, dialysis patients can develop hypertension and other cardiovascular-related complications. Clinical studies have shown that higher IDWG changes is associated with higher pre-dialysis blood pressure. [189] Also, sudden changes in blood pressure can compromise physiological stability among ESRD patients. [188, 190]

Previously, we observed increased risks of all-cause hospitalization and mortality during extreme heat events for ESRD patients residing in selected northeastern American cities. [56] From unpublished work, we found that extreme heat events can, on average, reduce systolic blood pressure (-1.6 mmHg; 95% CI: -1.8, -1.4) and IDWG percentage changes (-0.14%; 95% CI: -0.21%, -0.18%) when compared to non-extreme heat events. [57] Interdialytic weight gain (IDWG) change is the percentage of fluid accumulation changes between HD treatments. These observations present an interesting paradox for ESRD patients where both reduced blood pressure and weight changes can co-occur during extreme heat days.[38, 39,

191] Concomitant changes in IDWG and preSBP might have opposing effects in heat-related adverse risks in mortality and hospitalization. Changes in IDWG due to temperature changes could increase blood pressure variability among ESRD patients and subsequently enhance complications and result in hospitalization and premature death.[33-35, 39] Between decreasing IDWG changes and reduced blood pressure from heat exposure, the primary uncertainty is determining whether concomitant changes in blood pressure and IDWG may have a reduced or enhanced influence on the total effect. Underlying pathways for temperature-related effects is relatively unclear for the ESRD population. Investigating the role of blood pressure and interdialytic weight gain as mediators between warmer temperature exposures and mortality and hospitalization endpoints could potentially identify plausible interventions to protect ESRD patients from heat exposures.

This study aims to understand the role of intermediate effects due to ambient temperature exposures during warmer months between May-September (MJJAS) within an urban county with a high chronic renal disease prevalence. [192] By leveraging individual-level repeated clinical measurements, systolic blood pressure before HD treatment (preSBP, mmHg), and IDWG change (%), we can begin to describe mechanistic linkages to heat-related hospital and mortality events among ESRD patients. This work also linked discrete-time temperature exposures to individual-level time-varying intermediate responses using repeated clinical measurements from HD patients. To attain this objective, we tested the working hypothesis that preSBP and IDWG change, when modeled together as mediators, can each independently mediate the association between ambient temperature exposure

and hospitalization and mortality outcomes.[193] Through mediation analysis, we can better understand the extent of physiological mediators on temperature exposure-response pathways. Operating through these mediators, we also estimated its independent and conjoined effects on ESRD patients. The findings from this research could inform potential interventions to minimize the impact of extreme heat among ESRD patients.

5.3 Methods

5.3.1 Study participants

We conducted an open retrospective cohort study that included ESRD patients undergoing hemodialysis treatment at Fresenius Medical Care- North American (FMC-NA) clinics in Philadelphia County, PA, USA, from 2011 to 2019 (n=1981). Philadelphia had one of the largest county-wide ESRD populations within the northeastern United States serviced by FMC. Patient information on socio-demographic and medical information pertaining to sex, race/ethnicity, age, clinic site, and history of prescribed cardioprotective drugs, along with routine clinical anthropometric clinical treatment measurements were included. Since all the patient records were limited and deidentified, this study was determined exempt by the Western Institutional Review Board and the University of Maryland Institutional Review Board.

5.3.2 Meteorological data

Dry-bulb temperature is typically known as air temperature and is not influenced by moisture. Often, temperature-related epidemiological studies use dry-bulb temperature for shared exposure observations for a given population. [126] For this work, archived dry-bulb temperature data was extracted using an R interface package known as *rnooa* through the National Climatic Data Center at the National Oceanic and Atmospheric Agency (NOAA). [194] Observations were aggregated at the county-level and expressed as daily maximum air temperatures (TMAX) during warmer calendar months, May to September (MJJAS), from 2011 to 2019.

5.3.3 Outcome measures

We obtained all-cause hospital admission (ACHA) and all-cause mortality (ACM) medical records among HD patients from the Renal Research Institute (RRI). Patient medical records for ACHA and ACM events are considered highly accurate since records were tracked through FMC-NA billing and payment requirements and subject to Centers for Medicare & Medicaid (CMS) reporting. ACHA includes first and recurrent visits for each patient from the study population.

5.3.4 Blood pressure, inter-dialytic weight gain mediators

Blood pressure (BP) and fluid balance measures are routine diagnostics for determining clinical decisions for fluid volume removal during a dialysis session. We used preSBP as a proxy for blood pressure. Measurements were made using an oscillometric method when a patient is in a sitting position after 5 minutes. [188] To avoid concerns with collinearity, we did not include diastolic blood pressure in the analysis. [195] The IDWG change is the difference between current pre-dialysis

weight and previous post-dialysis weight divided by the patient's dry weight expressed as a percentage. Clinical studies have shown that higher IDWG change is associated with higher pre-dialysis blood pressure. [195, 196] More often, dialysis patients can develop hypertension and other cardiovascular-related complications due to IDWG-related fluid overloading. [38] We also adjusted for prescribed hypertension medication (Yes/No) as a confounder, given the expected higher prevalence of cardiovascular-related co-morbidities among patients.[41]

We specified potential confounders as race/ethnicity (Asian, Hispanic, non-Hispanic Black, non-Hispanic White, Other/Did Not Specify), sex (Male or Female), treatment facility site (27 identified HD treatment locations within Philadelphia), and age (continuous) into models. The selection of covariates were based *on a priori* research and clinical findings that suggest potential confounding between exposure and outcome, and mediator and outcome pathways.

5.3.5 Analytical approach

Given the lack of reported temperature effects among ESRD patients for blood pressure and IDWG change, we first estimated temperature-responses using the sample population. Random-intercept linear mixed-effects models were used to calculate mean patient responses for preSBP and IDWG change measures. Crude and adjusted models for lag structure specifications are explored.

We assessed whether TMAX could acutely affect ACM and ACHA outcomes by using time-to-event methods. Discrete-time Cox regression models with time-dependent covariates were used to estimate temperature effects by generating hazard

ratios (HR) based on specified lag periods for exposure and mediators. Despite the historically favored case-crossover design for characterizing short-term effects, a cohort design approach allows for studying subject-level effects such as physiological responses to temperature using subject-specific characteristics associated with hospitalization and mortality. This approach also increases our statistical power by including right-censored patients that may generally not be included in case-crossover studies. [197]

Cox models were generated for ACHA and ACM outcomes. Since hospital admissions recurrent events, the Andersen-Gill (AG) model can be applied to generalize the Cox model for repeated hospital events. [198] The correlation between recurrent hospital admissions events are assumed to be event-dependent and are clustered at the individual level. [199, 200] Studies related to ESRD and HD research typically apply AG models when using ACHA outcomes. [201-203] For ACM, we selected unshared frailty modeling to account for unmeasured heterogeneity not explained by selected covariates. [200, 204] This approach accounts for individuals with higher failure predispositions by including random effects to account for their individual-specific vulnerabilities. We specified a Gaussian distribution for the frailty and used restricted maximum likelihood (REML) approximation. [205]

Through sequential model building, we estimated TMAX effects (crude total effect), followed by the inclusion of baseline covariates (adjusted total effect), and then finally time-varying mediators (adjusted direct effect) for each outcome. Robust standard errors for all model specifications were calculated. All statistical tests were two-tailed and based on an alpha of 0.05. All analyses conducted using R statistical

software version 3.6.1. [128] Statistical software for Cox modeling and extensions are available from the *survival* R package through CRAN. [206] Lastly, we assessed proportional hazards assumption through Schoenfeld hypothesis testing and through plotting scaled Schoenfeld residuals for ACM models. We note that holding the assumption for recurrent events generally does not hold given the extended period for time at risk. [207]

5.3.6 Mediation analysis

To quantify the extent of the total effect of TMAX exposure on ACHA or ACM operating through preSBP and IDWG, we tested preSBP and IDWG (separate and combined) as selected mediators using VanderWeele's difference method (c-c') to estimate indirect effects (IE).[208, 209] Indirect effects for these analyses represent the change in daily maximum temperature β coefficients between adjusted total effect (c, no mediator) and adjusted direct effect (c', with mediator(s)) regression models. We calculated IEs for preSBP, IDWG, and both preSBP and IDWG as concomitant mediators.

We used IEs to characterize proportions of the total effect contributed by preSBP, IDWG, and preSBP and IDWG combined, as shown in **Figure 1**. [208, 209]. The proportion mediated statistic gives insight on the relative effect of exposure on the outcome that works through a mediator or mediators.[210] Pathway proportions were assessed through preSBP, IDWG, and preSBP and IDWG as individually separate mediated pathways and as combined pathways. Bootstrapping at 1000 repetitions was used to generate 95% confidence intervals for indirect associations.

Regression analysis quantifying mediator-outcome associations were also conducted and results are provided in supplementary materials

5.3.7 Lag structures

The study considered lag structures for exposures and mediator variables for up to two days (two-day lag [Lag 2]) before ACHA or ACM events. This parameterization aided in characterizing potential delayed effects associated with temperature. To assure temporal precedence, we focused on two-day lagged TMAX exposure and one-day lagged mediator (Lag 2-Lag 1) models to explore direct and indirect effects between our exposure, mediators, and outcomes (**Figure 1**). Additional discrete-time lagged models (Lag 2-only and Lag 1-only, **Figure S5-1**) are explored as associational models for sensitivity analysis.

5.3.8 Missing data

While there were no missing data for baseline measurements, we noted up to 30% missingness for preSBP and IDWG change values for subsequent visits. Through exploratory analysis, we were able to determine that physiological data were missing at random. Missing covariate data were imputed by using multivariate imputation by chain equations (MICE) as recommended by other studies. [211-214] We generated 5 imputed data sets using 5 iterations for each imputed data set and used predictive mean matching. All model coefficients and standard errors were pooled from imputed data sets by using the *mice* package in R. [215]

5.4 Results

Study participants (n=1981) contributed approximately a total of 4764 person-years. We estimated a median value of 518 days for person-time contributions with an interquartile range (IQR) of 1095 days by each participant. During the study period, the overall median daily maximum air temperature was 28.3°C (IQR=6.1°C) with a range of 11.7°C to 38.9°C. Among the 1981 HD patients treated within Philadelphia (**Table 1**), we studied 934 patients with recurrent hospital admissions (1+ hospital admissions) followed by 439 patients who reported one hospital admission visit. The remainder reported no hospital admissions during MJJAS months. Among cases with recurrent ACHAs, non-Hispanic (NH) Black (59%) and male (55%) patients made up most of the ACHA-based cohort. Mean preSBP (148 mm Hg, SD=25 mm Hg) and IDWG percentage (3.05%, SD=1.89%) measures also exhibit non-significant elevated mean levels for patients with recurrent hospital admissions compared to patients with no reported hospital admission visits. There were 276 cases of death (13.9%) within the sample population. Similar to the ACHA cohort, NH-Black (59%) and male (57%) patients were over-represented. The mean levels of blood pressure (146 mm Hg, SD=27.1) and IDWG (3.11%, SD=1.93) were slightly different among ACM cases when compared to censored patients (preSBP=147.0 mm Hg, SD=23.9; IDWG=2.85%, SD=1.81).

As depicted In **Table 2**, individual-level clinical measures (preSBP, IDWG) were negatively associated with increasing TMAX. Decreases in mean pre-SBP responses ranged between -2.33 mmHg to -1.68 mmHg across lag models in fully adjusted models. Likewise, the mean reduction in IDWG ranged between -0.19% to -

0.13% for each 10°C increase in dry-bulb temperature. Mediator-outcome analyses are provided in supplemental tables (**Tables S9-S12**).

Based on unadjusted total temperature association models (Model 1), 1°C increase in daily maximum temperature was associated with 7.5% greater ACHA risk (**Table 3**) and 6.9% greater ACM risk (**Table 4**). In this work, risk is defined as hazards. Slight incremental changes in coefficient estimates did occur across partially adjusted (confounders-only, Model 2; confounders and one mediator, Models 3 &4) and fully adjusted (confounders and both mediators, Model 5) models. One percent increase in IDWG change resulted in 8% increase in risk of hospital admission (HR, 1.082, 95%CI: 1.050-1.115) and 19% increase in risk of mortality (HR, 1.193, 95%CI: 1.106-1.287) in fully adjusted direct effect models (Model 5). One-unit increase in preSBP resulted in a small but significant, protection against hospital admissions risk (HR, 0.998, 95%CI: 0.997-0.999) shown in Model 3. Compared to Non-Hispanic Black and female patients, Hispanic (HR, 1.371, 95%CI: 1.090-1.724) and male (HR, 0.866, 95%CI: 0.773-0.970) patients appear to have a higher risk of hospital admissions. Whereas non-Hispanic White (HR, 1.515, 95%CI: 1.137-2.018) patients and age (HR, 1.034, 95%CI: 1.025-1.044) are positively associated with increased mortality risk. On average, patients prescribed blood pressure medication exhibit approximately 49% protective effects from death (HR, 0.514, 95%CI: 0.396-0.667) as shown in Model 5 (**Table 4**). Associational estimates for Lag 2 and Lag 1 lag model structures are consistent with the main results (**Supplemental Tables 1 to 4**). Also, we note all ACM models did not violate assumptions for proportional

hazards based on global tests. And, as expected, all ACHA models suggested non-proportionality for hazards corresponding to recurrent outcomes.

Mediation analysis for hospital admission events identified significant indirect effects for all three pathways (**Table 5**) and significant indirect effects for IDWG and concomitated preSBP + IDWG pathways for mortality (**Table 6**). Only 1.03% of the association between TMAX and mortality path was mediated through preSBP. For the remainder of the studied pathways, inconsistent mediation was observed that included negative indirect effect estimates. As a result, negative proportion mediated between total and direct effect models suggest suppression effects for temperature and outcome variables. We note that IDWG as a separate pathway in all lag structured models demonstrated lower proportion mediated estimates. In combined pathway analysis, the total association between ambient temperature with ACHA **(Figure 2)** and ACM **(Figure 3)** outcomes is explained by the combined preSBP + IDWG pathway at 0.04% and 0.30%, respectively. These estimates are drastic reductions when compared to preSBP + IDWG as a single, concomitated pathway. **Tables S5-S8** provide mediation results for Lag 2 and Lag 1 discrete time-dependent models. Significant, however modest, indirect effects were observed with consistent and inconsistent mediated effects in each model except for Lag 2-ACM models- all pathways demonstrated consistent mediation. We note that the preSBP, independent of IDWG, pathway in Lag 2 explained about 4.41% of the total effect between temperature and mortality. Whereas, Lag 1 models for IDWG, independent of preSBP, pathway yielded -2.15% and -4.51% for ACHA and ACM outcomes, respectively.

5.5 Discussion

Among ESRD patients (n=1981) treated in Philadelphia County, PA from 2011 to 2019, our study confirms that increased ambient temperature exposure is associated with an increased risk of mortality and hospital admission. Our study also found significant mean changes in blood pressure and IDWG responses inversely related to temperature. After one-day lag exposure to 10°C incremental increase, the estimated mean changes in preSBP (-2.34 mm Hg; SE, 0.04 mm Hg) and IDWG (-0.189 mm Hg; SE, 0.003 mm Hg) suggest plausible proximate physiological responses. We found evidence of significant pathways for all three (preSBP, IDWG, and preSBP + IDWG) and two of the three (IDWG and preSBP + IDWG) studied pathways for ACM and ACHA event outcomes, respectively. However, indirect effect estimates demonstrated inconsistent mediation and suggested suppression effects for certain mechanistic pathways.

The association between TMAX and increased risk of ACHA and ACM rates are consistent with other work related to ambient temperature exposure. [23, 25, 137, 140, 141] One study devoted to ESRD population found that seasonal changes can influence physiological responses and mortality, particularly in more temperate regions where climatic fluctuations are most pronounced.[44] A recent case-crossover study found consistent and significant increased mortality and hospital admissions rates associated with two-day cumulative exposure of extreme heat events in Boston and New York, and non-significant positive associations in Philadelphia. [56] The results observed in this study relates to the use of a climate-based dichotomous

exposure metric for an upper percentile threshold a continuous meteorological measure.

In this work, we measured the extent of thermoregulatory responses (IDWG change, preSBP) as mediators for hospital admissions and death events and explored the interesting paradox of both reduced blood pressure and IDWG changes co-occurring in ESRD patients. Our findings offer insight into the total effect decomposition between exposure-outcome relationships by estimating indirect effects through intermediated physiological responses. Our results found significant and consistent indirect effects for most IDWG (independent of preSBP) and IDWG + preSBP pathways. Absolute individual mediation estimates were less than 10%. Except for Lag 2 defined ACM models, we found indirect mediation evidence resulting from negative indirect effects between total effects and direct effects models. The inclusion of mediators into direct effect models yielded increased temperature β-coefficient magnitudes (**Tables 3-4 & S5-1 to S5-4**) and confirmed a third variable effect known as suppression. [210, 216]. As such, pathways between exposure and outcome variables displayed a combination of consistent and inconsistent mediation effects.

Despite the relatively low estimates of a proportion mediated, most significant pathways exhibited potential suppression effects. In the case of the IDWG pathway, independent of preSBP, we note that indirect effects operating through IDWG had an opposite effect with respect to total effect (**Figures 1&2**). This pathway also yielded the most dominant indirect effect among studied lag structures. For example, exposure to increased TMAX one-day before an ACM event may have had a slightly

protective effect. This inverse relationship was confirmed in the exposure-mediator analysis where one-day lag exposure to increased TMAX reduced IDWG change by -0.19%. Deductively, if increased IDWG change can result in ESRD complications, we could infer that IDWG could act as a modest suppressor from temperature-related health risks. Though, a serial mediation pathway between IDWG and blood pressure needs to be included. And more broadly, for Lag2- Lag 1 ACM mediation studied pathways (**Figure 2**), there is approximately 5% suppression of the overall effect between temperature and mortality when considering all three pathways. It appears that in this causal structure, using IDWG, preSBP, and combined IDWG + presSBP pathways may not adequately explain the total effect of temperature on mortality. This is similar for hospital admissions, where the three combined pathways demonstrate approximately 2% suppression.

As shown previously, mean preSBP and IDWG percent changes inversely respond to increased ambient temperatures. This an expected observation as typical thermoregulatory responses to elevated temperature among healthy individuals include reduced blood pressure. [40] Physiologically, fluid loss due to increased perspiration and restricted fluid replacement is plausibly attributed to reduced IDWG percent changes among the ESRD population. Though, such changes from increased temperatures do pose unintended health concerns. The literature on ESRD patient health found that blood pressure changes can enhance complications and result in hospitalization and premature death.[33-35, 39] Also, increased fluid-based weight gains between HD treatments can increase fluid overflow complications resulting in hospitalization or death. [39] In sequence, increased changes to IDWG can raise

blood pressure, and any sudden changes in blood pressure can compromise physiological stability. [36] The minor reduction in IDWG needs to be explored further as a potential independent protective pathway and as an antecedent mediator before blood pressure.

Concerning clinical implications, we found that blood pressure and interdialytic weight gain, while mechanistically significant, may not have substantive mediation effects. Instead, proportion mediated estimates were found to be small, and pathways mostly demonstrated suppression effects. The goal of determining an explanation of the observed relationship between TMAX and mortality/hospital admissions for potential clinical interventions was not necessarily achieved. However, considering additional passive heat responses related to electrolyte disorders is worth pursuing. Also, since patients using hypertension medication had nearly 50% reduction in all-cause mortality events in TMAX-adjusted models (**Table 2, S2, S4**), stratified analysis might provide enhanced statistical insight on the role of blood pressure medication in reducing mortality risk.

A major advantage of this study includes statistical robustness from using a longitudinal study design. As a study novelty, we inferred physiological responses using high-density patient-level health records specific to ESRD patients. Using repeated measurements of individual-level time-varying covariates, we established temporal precedence with mediator and outcome responses by considering two-day lag TMAX as the exposure and one-day lag preSBP and IDWG as proximal mediators. This time-varying approach assured one-day separation between each time-dependent variable. We adjusted for multiple explanatory factors that are

traditionally associated with increased risks of mortality and hospital admissions. And we also restricted our ACM and ACHA events to warmer month temperatures to focus on heat exposures. More notably, we incorporated hypertension prescription use to account for patients with high blood pressure. Lastly, we applied a practical mediation analysis approach as an exploratory method to understand the role of environmental exposures such as temperature.

There are a fair number of limitations to this work. First, this study is based on an overly simplified causal path model that included two measured mediators. Testing additional physiological responses as candidate mediators is needed to understand temperature-related causes of mortality and morbidity. Though, for now, it was a crucial step to establish and confirm potential pathways driven by regularly recorded clinical measures before dialysis treatments. We did not consider a U-shaped relationship between blood pressure and mortality among HD patients [37] since traditional mediation methods assume linearity. In a re-analysis, dichotomizing clinical mediators using clinically-meaningful or individual-based thresholds or trends could be explored [36] and may inform candidate mechanistic responses (e.g., suppression). In the current analysis, we assumed independent, parallel pathways with preSBP and IDWG mediators. IDWG might be considered as both an intermediate confounder that precedes blood pressure and a mediator since changes in IDWG could also influence blood pressure. Also, since we restricted exposure and outcome events to warmer months, we did not capture cold-temperature related effects. We did consider clinical measures on dialysis vintage (length of time on dialysis), estimated glomuluar filteration rate (eGFR), and alumbin to creatinine ratio (ACR) in thish

work. . Lastly, more advanced causal mediation approaches are needed to capture more complex pathways among multiple mediators while upholding rigorous assumptions to infer causal relationships. [217, 218]

5.6 Conclusions

This study found that increased ambient temperature is strongly associated with reduced blood pressure and IDWG and can increase mortality and hospital admissions risks. When combined in mediation analysis, we observed modest suppression effects operating through most proximal pathways in defined lag model structures. Our findings suggest that, statistically, blood pressure and IDWG may not explain the relationship between TMAX and mortality/hospital admissions, instead, those responses could exhibit protective effects. This suggests that causes of mortality and morbidity effects may involve other prognostic factors and more complex mechanistic pathways to describe temperature effects specific to the ESRD population.

5.7 Tables

Characteristics	Total	Hospital admissions			Mortality	
		None	1-only	1+	No	Yes
Patients, n (%)	1981	608 (31)	439 (22)	934 (47)	1705 (86)	276 (14)
Age, mean (SD)	60.1 (14.1)	60.2 (14.5)	60.5 (14.3)	59.9 (13.8)	59.5 (14.3)	64.1 (12.5)
Race/ethnicity, n (%)						
Asian	30 (2)	9 (1)	8 (2)	13 (1)	26 (2)	4 (1)
Hispanic	142 (7)	33 (5)	39 (9)	70 (7)	118 (7)	24 (9)
NH-Black	1079 (54)	307 (50)	221 (50)	551 (59)	916 (54)	163 (59)
NH-White	390 (2)	119 (20)	87 (20)	184 (20)	322 (19)	68 (25)
Other, Not-reported	340 (17)	140 (23)	84 (19)	116 (12)	323 (19)	17 (6)
Blood Pressure Medication						
Yes	739 (37%)	264 (43)	278 (63)	314 (34)	663 (39)	76 (28)
No	1242 (63%)	344 (57)	161 (37)	620 (66)	1042 (61)	200 (72)
Sex, n (%)						
Female	828 (42%)	243 (40)	169 (38)	416 (45)	708 (42)	120 (43)
Male	1153 (58%)	365 (60)	270 (62)	518 (55)	997 (58)	156 (57)
Treatment clinics, n	**27**	**24**	**22**	**25**	**27**	**19**
Daily Maximum Temperature, median (IQR)	28.3 (6.1)	28.3 (6.1)	28.3 (6.1)	28.3 (6.1)	28.3 (6.1)	28.3 (6.7)
PRE SBP, mean (SD)	147.0 (24.3)	145 (23.7)	147.0 (23.7)	148.0 (25.0)	147.0 (23.9)	146 (27.1)
IDWG %, mean (SD)	2.89 (1.83)	2.68 (1.73)	2.84 (1.81)	3.05 (1.89)	2.85 (1.81)	3.11 (1.93)

Table 1. Clinical and demographic characteristics of ESRD Philadelphia cohort stratified by hospital admissions and mortality status

		Crude		Adjusted	
Clinic measure	Lag	Mean effect	Std Error	Mean effect	Std Error
IDWG	Lag 2	-0.145	0.003	-0.149	0.003
	Lag 1	-0.188	0.003	-0.189	0.003
	Lag 0	-0.138	0.003	-0.130	0.003
preSBP	Lag 2	-1.693	0.038	-1.680	0.038
	Lag 1	-2.350	0.038	-2.337	0.038
	Lag 0	-2.381	0.039	-2.287	0.038

Table 2. Crude and adjusted IDWG and preSBP mean changes to 10°C increase in maximum daily temperature increase based on linear mixed effects regression. Crude models contain daily maximum temperature. Adjusted models contain daily maximum temperature, age, race/ethnicity, treatment clinic, sex, and blood pressure medication use variables.

	Model 1: unadjusted total temperature association	Model 2: adjusted total temperature association	Model 3: adjusted direct temperature association (preSBP)	Model 4: adjusted direct temperature association (IDWG %)	Model 5: adjusted direct temperature association (preSBP + IDWG%)
Daily Max Temp (Lag2)	**1.075 (1.069-1.081)**	**1.075 (1.069-1.080)**	**1.074 (1.068-1.080)**	**1.077 (1.071-1.082)**	**1.076 (1.070-1.082)**
preSBP (Lag1)			**0.998 (0.997-0.999)**		**0.998 (0.996-0.999)**
IDWG change (Lag1)				1.079 (1.047-1.111)	**1.082 (1.050-1.115)**
Age (yr)		0.999 (0.994-1.003)	0.998 (0.996-1.000)	0.999 (0.995-1.004)	0.999 (0.995-1.003)
Race/Ethnicity					
Non-Hispanic Black		1.000	1.000	1.000	1.000
Asian		0.998 (0.687-1.451)	1.004 (0.786-1.282)	0.932 (0.645-1.346)	0.936 (0.647-1.353)
Hispanic		**1.393 (1.105-1.756)**	**1.402 (1.271-1.546)**	**1.361 (1.082-1.711)**	**1.371 (1.090-1.724)**
Non-Hispanic White		1.083 (0.939-1.251)	**1.080 (1.000-1.167)**	1.076 (0.932-1.243)	1.072 (0.929-1.238)
Other/Not Reported		0.943 (0.797-1.116)	0.941 (0.850-1.042)	0.959 (0.810-1.135)	0.958 (0.810-1.132)
Blood Pressure Medication					
No		1.000	1.000	1.000	1.000
Yes		**0.884 (0.788-0.992)**	**0.880 (0.830-0.932)**	**0.872 (0.779-0.977)**	**0.866 (0.773-0.970)**
Sex					
Female		1.000	1.000	1.000	1.000
Male		1.051 (0.944-1.170)	1.059 (0.991-1.130)	1.067 (0.957-1.189)	1.077 (0.968-1.198)

Table 3. Hazard ratio (HR) and 95% confidence intervals for the association of daily maximum daily temperature and all-cause hospital admissions (ACHA) based on Lag 2- Lag 1 discrete-time model structure. Due to the large number of categorical factors, treatment clinics associations were not reported. Bold indicates statistically significant hazard ratio at $p < 0.05$.

	Model 1: unadjusted total temperature association	Model 2: adjusted total temperature association	Model 3: adjusted direct temperature association (preSBP)	Model 4: adjusted direct temperature association (IDWG %)	Model 5: adjusted direct temperature association (preSBP + IDWG%)
Daily Max Temp (Lag2)	**1.069 (1.045-1.094)**	**1.071 (1.047-1.096)**	**1.071 (1.046-1.096)**	**1.076 (1.051-1.101)**	**1.075 (1.050-1.100)**
preSBP (Lag1)			0.997 (0.992-1.003)		0.996 (0.991-1.002)
IDWG change (Lag1)				**1.186 (1.100-1.280)**	**1.193 (1.106-1.287)**
Age (yr)		**1.0334 (1.024-1.043)**	**1.033 (1.023-1.043)**	**1.035 (1.025-1.044)**	**1.034 (1.025-1.044)**
Race/Ethnicity					
Non-Hispanic Black		1.000	1.000	1.000	1.000
Asian		1.128 (0.418-3.048)	1.140 (0.411-3.165)	0.977 (0.359-2.654)	0.987 (0.365-2.674)
Hispanic		1.516 (0.985-2.334)	1.533 (0.980-2.396)	1.412 (0.916-2.177)	1.436 (0.932-2.212)
Non-Hispanic White		**1.575 (1.182-2.099)**	**1.567 (1.163-2.110)**	**1.527 (1.144-2.036)**	**1.515 (1.137-2.018)**
Other/Not Reported		0.769 (0.459-1.289)	0.769 (0.456-1.297)	0.796 (0.475-1.336)	0.798 (0.476-1.337)
Blood Pressure Medication					
No		1.000	1.000	1.000	1.000
Yes		**0.493 (0.381-0.638)**	**0.499 (0.385-0.646)**	**0.504 (0.388-0.654)**	**0.514 (0.396-0.667)**
Sex					
Female		1.000	1.000	1.000	1.000
Male		1.027 (0.807-1.307)	1.017 (0.799-1.294)	1.010 (0.792-1.288)	0.994 (0.781-1.267)

Table 4. Hazard ratio (HR) and 95% confidence intervals for the association of daily maximum daily temperature and all-cause mortality (ACM) based on Lag 2- Lag 1 discrete-time model structure. Due to the large number of categorical factors, treatment clinics associations were not reported. Bold indicates statistically significant hazard ratio at $p < 0.05$.

Estimate	Model 1: Temperature and confounders only	Model 2: Temperature, confounders, and SBP	Model 3: Temperature, confounders, and IDWG	Model 4: Temperature, confounders, IDWG, and SBP
Temperature β	0.0719	0.0723	0.0726	0.0733
Indirect Effect	--	**0.0004 (0.0002, 0.0007)**	**-0.0007 (-0.0011, -0.0003)**	**-0.0015 (-0.0018, -0.0010)**
3Percent Mediated	--	0.60%	-2.67%	-2.13%

Table 5. Effect size estimates and bootstrap-generated two-sided 95% confidence intervals for mediation effects of the association between daily maximum temperature and all-cause hospital admissions (ACHA) based on Lag 2-Lag 1 discrete-time model structure. Bold indicates statistically significant estimate at $p<0.05$.

Estimate	Model 1: Temperature and confounders only	Model 2: Temperature, confounders, and SBP	Model 3: Temperature, confounders, and IDWG	Model 4: Temperature, confounders, IDWG, and SBP
Temperature β	0.0689	0.06817	0.0732	0.07228
Indirect Effect	--	0.0007 (-0.0012, 0.00111)	**-0.0043 (-0.0052, -0.0015)**	**-0.0034 (-0.0061, -0.0016)**
Percent Mediated	--	1.03%	-6.26%	-4.94%

Table 6. Effect size estimates and bootstrap-generated two-sided 95% confidence intervals for mediation effects of the association between daily maximum temperature and all-cause mortality (ACM) based on Lag 2- Lag 1 discrete-time model structure. Bold indicates statistically significant estimate at $p<0.05$.

5.8 Figures

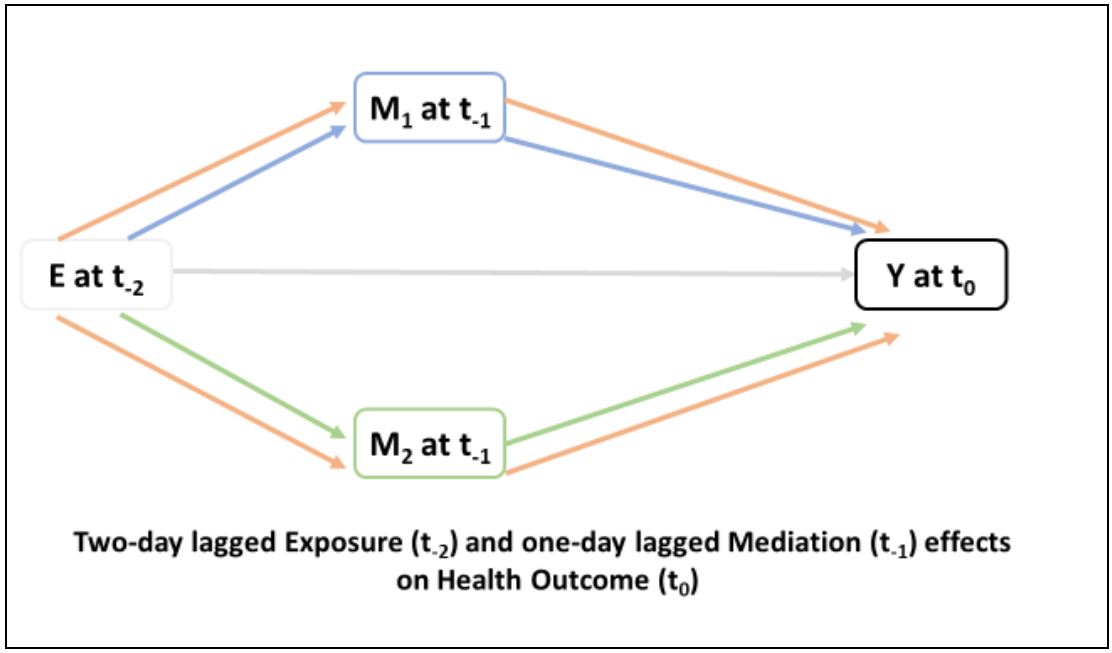


Figure 1. Directed acyclic graph (DAGs) depicting mechanistic pathways between time-dependent daily maximum temperature exposures (E), and IDWG change (M_1) and preSBP (M_2) mediators. DAG represents Lag 2-Lag1 specific pathways using t_{-2}, t_{-1}, and t_0 variables that correspond to time-dependent measures before hospital admission or mortality events (t_0). Grey arrow represents total effect pathway; Single blue arrow represents an indirect pathway operating through M_1. Single green arrow represents an indirect pathway operating through M_2. And double orange arrows represent combined indirect pathways operating through M_1 and M_2.

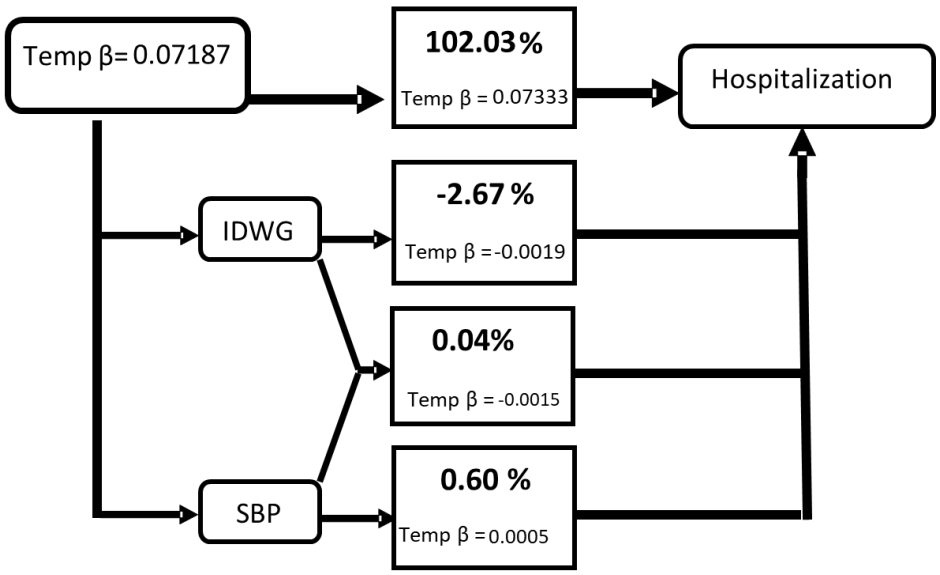


Figure 2. Combined pathway analysis of the association between daily maximum temperature and all-cause hospital admissions (ACHA) and mediating paths for combined mediators based on Lag 2- Lag 1 discrete-time model structure. For indirect paths: IDWG path is considered independent of preSBP, and preSBP indirect effect is independent of IDWG, and IDWG + preSBP path is independent of IDWG and preSBP indirect effects. Direct effects greater than 100% can occur when inconsistent mediation is present in one or more of the paths.

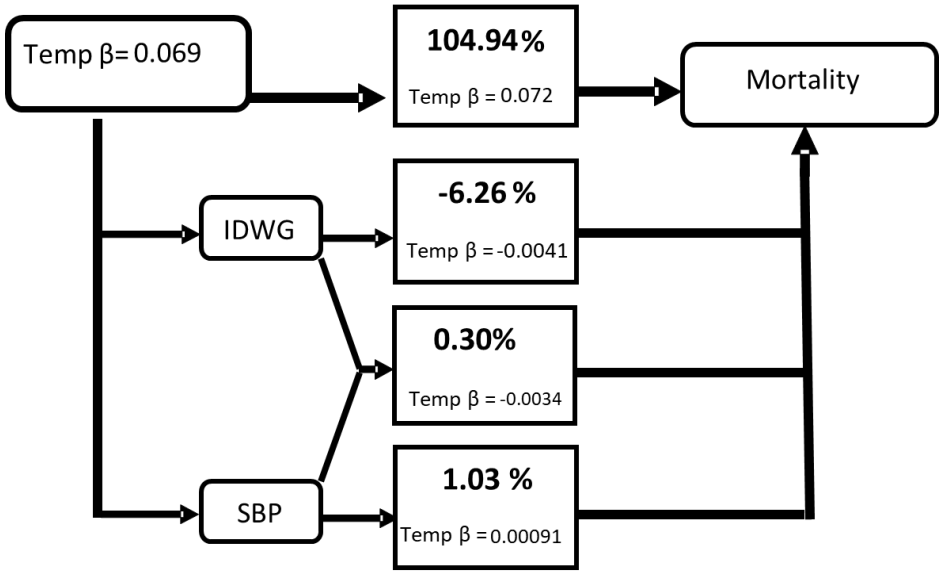


Figure 3. Combined pathway analysis of the association between daily maximum temperature and all-cause mortality (ACM) and mediating paths for combined mediators based on Lag 2- Lag 1 discrete-time model structure For indirect paths: IDWG path is considered independent of preSBP, and preSBP indirect effect is independent of IDWG, and IDWG + preSBP path is independent of IDWG and preSBP indirect effects. Direct effects greater than 100% can occur when inconsistent mediation is present in one or more of the paths.

Chapter 6: Conclusions, Limitations, Public Health Implications, and Directions for Future Research

This dissertation work presents a focused study on the effects of acute environmental exposures on a vulnerable population living with a chronic kidney condition known as end-stage renal disease (ESRD). Individuals living with ESRD require life-long and highly frequent dialysis treatments. The study chapters expanded on the critical risks uniquely contributed by extreme heat events, air pollution, and ambient temperature as outdoor exposures within the United States' northeastern region. Individual-level determinants related to socio-demographics, medical history, and location provided enhanced context to observed risks. And by leveraging a longitudinal study design informed by repeated clinical measures, this dissertation also explored the role of increased temperature on individual-level physiological responses as potential proximate mediators to hospital admissions and mortality outcomes.

6.1 Key Findings: Role of extreme heat events on the ESRD population (Chapter 2 and 3)

The research contributed significant findings that linked extreme heat events to increased rates of all-cause mortality (ACM) and all-cause hospital admissions (ACHA) stratified by location, race/ethnicity, and pre-existing comorbidities. Our case-crossover study applied same-day, one-day lag, and cumulative (0-1) lag EHE exposure metrics. Our preliminary findings (Chapter 2) established plausible acute risk based on a limited sample population exclusively treated in Boston, MA;

New York, NY; and Philadelphia, PA from 2003-2012. Overall, cumulative risk estimates for hospital admission and mortality were estimated at 36% and 32%, respectively, after pooling all three cities. Though city-specific rate ratios did differ, the result highlighted the observed geographic variability with EHE-related effects. This work also showed that patients living with additional comorbidities had consistently higher mortality rates from short-term EHE exposures. We also noted heterogeneity in risks by race/ethnicity and by pre-existing comorbidities for hospital admissions.

In Chapter 3, the research aim broadened the preliminary three-city study (n=7,445) to 28 counties within Northeast US (n=60,717). We applied the same design methods, exposure metrics, and lag structures to a widen catchment area within the northeastern region from 2001-2019. The data used to determine the exposure-response association came from the same environmental and medical data sources as Chapter 2. We observed notable attenuation for all-cause mortality and all-cause hospital admission effects across each short-term lag structure in our pooled analysis. The association between same-day EHE effects and mortality remained significant. We noted consistent variability in risk estimates across latitudes. Though, hospital admission risk by latitude and race/ethnicity displayed mostly non-significant null associations. In all, we found that same-day EHE exposure is typically more pronounced compared to one-day lag EHE exposures, except for cerebrovascular and ischemic heart disease subgroups. Lastly, we observed that comorbidity as an individual-level determinant is a critical characteristic for intervention from EHE effects.

6.2 Key Findings: Air pollution impacts on ESRD population (Chapter 4)

Our goals for this project on characterizing the short-term effects of ambient air pollution exposure among the ESRD population were 1) to investigate the main effects of daily $PM_{2.5}$ and O3 concentrations after adjusting for EHE on ACHA and ACM outcomes and, 2) to investigate the modifying effects of EHE between air pollutants and health endpoints.

In Chapter 4, we pooled daily ACHA and ACM events from our northeastern ESRD study population. Data for county-level air pollution were obtained using resolved coupled model outputs from Climate-Weather Research and Foresting and Community Multiscale Air Quality (CWRF-CMAQ) simulations from 2001-2016. We found that using this data source helped to reduce potential exposure misclassification by improving spatial and temporal granularity. In all, short-term exposure to $PM_{2.5}$ and O_3 for up to 3 days is associated with increased ACM risk, and we found a negligible short-term risk of ACHA among ESRD patients. There is a substantive increase in mortality risk from 3-day and 4-day cumulative O_3 exposures that exceed air quality criteria during EHE days compared to non-EHE days. We found potential effect modification from extreme heat events in Lag 0-3 O_3-ACM and Lag 0-3 $PM_{2.5}$-ACM models. Null associations between acute air pollutants and ACHA did not exhibit statistical evidence of effect modification by EHE.

6.3 Key Findings: Mediation by proximate physiological responses (Chapter 5)

Lastly, this study aimed to understand better the intermediate role of acute physiological responses associated with ambient temperature changes during warmer months of 2011-2019 in Philadelphia, PA. We used blood pressure and interdialytic weight gain (IDWG) change as mediators to conduct mediation analysis. This approach assessed the mechanistic validity of individual and combined pathways that could explain the total effect between temperature and ACM or ACHA outcomes. Methodologically, this work involved four major components: 1) determine appropriate Cox regression models for survival outcomes, 2) identify an appropriate lag model structure that represents temporal precedence, 3) apply imputation methods to account for missing data related to time-varying covariates, and 4) conduct traditional mediation analysis using two time-dependent mediators.

Chapter 5 confirmed that ambient temperature as a continuous exposure could predict ACHA and ACM risks after adjusting for race/ethnicity, sex, age, blood pressure medication use, and treatment clinic. We also found that patients that are prescribed blood pressure medication for managing hypertension demonstrated nearly 50% protection from mortality. Additionally, specific to exposure-mediator models, ambient temperature was negatively associated with blood pressure and IDWG percent changes.

In individual mediation analysis (single pathway only), we found interesting evidence of significant pathways for all three (preSBP, IDWG, and preSBP + IDWG), and two of the three (IDWG and preSBP + IDWG) studied pathways for ACM and ACHA event outcomes, respectively. However, indirect effect estimates

demonstrated inconsistent mediation that suggested suppression effects for some mechanistic pathways. For example, the pathway for IDWG, independent of preSBP, showed inconsistent mediation in ACHA (-2.67%) and ACM (-6.26%) based on combined pathway models. Those pathways are working against, instead of explaining, the effect attributed to reduced mean blood pressure and IDWG estimates. This observation could hint as a protective effect from increased temperature exposures. Proportion mediated estimates from preSBP + IDWG pathways achieved near 0% in combined pathway analysis. This suggests that preSBP and IDWG, as a concatenated pathway, may not mechanistically explain the relationship between temperature and mortality/hospital admissions. Due to the modest proportion mediate estimates, our findings also imply that the causes of mortality and morbidity effects may involve other additional explanatory factors and more complex mechanistic pathways to describe temperature effects specific to the ESRD population.

6.4 Study Limitations

While chapter-specific limitations have been discussed at the end of Chapters 2 through 5, this section provides the dissertation's at-large study limitations. Firstly, findings from our northeastern region-focused analyses are not necessarily generalizable to other US regions. Environmental conditions related to climate and air quality are often location-specific, where seasonal variability and urban densities are conditioned by geography. Our work did observe environmental variability across the northeastern US and remarkable heterogeneity in population-level responses. Additionally, the overall composition of the sample population does not allow for generalizability. An overarching reason is that our sample population was not

randomized. Also, we observed suggestions of this bias based on our near-equivalent prevalence of non-Hispanic Black and non-Hispanic White patients living with ESRD at the regional level. Nationally, the United States Renal Disease System (USRDS) Annual Report reports 3.4 times higher prevalence among non-Hispanic Blacks than Whites. [30] In addition, ESRD patients with CVD within the study population were notably under-represented (1.6%) when compared to the target population (76.5%). [30]

Another consistent limitation relates to using 'all-cause' as a health endpoint to describe morbidity and mortality outcomes. Each study did not use cause-specific outcomes due to concerns with dramatically reduced sample sizes after selecting cause-defined cases. One study characterized the relationship between wildfire smoke-derived $PM_{2.5}$ exposure and mortality among ESRD patients used cause-specific mortality outcomes.[123] The authors' findings did note differences in risk magnitudes and direction between all-cause and cause-specific mortalities. In this work, we learned that identifying meaningful clinical interventions from acute environmental exposures requires specifying proximal health-related complications that result in hospital admissions and premature death. This understanding can bridge our empirical evidence of associational relationships to causal effects and establish clinically meaningful, evidence-based interventions.

A running assumption in this work was that outdoor ambient conditions could influence indoor environmental conditions and, as a result, pose a risk. This indirect relationship between outdoor and indoor environments has been studied in numerous validation studies. [67, 219, 220] However, a critical determinant that can obfuscate

the relationship is air conditioning access and use.[221, 222] Air conditioning during elevated temperature is a reliable protective intervention. In this work, we were not able to determine air conditioning use at the individual level.

Another limitation to the overall work relates to the seemingly lower prevalence of ESRD patients with CVD within the study population (1.6%). The most recent USRDS Annual Report [30] estimated CVD prevalence at 76.5% among patients receiving hemodialysis. This discrepancy might be primarily attributed to potential reporting and misclassification errors. According to FKC, there is a possibility that CVD may have been diagnosed earlier in a patient's dialysis career and not reported into FKC's medical records. Another reason may relate to changes in CVD documentations over time since 2001. These types of internal changes may have resulted in information loss in FKC's data warehouse. Thus, identifying patients with CHF, IHF, and MI as a direct classification of CVD co-morbidities since 2001 may have misclassified true CVD cases as non-CVD cases within our study population. A potential indirect approach to estimate CVD prevalence is to consider cause-specific hospital admissions or cause-specific mortality and cross-reference CVD-related categories associated with ICD codes.

Lastly, we restricted our time period to include only warmer months of the year- namely May-September (MJJAS)- and excluded the remaining calendar months. Our overall approach focused on extreme heat and increasing temperature effects. As such, characterizing the role of colder temperatures, especially pertaining to air quality and physiological responses, overlooked the role of colder temperature exposures as a potential risk factor. Incorporating cold-related weather and climate

may improve the understanding of environmental vulnerability among ESRD patients, especially in regions that experience abnormally higher snowfall seasons and more extreme cold events. Also, considering cold exposures during colder months could also provide insight into interactive effects with PM2.5 in degraded air quality locations.

6.5 Public Health and Clinical Implications

- Location-specific heat management plans and air quality guidance to protect ESRD patients

The National Integrated Heat Health Information System (NIHHIS), a US federal consortium that includes the National Ocean and Atmospheric Agency (NOAA), Centers for Disease Control and Prevention (CDC), and the US Environmental Protection Agency (USEPA), provide comprehensive resources and guidance for developing excessive heat notification and response programs. Many local public health agencies have adopted critical heat management strategies as part of their emergency response and inclement weather response plans. Similar guidance for outdoor activity from the USEPA and CDC is also available to protect public health from harmful air quality levels. In this research, we found that risk vulnerability and risk assessment for the ESRD population is consistent with other at-risk populations, including children and older adults. Despite their chronic renal health and special healthcare needs, the ESRD population is not explicitly identified as a vulnerable population.

Exposure to extreme heat events (Chapters 2 & 3) and harmful levels of air pollution (Chapter 4) does promote health risk. The Agency for Health Research and Quality (AHRQ) considers populations living with chronic renal diseases and receiving dialysis treatments as a priority population. Therefore, enhanced health services and surveillance during periods of extreme heat and elevated air pollution episodes should be incorporated into location-level public health emergency plans. As part of a proactive public health protectiveness campaign, early warning systems informed by ambient temperature and air quality forecasts may be effective in preventing heat-related and air pollution-related harm. Risk forecasting for extreme heat events combined with air pollution surveillance can potentially enhance medical care preparedness and delivery for health service providers on the ground. For example, special advisories could initiate in-person visits to ESRD patients through coordination between dialysis centers and public health agencies. Developing adaptation strategies informed by air quality indices and warning systems can benefit ESRD patients and other highly-vulnerable populations. Though, active follow-up efforts and engagement should be adopted to verify the extent of preparedness and stress vulnerability.

- Develop and implement air quality standards that consider sensitive populations.

Typically, urban environments during warmer months are at high risk of increased ambient ozone levels. [223] As an added concern, atmospheric warming attributed to climate change will increase ozone chemical production at the ground-level. Our findings suggested that exceeding regulatory National Ambient Air Quality Standards

(NAAQS) criteria limits for O_3 may substantially increase mortality risk (Chapter 4). This could have implications for the general population, especially among older subpopulations, living with pre-existing cardiopulmonary conditions, and outdoor laborers. An additional layer of public health importance, regulatory agencies could consider revising NAAQS to reflect protection for the most vulnerable, including the ESRD population. It might also be critical to consider near-term climate-driven ozone production and weigh its risks as well.

- Potential clinical interventions to minimize the impact of extreme heat

Leveraging data on individual-level determinants (Chapters 2, 3, and 5) and clinical measurements (Chapter 5) allowed insight into potential health impacts within the ESRD population. Some of the studied risk factors identified at-risk subgroups like individuals diagnosed with additional comorbidities (Chapters 2&3). We also note that clinical measures such as IDWG change did have a modest role in suppressing hospitalization and mortality outcomes associated with elevated temperature. Through preliminary mediation analysis, reduced IDWG changes may have promoted survival advantage during periods of increased ambient temperature. We also noted that the association between anti-hypertension medication and mortality (Chapter 5) suggested protective effects. Prescribed anti-hypertension medication may have promise as a clinical intervention to decreased vulnerability from the elevated ambient temperature. Specialized patient-level findings can be used to inform treatment protocols for preventing and mitigate heat-related illnesses.

6.6 Directions for Future Research

There are multiple possibilities for enhancing climate and health research specific for populations living with chronic renal diseases. Fortunately, many of these considerations can be achieved through the continued collaboration relationship between the University of Maryland and the Renal Research Institute.

We assumed that indoor conditions should indirectly match outdoor environments in our exposure assessments. While some studies have validated this assumption [67, 220, 224], it is critical to collect personal-level environmental measures since this assumption is conditioned on numerous lifestyle and socio-demographic determinants. Environmental exposures from empirically measured indoor environmental quality measurements can be collected by using passive and wearable personalized devices. Qualitative methods that include interviews and surveys can also describe personal thermal comfort, stress, and perception. [66, 225] The inclusion of health insurance coverage status may serve as a resourceful proxy for socioeconomic status, and by extension, the quality of indoor environments for ESRD patients. A study conducted in New York City did find that perception of indoor temperature was strongly associated with measured outdoor air temperature. [219] And further, reported heat-related illness during the summer months is also associated with perceived indoor temperature. [219] Such information can provide invaluable insight into heat and air quality responses that are not directly gathered from in-situ monitoring instruments. A critical component for characterizing indoor environmental conditions relates to identifying and accounting for mechanical and non-mechanical cooling conditions. Cooling and ventilation resources can serve as a protective agent against heat-related illness, however, its access and use does depend

on contextual factors like socio-economic position and neighborhood. [220-222] In all, the systematic collection of exposure measures from indoor environments can be similarly applied to epidemiological models to assess temperature and air quality-related risks.

Urban communities are disproportionately affected by extreme heat because of higher poverty rates and more intense heat exposure due to the urban heat island effect [64-68]. As a result, heat-related health risks may be different in urban, suburban, and rural landscapes. Stratification analyses by defined geographic types would be a logical next step to disentangle urban-specific and rural-specific effects from targeted environmental exposures within the ESRD population.

Accessing essential health care services can be a major challenge during weather disturbances. Inclement weather events can act as an adherent for timely dialysis treatments. Consequently, ESRD patients who routinely receive outpatient dialysis are vulnerable to increased morbidity and mortality due to missing critical therapies.[226] In many cases, missing a single appointment is not immediately problematic or life-threatening. However, multiple missed appointments due to prolonged clinic closures caused by electrical outages, dangerous road conditions, and the lack of accessible transportation can pose life-threatening burdens for delivering life-saving care and treatment for clinicians and patients. Future work needs to consider the 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 at the local level. Recently, Winter Storm Uri caused mass power outages throughout Texas that directly

impacted about 54,000 dialysis patients. [227] This work can promote enhanced climate readiness for reducing public health burdens caused by severe weather events by developing disaster response plans for delivering and maintaining uninterrupted dialysis-related health services.

Incorporating temperature-related climate change projections to assess health impacts specific to the ESRD population would be a powerful approach to identify near-term and long-term vulnerabilities. The spatial scalability for evaluating climate change's health impacts under varying global warming scenarios can range from global [228] to local levels [229, 230]. Fortunately, processed downscaled climate models and data sets are available to develop applicable exposure metrics and characterize temporally-scaled health impacts. Some studies have used temperature projections to estimate heat-related health impacts into 2100. [94, 228] Though evaluating projections in wildfires and flooding and its implications to human health, and more specifically to the ESRD population, is a critical need as well.

There are a few additional possibilities for future work on study design. Our original analysis focused entirely on all-cause mortality and all-cause hospital admissions for ESRD patients. Studying cause-specific morbidity and mortality outcomes would be a practical approach for identifying organ-targeted linkages to acute heat and air pollution exposures. However, to achieve an acceptable statistical sample size for an acceptable effect size detection, increased geographical scaling beyond the northeastern region is essential. For example, conducting a nationally-scaled study similar to prior studies using Medicare-Medicaid medical records is a feasible next step to incorporate cause-specific endpoints. [24, 123] And lastly,

alternative approaches to studying the effects of extreme weather and high air pollution episodes for population health is needed. Case crossover studies have had a long record in estimating acute environmental impact. However, quasi-experimental methods may be more appropriate for making casual inferences by comparing population health-level responses before and after defined exposure events. [119, 231] By applying natural experiment conditions, there is greater flexibility in disentangling extreme weather events from underlying secular trends and accounting for unmeasured confounding.

Lastly, despite lowered mediated proportions and evidence of suppression effects, more investigation is still needed to account for complex pathways among multiple mediators while upholding rigorous assumptions to infer causal relationships. [232] As a starting point, new pathways should include responses consistent with systemic inflammatory response syndrome (SIRS) as seen with electrolyte disorders from passive heat stress. Incorporating advanced causal mediation allows for model flexibility in considering ordered mediation [232], nonlinear trends with preSBP and IDWG [233, 234], and incorporating likely interaction [235] between anti-hypertension medication and temperature. Such approaches would also address time-varying confounding affected by lagged exposure and mediator measures. [236]

Appendices

Chapter 2 Supplemental materials

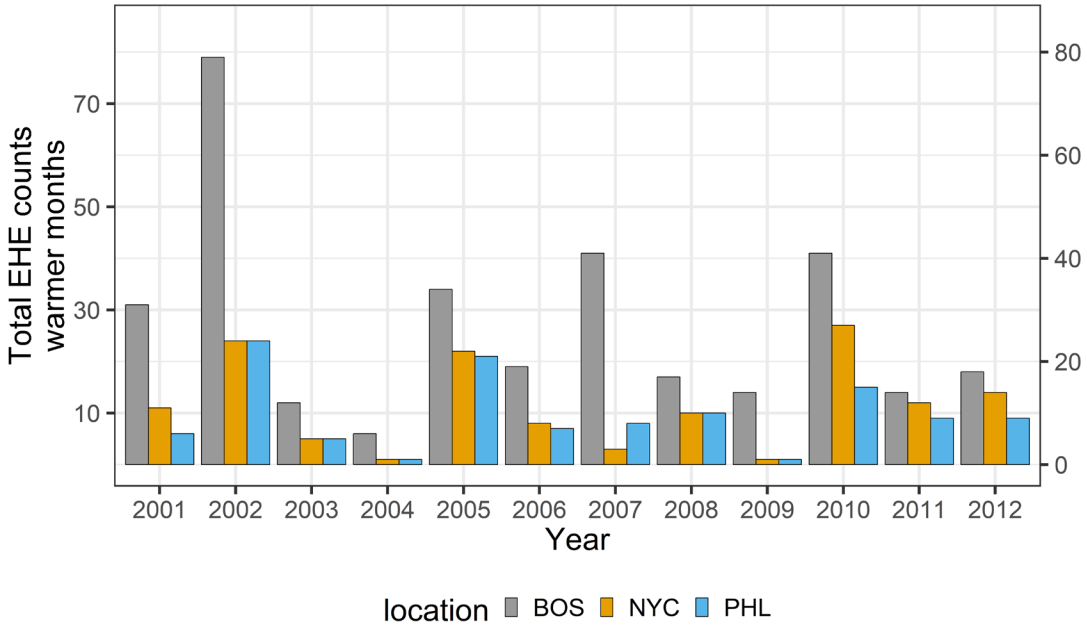


Figure S2-1. Yearly total extreme heat events in May through September by city

Chapter 3 Supplemental materials

County, State	Number of EHE days	EHE Rate
Wicomico County, MD	266	0.092
New Haven County, CT	253	0.087
Kings County, NY	228	0.078
Bronx County, NY	223	0.077
Hartford County, CT	221	0.076
New York County, NY	218	0.075
Essex County, NJ	215	0.074
Hillsborough County, NH	214	0.074
Norfolk County, MA	201	0.069
Rockingham County, NH	189	0.065
Kent County, RI	182	0.063
Suffolk County, MA	181	0.062
Hampden County, MA	177	0.061
Mercer County, NJ	173	0.060
Lehigh County, PA	165	0.057
Monroe County, NY	161	0.055
Philadelphia County, PA	161	0.055
District of Columbia, DC	150	0.052
New Castle County, DE	149	0.051
Allegheny County, PA	143	0.049
Baltimore City, MD	130	0.045
Androscoggin County, ME	127	0.044
Washington County, MD	114	0.039

Table S3-1. Overall EHE rates during MJJAS for sampled NE counties from 2001-2019

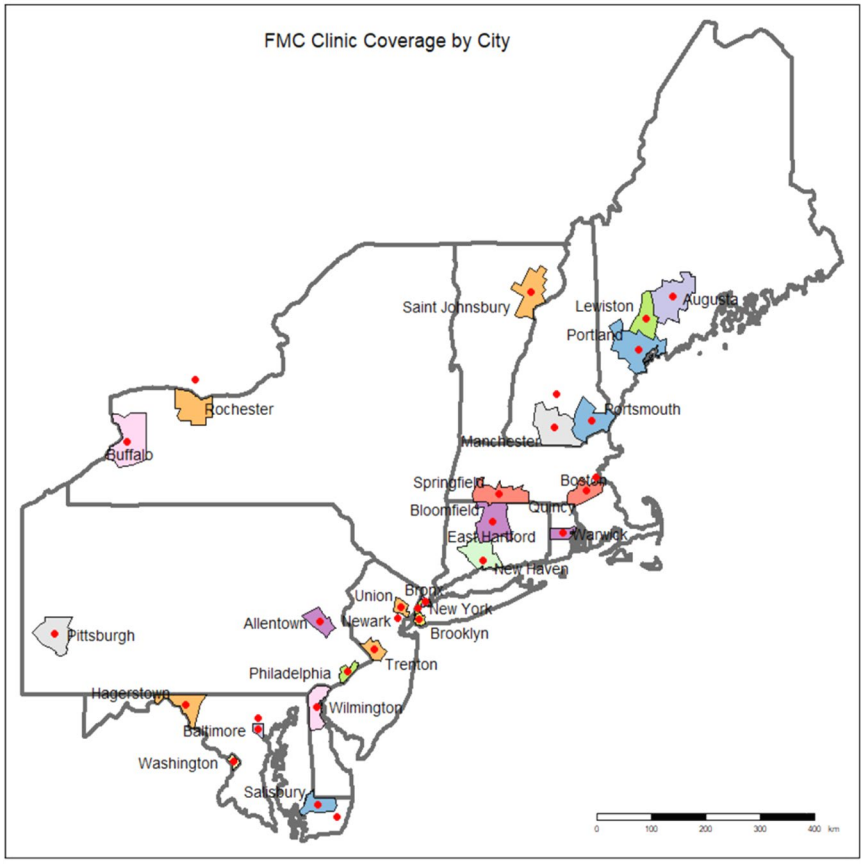


Figure S3-1. Map of focused counties within Northeastern study catchment

Figure S3-2. Total EHEs per year in 28 northeastern US county, 2001-2019

Sensitivity Analysis

We conducted a sensitivity analysis using observed daily mean apparent temperature for sampled counties. Our main analysis estimated the association between EHE and health endpoints for location, race/ethnicity, and comorbidity. Here, we replicated the modeling approach but applied daily mean apparent temperature. These results are presented in Tables S3-2 to S3-9, and we adopted a 5°C incremental increase for our risk interpretations.

	All-cause mortality		All-cause hospital admissions	
	RR	95% CI	RR	95% CI
Lag 0	1.06	1.03-1.09	1.01	0.99-1.02
Lag 1	0.96	0.93-0.99	0.99	0.97-1.00
Cumulative Lag 0-1	1.02	1.00-1.04	0.99	0.98-1.00

Table S3-2. Pooled rate ratio (RR) and 95% confidence interval of mortality and hospital admissions 5°C incremental increases in apparent temperature across the northeastern region.

latitude	county	Lag 0	Lag 1	Lag 0-1
44.470	All	1.06 (1.03-1.09)	0.96 (0.93-0.99)	1.02 (1.00-1.04)
44.469	Caledonia County, VT	2.73 (2.16-3.45)	0.50 (0.40-0.64)	1.38 (1.17-1.63)
44.417	Kennebec County, ME	0.71 (0.60-0.83)	1.10 (0.93-1.31)	0.78 (0.68-0.90)
44.168	Androscoggin County, ME	0.94 (0.79-1.12)	1.62 (1.35-1.96)	1.52 (1.32-1.76)
43.464	Monroe County, NY	1.14 (0.99-1.30)	0.93 (0.81-1.07)	1.06 (0.96-1.17)
42.989	Rockingham County, NH	1.14 (0.97-1.34)	0.78 (0.66-0.91)	0.88 (0.78-1.00)
42.912	Hillsborough County, NH	1.11 (0.93-1.32)	1.05 (0.90-1.24)	1.17 (1.03-1.33)
42.753	Erie County, NY	1.07 (0.86-1.33)	0.80 (0.64-1.00)	0.86 (0.74-0.99)
42.332	Suffolk County, MA	1.14 (1.00-1.31)	1.11 (0.97-1.27)	1.27 (1.14-1.42)
42.170	Norfolk County, MA	0.90 (0.78-1.03)	1.13 (0.98-1.29)	1.01 (0.91-1.13)
42.136	Hampden County, MA	1.20 (1.03-1.40)	0.94 (0.80-1.10)	1.12 (0.99-1.27)
41.806	Hartford County, CT	1.21 (1.04-1.40)	0.79 (0.68-0.91)	0.95 (0.85-1.06)
41.678	Kent County, RI	1.04 (0.87-1.23)	1.01 (0.85-1.21)	1.05 (0.91-1.21)
41.350	New Haven County, CT	0.86 (0.72-1.04)	0.96 (0.80-1.16)	0.83 (0.72-0.96)
40.849	Bronx County, NY	1.14 (0.99-1.31)	0.92 (0.80-1.05)	1.05 (0.94-1.16)
40.787	Essex County, NJ	1.22 (1.06-1.40)	0.81 (0.70-0.94)	0.99 (0.89-1.10)
40.777	New York County, NY	0.88 (0.75-1.02)	1.19 (1.02-1.39)	1.04 (0.93-1.16)
40.660	Union County, NJ	1.28 (1.10-1.49)	0.66 (0.57-0.77)	0.85 (0.76-0.95)
40.635	Kings County, NY	1.12 (0.95-1.32)	0.98 (0.83-1.15)	1.10 (0.96-1.25)
40.614	Lehigh County, PA	0.85 (0.73-1.00)	1.25 (1.07-1.46)	1.07 (0.95-1.20)
40.469	Allegheny County, PA	1.14 (0.94-1.37)	1.00 (0.82-1.22)	1.14 (1.00-1.31)
40.283	Mercer County, NJ	0.96 (0.81-1.13)	1.05 (0.89-1.24)	1.01 (0.90-1.13)
40.009	Philadelphia County, PA	1.00 (0.90-1.12)	1.00 (0.89-1.12)	1.00 (0.92-1.09)
39.604	Washington County, MD	1.35 (1.13-1.63)	0.70 (0.58-0.85)	0.95 (0.84-1.08)
39.576	New Castle County, DE	1.12 (0.96-1.32)	0.93 (0.80-1.10)	1.05 (0.94-1.17)
39.300	Baltimore City, MD	0.99 (0.85-1.14)	1.10 (0.94-1.28)	1.08 (0.98-1.20)
38.904	District of Columbia, DC	1.01 (0.88-1.17)	0.92 (0.80-1.07)	0.93 (0.84-1.04)
38.367	Wicomico County, MD	0.89 (0.74-1.08)	1.10 (0.92-1.31)	0.98 (0.86-1.13)

Table S3-3. County-specific rate ratio (RR) and 95% confidence interval of mortality for 5°C incremental increases in apparent temperature across (a) latitudes, north to south; (b) Lag 0 (same-day) , (c) Lag 1 (one-day lag), and (d) cumulative lag (Lag 0-1). All category represents all patients within this sample population for location.

latitude	county	Lag 0	Lag 1	Lag 0-1
44.470	All	1.01 (0.99-1.02)	0.99 (0.97-1.00)	0.99 (0.98-1.00)
44.469	Caledonia County, VT	1.00 (0.84-1.19)	1.06 (0.88-1.27)	1.06 (0.93-1.20)
44.417	Kennebec County, ME	0.94 (0.82-1.06)	1.03 (0.90-1.18)	0.97 (0.87-1.07)
44.168	Androscoggin County, ME	1.12 (0.97-1.29)	0.86 (0.75-1.00)	0.97 (0.86-1.09)
43.464	Monroe County, NY	1.03 (0.97-1.08)	1.00 (0.95-1.05)	1.02 (0.99-1.06)
42.989	Rockingham County, NH	0.93 (0.82-1.05)	1.01 (0.89-1.15)	0.94 (0.85-1.04)
42.912	Hillsborough County, NH	0.97 (0.88-1.07)	0.95 (0.86-1.05)	0.92 (0.86-0.99)
42.753	Erie County, NY	1.10 (0.95-1.28)	0.94 (0.81-1.09)	1.04 (0.93-1.15)
42.332	Suffolk County, MA	1.04 (0.96-1.13)	0.97 (0.89-1.05)	1.01 (0.94-1.08)
42.170	Norfolk County, MA	0.97 (0.89-1.05)	1.01 (0.92-1.09)	0.97 (0.91-1.04)
42.136	Hampden County, MA	1.01 (0.95-1.08)	0.98 (0.92-1.05)	0.99 (0.94-1.05)
41.806	Hartford County, CT	1.00 (0.92-1.09)	0.99 (0.91-1.07)	0.99 (0.93-1.05)
41.678	Kent County, RI	1.04 (0.94-1.14)	0.94 (0.85-1.04)	0.98 (0.91-1.05)
41.350	New Haven County, CT	1.01 (0.91-1.12)	0.96 (0.87-1.07)	0.97 (0.90-1.05)
40.849	Bronx County, NY	0.99 (0.93-1.04)	1.03 (0.97-1.09)	1.01 (0.97-1.06)
40.787	Essex County, NJ	0.98 (0.92-1.04)	1.01 (0.95-1.07)	0.99 (0.95-1.04)
40.777	New York County, NY	0.99 (0.94-1.05)	1.01 (0.95-1.06)	1.00 (0.96-1.04)
40.660	Union County, NJ	1.06 (0.97-1.17)	0.94 (0.86-1.04)	1.01 (0.94-1.08)
40.635	Kings County, NY	0.99 (0.93-1.06)	0.98 (0.92-1.05)	0.97 (0.93-1.02)
40.614	Lehigh County, PA	0.99 (0.92-1.06)	1.00 (0.93-1.08)	0.99 (0.94-1.04)
40.469	Allegheny County, PA	1.06 (0.98-1.14)	0.96 (0.89-1.04)	1.02 (0.97-1.08)
40.283	Mercer County, NJ	1.02 (0.95-1.10)	1.00 (0.93-1.08)	1.02 (0.97-1.08)
40.009	Philadelphia County, PA	1.01 (0.98-1.04)	0.97 (0.94-1.00)	0.98 (0.96-1.00)
39.604	Washington County, MD	1.02 (0.92-1.13)	1.03 (0.93-1.15)	1.05 (0.98-1.13)
39.576	New Castle County, DE	0.97 (0.91-1.04)	1.02 (0.96-1.08)	0.99 (0.95-1.04)
39.300	Baltimore City, MD	0.99 (0.92-1.07)	0.98 (0.91-1.06)	0.98 (0.93-1.03)
38.904	District of Columbia, DC	1.02 (0.97-1.07)	0.98 (0.93-1.03)	1.00 (0.96-1.03)
38.367	Wicomico County, MD	1.04 (0.95-1.13)	0.97 (0.89-1.06)	1.01 (0.94-1.08)

Table S3-4. County-specific rate ratio (RR) and 95% confidence interval of hospital admission for 5°C incremental increases in apparent temperature across (a) latitudes, north to south; (b) Lag 0 (same-day), (c) Lag 1 (one-day lag), and (d) cumulative lag (Lag 0-1). All category represents all patients within this sample population for location.

race_ethnicity	Lag 0	Lag 1	Lag 0-1
All	1.05 (1.01-1.08)	0.98 (0.95-1.01)	1.02 (1.00-1.04)
Asian	1.42 (1.36-1.49)	0.55 (0.52-0.58)	0.78 (0.76-0.81)
Hispanic	1.46 (1.41-1.52)	0.81 (0.78-0.84)	1.18 (1.15-1.21)
NH Black	1.02 (0.99-1.05)	0.98 (0.95-1.01)	1.00 (0.98-1.03)
NH White	0.99 (0.96-1.02)	1.03 (1.00-1.06)	1.01 (0.99-1.04)

Table S3-5. Subgroup rate ratio (RR) and 95% confidence interval of mortality for 5°C incremental increases in apparent temperature across (a) race/ethnicity groups; (b) Lag 0 (same-day) , (c) Lag 1 (one-day lag), and (d) cumulative lag (Lag 0-1). All category represents all patients within this sample population for race/ethnicity.

race_ethnicity	Lag 0	Lag 1	Lag 0-1
All	1.00 (0.99-1.02)	0.99 (0.97-1.00)	0.99 (0.98-1.00)
Asian	1.03 (1.00-1.07)	0.95 (0.92-0.99)	0.99 (0.96-1.01)
Hispanic	0.98 (0.96-1.01)	1.00 (0.97-1.02)	0.98 (0.96-1.00)
NH Black	1.01 (0.99-1.02)	0.98 (0.97-1.00)	0.99 (0.98-1.00)
NH White	1.01 (0.99-1.03)	0.99 (0.97-1.01)	1.00 (0.98-1.01)

Table S3-6. Subgroup rate ratio (RR) and 95% confidence interval of hospital admission for 5°C incremental increases in apparent temperature across (a) race/ethnicity groups; (b) Lag 0 (same-day), (c) Lag 1 (one-day lag), and (d) cumulative lag (Lag 0-1). All category represents all patients within this sample population for race/ethnicity.

comorbidity	Lag 0	Lag 1	Lag 0-1
All	1.08 (1.06-1.10)	0.96 (0.94-0.98)	1.03 (1.02-1.05)
Any	1.07 (1.04-1.11)	0.96 (0.93-0.99)	1.03 (1.01-1.05)
Any CVD	1.18 (1.12-1.25)	0.92 (0.88-0.98)	1.09 (1.06-1.13)
Cerebrovascular	1.42 (1.29-1.55)	0.60 (0.55-0.66)	0.85 (0.80-0.90)
CHF	1.25 (1.17-1.33)	1.04 (0.97-1.10)	1.30 (1.24-1.35)
COPD	1.05 (0.97-1.14)	0.97 (0.90-1.04)	1.01 (0.95-1.08)
Diabetes	1.07 (1.04-1.11)	0.96 (0.93-0.99)	1.03 (1.01-1.06)
IHD	1.03 (0.96-1.09)	0.86 (0.81-0.92)	0.89 (0.85-0.92)

Table S3-7. Subgroup rate ratio (RR) and 95% confidence interval of mortality for 5°C incremental increases in apparent temperature across (a) comorbidity type; (b) Lag 0 (same-day) , (c) Lag 1 (one-day lag), and (d) cumulative lag (Lag 0-1). All category represents all patients within this sample population; Any category represents patients with any studied comorbidity; and Any CVD represents patients with any cardiovascular-related comorbidities like CHF, IHD, and MI.

comorbidity	Lag 0	Lag 1	Lag 0-1
All	1.01 (1.00-1.03)	0.99 (0.97-1.00)	1.00 (0.99-1.01)
Any	1.01 (1.00-1.03)	0.98 (0.97-1.00)	1.00 (0.99-1.01)
Any CVD	0.98 (0.94-1.01)	0.99 (0.96-1.03)	0.97 (0.94-1.00)
Cerebrovascular	1.17 (1.11-1.24)	1.06 (1.00-1.12)	1.24 (1.19-1.30)
CHF	1.00 (0.95-1.04)	0.95 (0.91-0.99)	0.94 (0.91-0.97)
COPD	1.09 (1.02-1.16)	0.87 (0.81-0.93)	0.95 (0.90-1.00)
Diabetes	1.01 (1.00-1.03)	0.99 (0.97-1.00)	1.00 (0.99-1.01)
IHD	0.92 (0.88-0.96)	1.10 (1.05-1.14)	1.01 (0.98-1.04)

Table S3-8. Subgroup rate ratio (RR) and 95% confidence interval of hospital admission for 5°C incremental increases in apparent temperature across (a) comorbidity type; (b) Lag 0 (same-day) , (c) Lag 1 (one-day lag), and (d) cumulative lag (Lag 0-1). All category represents all patients within this sample population; Any category represents patients with any studied comorbidity; and Any CVD represents patients with any cardiovascular-related comorbidities like CHF, IHD, and MI.

Chapter 4 Supplemental materials

variable	county	mean	sd	min	q1	med	q3	max	mad	iqr	cv	skewness	se.skewness	kurtosis
cmaq_PM2.5	Allegheny County	7.62	4.68	0.69	4.66	6.8	9.52	53.07	3.51	4.87	0.61	2.78	0.07	16.8
	Androscoggin County	7.06	5.94	0.18	3.46	5.68	9.19	110.63	3.9	5.73	0.84	4.95	0.05	55.36
	Baltimore City	11.19	5.92	0.88	6.95	10.04	14.25	45.54	5.16	7.29	0.53	1.43	0.05	3.5
	Bronx County	6.8	4.95	0.24	3.97	6.01	8.47	68.32	3.29	4.5	0.73	4.38	0.05	35.71
	Caledonia County	6.74	4.97	0.68	4.12	5.94	8.33	68.32	3.08	4.21	0.74	4.86	0.07	41.77
	Cumberland County	8.51	6.37	0.29	4.41	7.15	11.14	117.27	4.7	6.72	0.75	4.19	0.05	46.62
	District of Columbia	7.58	4.25	0.42	4.73	6.72	9.5	40.96	3.41	4.77	0.56	1.79	0.05	6.34
	Erie County	7.51	4.48	1.06	4.75	6.73	9.08	50.56	3.27	4.33	0.6	3.04	0.08	18.8
	Essex County	8.51	6.37	0.29	4.41	7.15	11.14	117.27	4.7	6.72	0.75	4.19	0.05	46.62
	Hampden County	8.84	5.14	0.47	5.28	8	11.49	82.98	4.49	6.2	0.58	2.46	0.05	21.09
	Hartford County	8.53	5.06	0.45	4.95	7.67	11.18	79.98	4.42	6.23	0.59	2.32	0.05	18.9
	Hillsborough County	7.1	5.87	0.13	3.6	5.93	9.23	100.79	3.95	5.63	0.83	5.06	0.05	52.93
	Kennebec County	6.36	5.61	0.11	3	5.09	8.21	95.79	3.61	5.21	0.88	4.9	0.05	48.37
	Kent County	7.5	4.55	0.36	4.28	6.43	9.67	58.83	3.78	5.37	0.61	1.99	0.05	10.72
	Kings County	11.52	6.03	1.39	7.02	10.39	14.9	44.55	5.64	7.88	0.52	1.12	0.05	1.8
	Lehigh County	9.75	5.8	0.27	5.53	8.65	12.73	52.81	5.23	7.2	0.6	1.29	0.05	2.97
	Mercer County	9.03	4.72	1.08	5.73	8.23	11.32	60.36	4.09	5.59	0.52	2.03	0.05	11.06
	Monroe County	9.48	5.38	0.89	6.06	8.7	11.84	71.66	4.24	5.77	0.57	2.82	0.05	19.51
	New Castle County	8.09	4.63	0.67	4.87	7.12	10.24	47.45	3.85	5.37	0.57	1.85	0.05	6.75
	New Haven County	11.14	6.38	0.69	6.65	10.06	14.36	105.31	5.58	7.7	0.57	2.45	0.05	21.94
	New York County	11.53	6.04	1.39	7.04	10.4	14.9	44.55	5.63	7.86	0.52	1.12	0.05	1.81
	Norfolk County	7.22	4.92	0.52	4.26	6.42	9.13	110.55	3.53	4.87	0.68	5.97	0.05	92.22
	Philadelphia County	8.65	4.55	1.22	5.53	7.85	10.8	56.14	3.87	5.27	0.53	1.9	0.05	9.05
	Rockingham County	10.62	7.01	1.06	6.14	9.53	13.46	125.44	5.38	7.32	0.66	4.43	0.05	48.78
	Suffolk County	9.19	5.76	1.01	5.63	8.24	11.5	124.58	4.19	5.88	0.63	5.57	0.05	80.39
	Union County	9.21	5.17	0.94	5.61	8.26	11.81	71	4.43	6.2	0.56	2.31	0.05	15.33
	Washington County	7.5	4.54	0.22	4.3	6.58	9.83	36.89	3.69	5.53	0.6	1.57	0.06	4.57
	Wicomico County	6.94	5.33	0.61	3.99	5.79	8.4	128.82	3.04	4.4	0.77	9.21	0.06	183.28

Table S4-1. Summary statistics for average daily $PM_{2.5}$ measurements derived from CWRF-CMAQ simulations by county

variable	county	mean	sd	min	q1	med	q3	max	mad	iqr	cv	skewness	se.skewness	kurtosis
cmaq_O3	Allegheny County	57.65	7.62	35.21	52.56	57.24	62.47	86.72	7.25	9.91	0.13	0.25	0.07	0.43
	Androscoggin County	57.46	13.25	22.51	47.9	55.3	65.81	112.09	12.73	17.9	0.23	0.66	0.05	0.38
	Baltimore City	69.71	16.89	27.02	58.08	68.04	79.46	154.98	15.84	21.36	0.24	0.63	0.05	0.85
	Bronx County	56.03	8.61	28.72	50.09	55.35	61.41	92.56	8.41	11.31	0.15	0.37	0.05	0.35
	Caledonia County	53.3	7.07	28.72	48.6	53.17	57.88	76.19	6.81	9.27	0.13	0.11	0.07	0.31
	Cumberland County	61.48	16.18	22.96	49.86	58.75	72.21	122.93	16.3	22.34	0.26	0.53	0.05	-0.02
	District of Columbia	63.04	12.54	29.26	54.92	61.77	69.8	130.49	10.9	14.86	0.2	0.76	0.05	1.63
	Erie County	60.01	8.98	37.55	54.15	58.5	64.75	108.98	7.96	10.61	0.15	1.12	0.08	2.76
	Essex County	61.48	16.18	22.96	49.86	58.75	72.21	122.93	16.3	22.34	0.26	0.53	0.05	-0.02
	Hampden County	66.58	16.48	23.63	54.49	64.14	76.74	128.81	15.67	22.24	0.25	0.59	0.05	0.19
	Hartford County	68.75	17.85	21.19	55.61	66.05	80.55	132.69	18.07	24.94	0.26	0.48	0.05	-0.09
	Hillsborough County	59.19	11.46	28.69	51.11	58.01	66.19	112.68	11.11	15.07	0.19	0.67	0.05	1.07
	Kennebec County	56.24	12.37	24.29	47.39	54.38	64.01	104.81	11.81	16.62	0.22	0.65	0.05	0.39
	Kent County	63.43	18.36	21.66	50.58	61.26	74.93	134.46	18.01	24.3	0.29	0.46	0.05	-0.06
	Kings County	70.75	26.87	17.68	51.63	65.02	85.84	191.16	23.93	34.18	0.38	0.98	0.05	1.15
	Lehigh County	63.92	11.31	25.23	55.74	62.92	71.23	109.93	11.21	15.48	0.18	0.4	0.05	0.3
	Mercer County	68.12	14.91	26.17	57.99	67.47	78.21	122.35	15.02	20.21	0.22	0.12	0.05	-0.09
	Monroe County	62.03	10.57	35.67	54.5	60.59	68.32	107.43	10.11	13.82	0.17	0.59	0.05	0.34
	New Castle County	66.36	13.84	27.1	57.39	65.53	74.94	122.18	13.19	17.55	0.21	0.24	0.05	0.31
	New Haven County	71.59	24.04	20.17	53.64	67.75	87.16	191.71	23.62	33.49	0.34	0.66	0.05	0.26
	New York County	71.02	26.91	17.68	51.8	65.17	85.97	191.16	24.1	34.16	0.38	0.98	0.05	1.13
	Norfolk County	63.6	15.59	21.51	52.91	61.78	73.34	120.87	14.67	20.41	0.25	0.43	0.05	0.07
	Philadelphia County	65.9	13.64	27.38	56.98	64.95	75.01	123.14	13.16	18.02	0.21	0.23	0.05	0.36
	Rockingham County	62.47	15.11	19.71	51.92	61.49	71.7	142.33	14.69	19.78	0.24	0.56	0.05	1
	Suffolk County	62.54	15.56	19.02	51.78	61.8	72.63	128.04	15.39	20.84	0.25	0.27	0.05	0.02
	Union County	68.42	16	19.48	57.39	67.82	79.25	128.86	16.23	21.84	0.23	0.14	0.05	-0.04
	Washington County	56.9	8.2	30.12	51.93	56.24	61.44	96.23	6.92	9.5	0.14	0.52	0.06	1.6
	Wicomico County	54.68	10.76	22.07	47.55	55.17	62.03	90.72	10.43	14.44	0.2	-0.14	0.06	0.1

Table S4-2. Summary statistics for maximum daily 8-hour moving average O_3 measurements derived from CWRF-CMAQ simulations by county

	O3_AQS	O3_CMAQ	PM2.5_AQS	PM2.5_CMAQ
Mean	32.70	63.41	10.65	8.64
Std.Dev	11.77	16.40	7.29	5.67
Min	0.00	17.68	0.00	0.11
Q1	24.21	52.48	5.80	4.87
Median	31.77	60.99	8.70	7.51
Q3	40.15	72.14	13.40	11.09
Max	112.29	191.71	114.85	128.82
MAD	11.77	14.17	5.19	4.43
IQR	15.94	19.66	7.60	6.22
CV	0.36	0.26	0.68	0.66
Skewness	0.50	1.03	2.07	3.23
SE.Skewness	0.01	0.01	0.01	0.01
Kurtosis	0.38	2.63	8.22	32.55
N.Valid	58697.00	61440.00	42058.00	61440.00
Pct.Valid	83.84	87.76	60.08	87.76

Table S4-3. Side-by-side regional-scaled summary statistics for Air Quality System (AQS) derived ozone (O3_AQS), CWRF-CMAQ-derived ozone (O3_CMAQ), AQS-derived $PM_{2.5}$ (PM2.5_AQS), and CWRF-CMAQ-derived $PM_{2.5}$ (PM2.5_CMAQ)

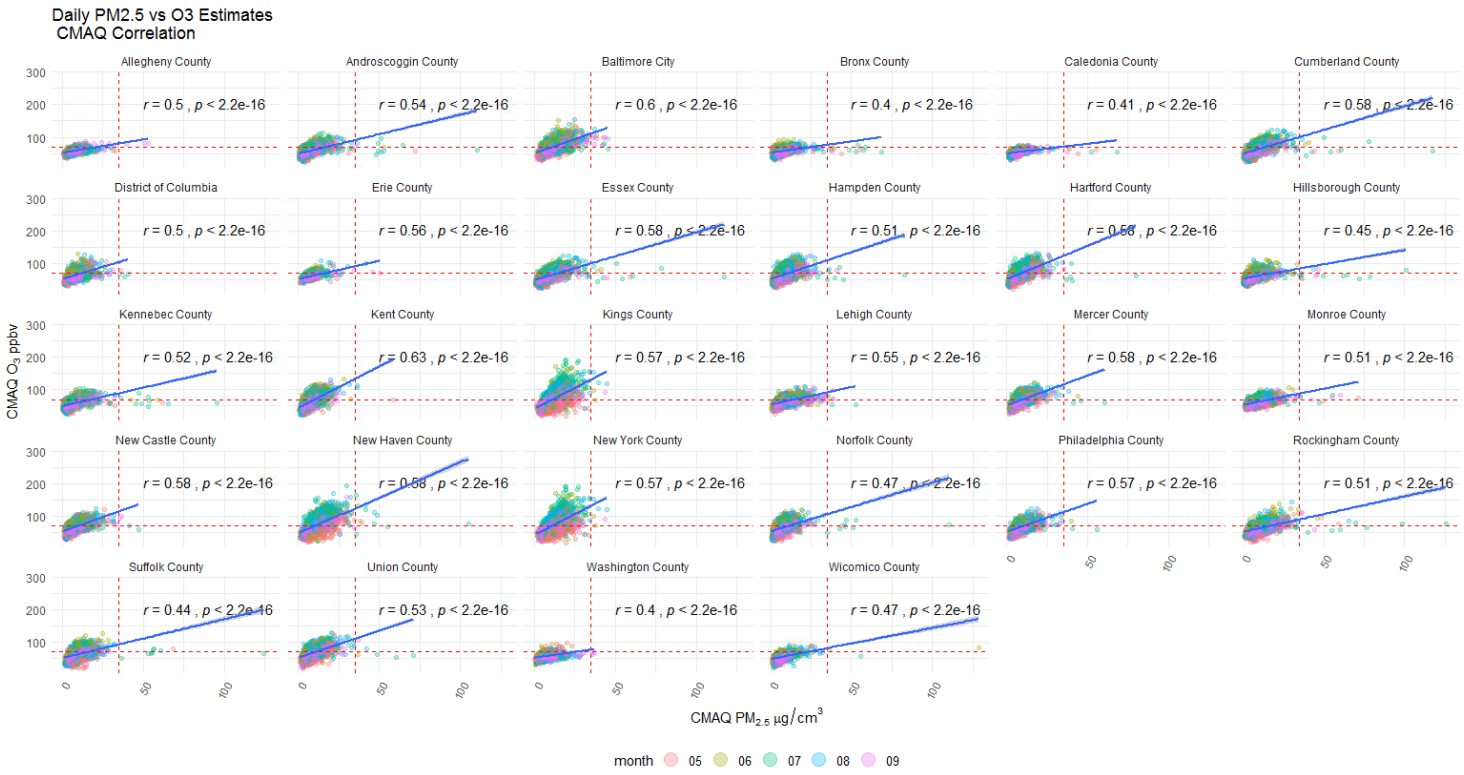


Figure S4-1. County-specific correlations for CWRF-CMAQ $PM_{2.5}$ and O_3 estimates.

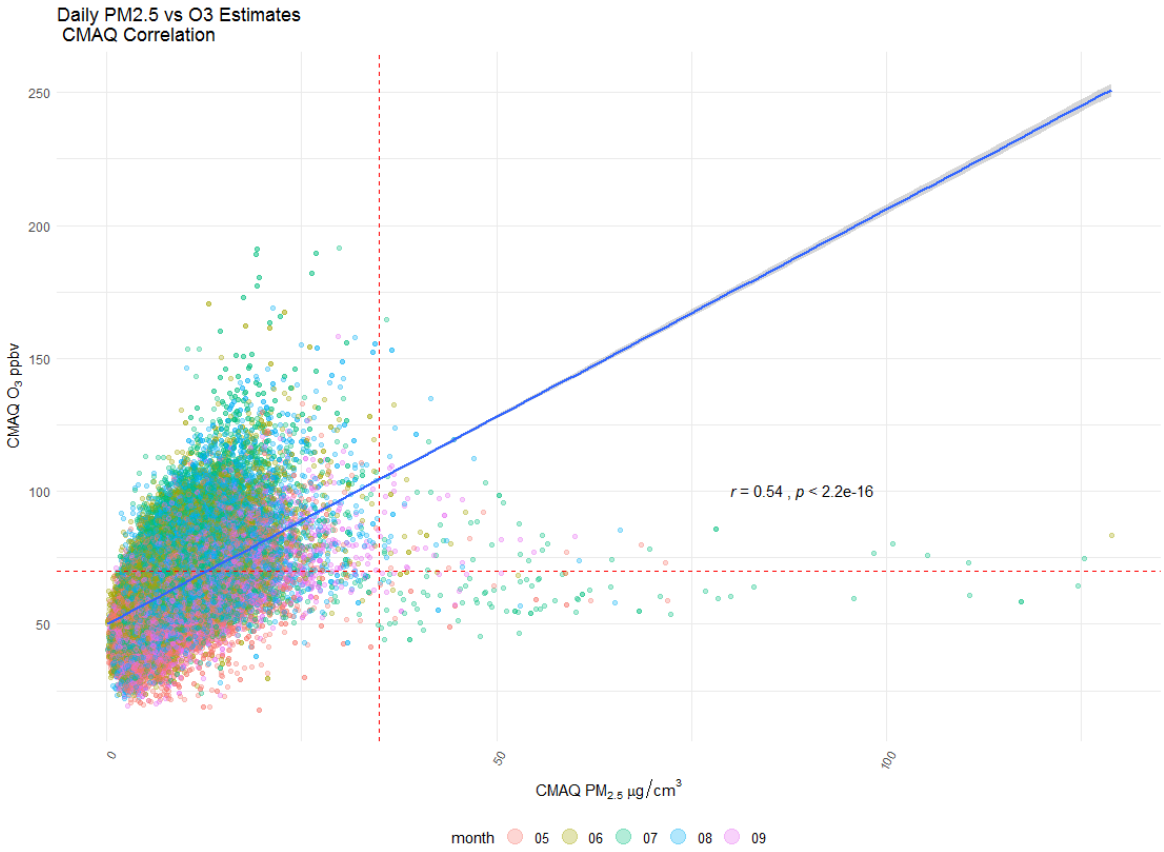


Figure S4-2. Aggregated northeastern correlation for CWRF-CMAQ $PM_{2.5}$ and O_3 estimates.

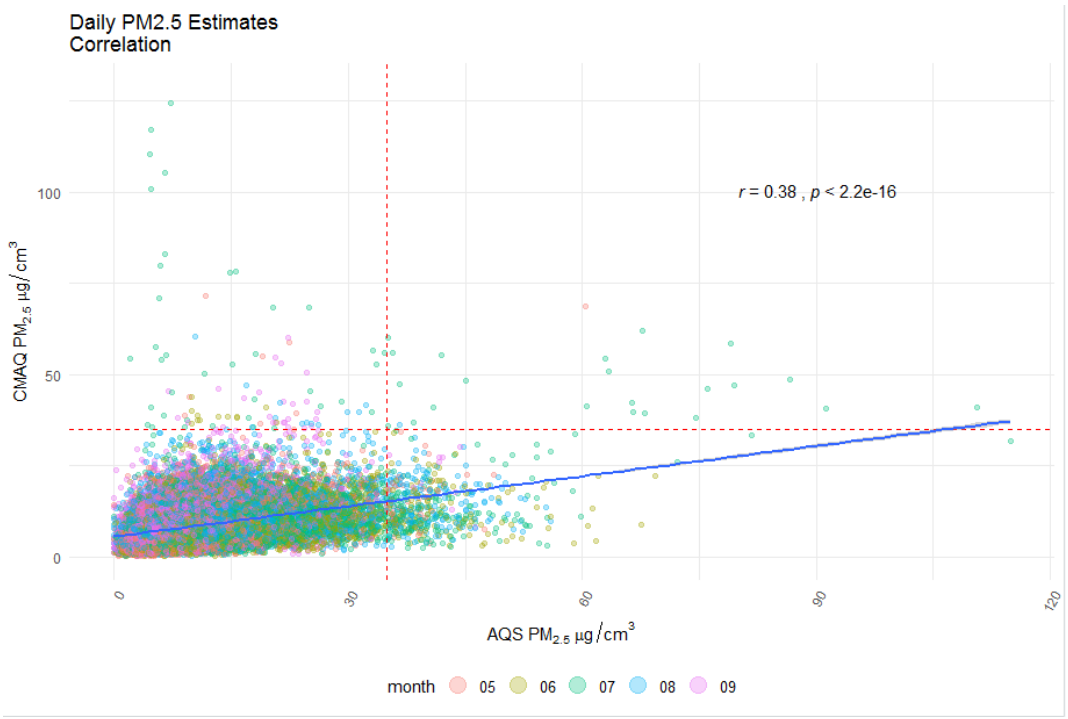


Figure S4-3. Aggregated northeastern correlation for $PM_{2.5}$ between CWRF-CMAQ and AQS observations

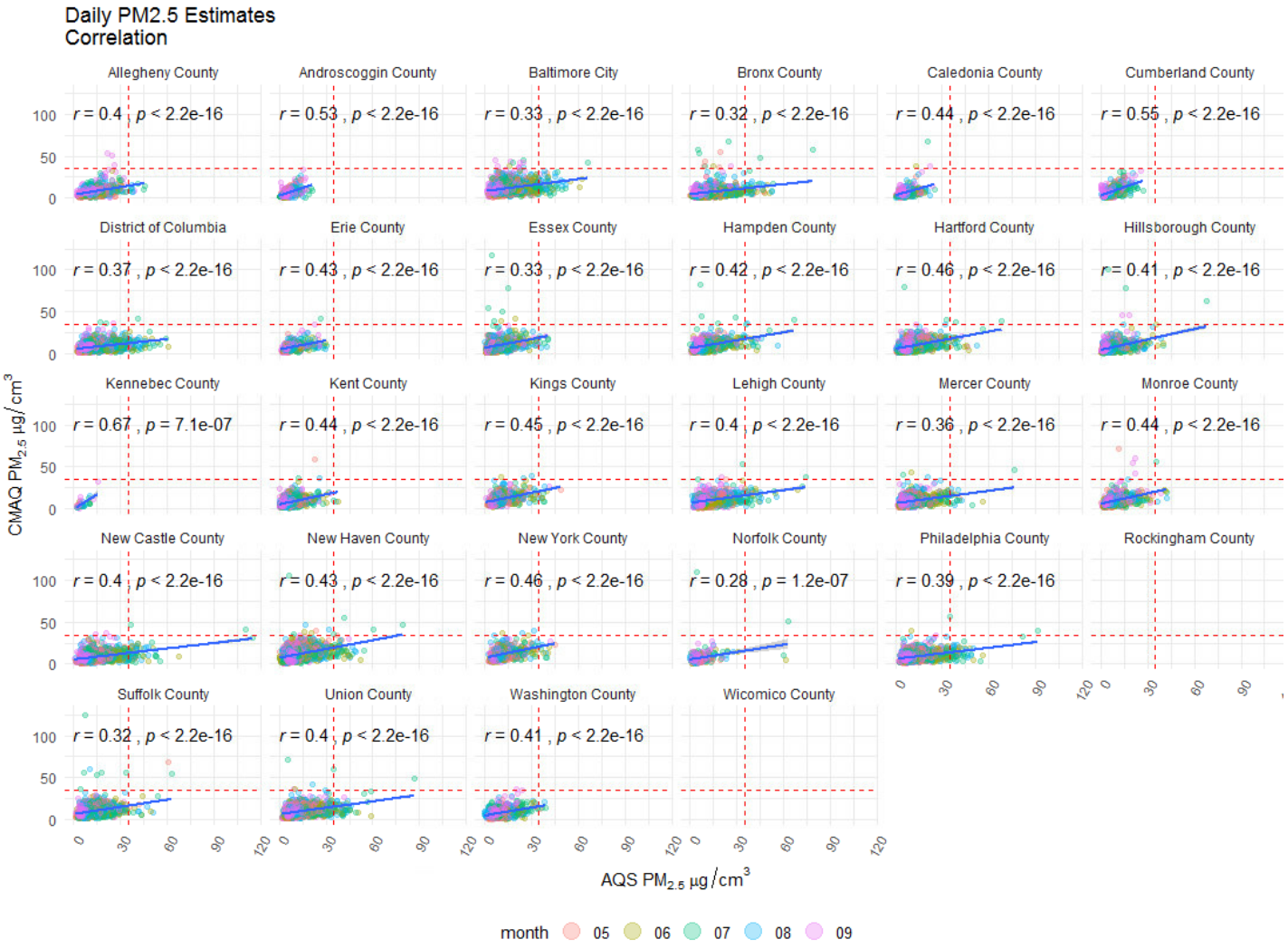


Figure S4-4. County-specific correlations for $PM_{2.5}$ between CWRF-CMAQ and AQS observations

Figure S4-5

Figure S4-5. Aggregated northeastern correlation for O_3 between CWRF-CMAQ and AQS observations

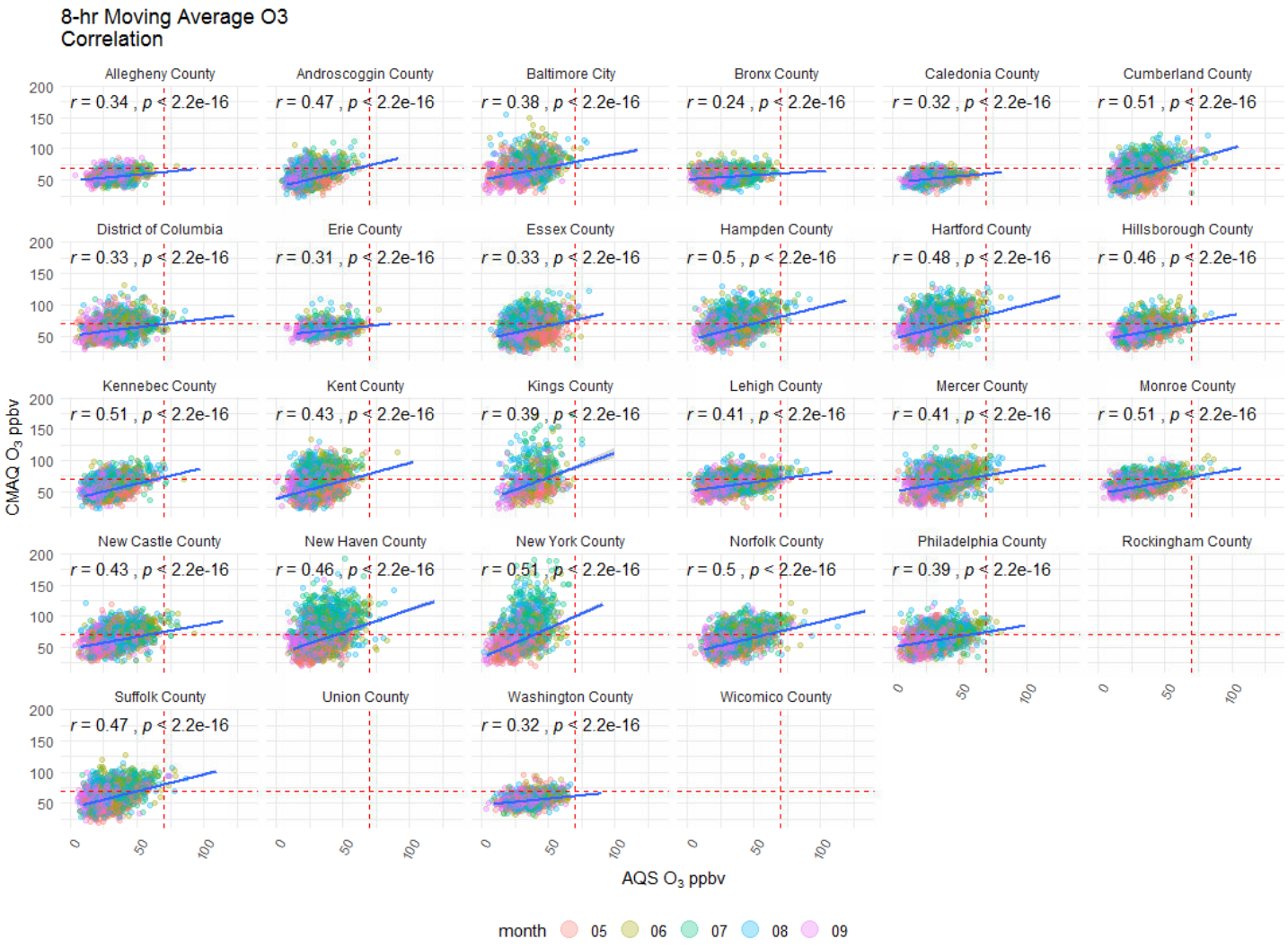


Figure S4-6. County-specific correlations for O_3 between CWRF-CMAQ and AQS observations

Chapter 5 Supplemental materials

	Model 1: unadjusted total temperature association	Model 2: adjusted total temperature association	Model 3: adjusted direct temperature association (preSBP)	Model 4: adjusted direct temperature association (IDWG %)	Model 5: adjusted direct temperature association (preSBP + IDWG%)
Daily Max Temp (Lag2)	**1.075 (1.069-1.081)**	**1.075 (1.069-1.080)**	**1.074 (1.068-1.080)**	**1.075 (1.070-1.081)**	**1.075 (1.069-1.081)**
preSBP (Lag2)			0.998 (0.996-1.000)		0.998 (0.996-1.000)
IDWG change (Lag2)				**1.048 (1.012-1.085)**	**1.051 (1.015-1.088)**
Age (yr)		0.999 (0.994-1.003)	0.998 (0.994-1.002)	0.999 (0.995-1.003)	0.999 (0.995-1.003)
Race/Ethnicity					
Non-Hispanic Black		1.000	1.000	1.000	1.000
Asian		0.998 (0.687-1.451)	1.004 (0.690-1.461)	0.957 (0.662-1.384)	0.961 (0.664-1.390)
Hispanic		**1.393 (1.105-1.756)**	**1.401 (1.111-1.766)**	**1.376 (1.093-1.732)**	**1.384 (1.100-1.743)**
Non-Hispanic White		1.083 (0.939-1.251)	1.080 (0.936-1.246)	1.081 (0.936-1.248)	1.077 (0.933-1.243)
Other/Not Reported		0.943 (0.797-1.116)	0.941 (0.796-1.114)	0.954 (0.806-1.128)	0.952 (0.806-1.126)
Blood Pressure Medication					
No		1.000	1.000	1.000	1.000
Yes		1.051 (0.944-1.170)	1.058 (0.951-1.176)	1.059 (0.950-1.180)	1.068 (0.959-1.188)
Sex					
Female		1.000	1.000	1.000	1.000
Male		**0.884 (0.788-0.992)**	**0.880 (0.784-0.987)**	**0.876 (0.782-0.981)**	**0.871 (0.777-0.976)**

Table S5-1. Hazard ratio (HR) and 95% confidence intervals for the association of daily maximum daily temperature and all-cause hospital admissions (ACHA) based on Lag 2 discrete time model structure. Due to the large number of categorical factors, treatment clinics associations were not reported. Bold indicates statistically significant hazard ratio at $p < 0.05$.

	Model 1: unadjusted total temperature association	Model 2: adjusted total temperature association	Model 3: adjusted direct temperature association (preSBP)	Model 4: adjusted direct temperature association (IDWG %)	Model 5: adjusted direct temperature association (preSBP + IDWG%)
Daily Max Temp (Lag2)	**1.069 (1.045-1.094)**	**1.071 (1.047-1.096)**	**1.068 (1.044-1.093)**	**1.070 (1.045-1.095)**	**1.067 (1.042-1.092)**
preSBP (Lag2)			**0.989 (0.983-0.994)**		**0.989 (0.984-0.995)**
IDWG change (Lag2)				0.927 (0.843-1.019)	0.944 (0.858-1.037)
Age (yr)		**1.034 (1.024-1.043)**	**1.032 (1.022-1.041)**	**1.034 (1.024-1.043)**	**1.032 (1.022-1.041)**
Race/Ethnicity					
Non-Hispanic Black		1.000	1.000	1.000	1.000
Asian		1.128 (0.418-3.048)	1.200 (0.443-3.247)	1.194 (0.440-3.237)	1.249 (0.461-3.387)
Hispanic		1.516 (0.985-2.334)	**1.595 (1.034-2.460)**	**1.559 (1.011-2.404)**	**1.622 (1.051-2.503)**
Non-Hispanic White		**1.575 (1.182-2.099)**	**1.547 (1.159-2.063)**	**1.597 (1.197-2.130)**	**1.563 (1.171-2.085)**
Other/Not Reported		0.769 (0.459-1.289)	0.767 (0.459-1.282)	0.759 (0.453-1.271)	0.758 (0.453-1.269)
Blood Pressure Medication					
No		1.000	1.000	1.000	1.000
Yes		**0.493 (0.381-0.638)**	**0.518 (0.400-0.671)**	**0.486 (0.375-0.629)**	**0.511 (0.395-0.661)**
Sex					
Female		1.000	1.000	1.000	1.000
Male		1.027 (0.807-1.307)	0.991 (0.778-1.261)	1.037 (0.815-1.319)	0.998 (0.784-1.271)

Table S5-2. Hazard ratio (HR) and 95% confidence intervals for the association of daily maximum daily temperature and all-cause mortality (ACM) based on Lag 2 discrete time model structure. Due to the large number of categorical factors, treatment clinics associations were not reported. Bold indicates statistically significant hazard ratio at $p < 0.05$.

	Model 1: unadjusted total temperature association	Model 2: adjusted total temperature association	Model 3: adjusted direct temperature association (preSBP)	Model 4: adjusted direct temperature association (IDWG %)	Model 5: adjusted direct temperature association (preSBP + IDWG%)
Daily Max Temp (Lag1)	**1.083 (1.075-1.090)**	**1.082 (1.075-1.090))**	**1.082 (1.074-1.090)**	**1.084 (1.076-1.092)**	**1.084 (1.076-1.092)**
preSBP (Lag1)			0.998 (0.996-1.000)		0.998 (0.995-1.000)
IDWG change (Lag1)				**1.071 (1.040-1.104)**	**1.075 (1.043-1.107)**
Age (yr)		0.999 (0.995-1.003)	0.999 (0.994-1.003)	1.000 (0.995-1.004)	0.999 (0.995-1.003)
Race/Ethnicity					
Non-Hispanic Black		1.000	1.000	1.000	1.000
Asian		0.992 (0.682-1.442)	0.997 (0.685-1.452)	0.933 (0.646-1.348)	0.937 (0.647-1.356)
Hispanic		**1.390 (1.104-1.751)**	**1.399 (1.111-1.762)**	**1.362 (1.084-1.711)**	**1.372 (1.092-1.723)**
Non-Hispanic White		1.077 (0.933-1.243)	1.074 (0.931-1.240)	1.071 (0.928-1.237)	1.068 (0.925-1.232)
Other/Not Reported		0.914 (0.772-1.082)	**1.074 (0.931-1.240)**	0.927 (0.783-1.097)	0.926 (0.783-1.095)
Blood Pressure Medication					
No		1.000	1.000	1.000	1.000
Yes		1.050 (0.943-1.168)	1.058 (0.952-1.175)	1.063 (0.955-1.184)	1.073 (0.965-1.194)
Sex					
Female		1.000	1.000	1.000	1.000
Male		**0.882 (0.787-0.989)**	**0.878 (0.783-0.985)**	**0.872 (0.779-0.976)**	**0.866 (0.773-0.970)**

Table S5-3. Hazard ratio (HR) and 95% confidence intervals for the association of daily maximum daily temperature and all-cause hospital admissions (ACHA) based on Lag 1 discrete-time model structure. Due to the large number of categorical factors, treatment clinics associations were not reported. Bold indicates statistically significant hazard ratio at $p < 0.05$.

	Model 1: unadjusted total temperature association	Model 2: adjusted total temperature association	Model 3: adjusted direct temperature association (preSBP)	Model 4: adjusted direct temperature association (IDWG %)	Model 5: adjusted direct temperature association (preSBP + IDWG%)
Daily Max Temp (Lag1)	**1.086 (1.058-1.116)**	**1.089 (1.060-1.118)**	**1.088 (1.059-1.118)**	**1.093 (1.063-1.123)**	**1.092 (1.062-1.122)**
preSBP (Lag1)			0.997 (0.992-1.003)		0.996 (0.991-1.002)
IDWG change (Lag1)				**1.179 (1.093-1.272)**	**1.186 (1.100-1.280)**
Age (yr)		**1.034 (1.025-1.044)**	**1.034 (1.024-1.043)**	**1.035 (1.026-1.045)**	**1.034 (1.025-1.044)**
Race/Ethnicity					
Non-Hispanic Black		1.000	1.000	1.000	1.000
Asian		1.113 (0.412-3.007)	1.124 (0.416-3.037)	0.971 (0.358-2.634)	0.981 (0.362-2.655)
Hispanic		1.500 (0.975-2.308)	1.517 (0.986-2.335)	1.402 (0.909-2.162)	1.426 (0.926-2.196)
Non-Hispanic White		**1.563 (1.173-2.082)**	**1.554 (1.165-2.073)**	**1.516 (1.136-2.022)**	**1.506 (1.130-2.006)**
Other/Not Reported		0.769 (0.459-1.289)	0.739 (0.440-1.239)	0.761 (0.453-1.279)	0.764 (0.456-1.282)
Blood Pressure Medication					
No		1.000	1.000	1.000	1.000
Yes		**0.500 (0.386-0.647)**	**0.506 (0.391-0.655)**	**0.511 (0.394-0.663)**	**0.521 (0.402-0.676)**
Sex					
Female		1.000	1.000	1.000	1.000
Male		1.022 (0.803-1.300)	1.011 (0.795-1.286)	1.004 (0.789-1.277)	0.988 (0.776-1.259)

Table S5-4. Hazard ratio (HR) and 95% confidence intervals for the association of daily maximum daily temperature and all-cause mortality (ACM) based on Lag 1 discrete time model structure. Due to the large number of categorical factors, treatment clinics associations were not reported. Bold indicates statistically significant hazard ratio at $p < 0.05$.

Estimate	Model 1: Temperature and confounders only	Model 2: Temperature, confounders, and SBP	Model 3: Temperature, confounders, and IDWG	Model 4: Temperature, confounders, IDWG, and SBP
Temperature β	0.0719	**0.0715**	0.0728	0.0723
Indirect Effect	--	**0.0004 (0.0000, 0.0008)**	**-0.0009 (-0.0014, -0.0006)**	**-0.0005 (-0.0006, -0.0001)**
Percent Mediated	--	0.58%	-1.25%	-0.65%

Table S5-5. Effect size estimates and bootstrap-generated two-sided 95% confidence intervals for mediation effects of the association between daily maximum temperature and all-cause hospital admissions (ACHA) based on Lag 2 discrete-time model structure. Bold indicates statistically significant estimate at p<-0.05

Estimate	Model 1: Temperature and confounders only	Model 2: Temperature, confounders, and SBP	Model 3: Temperature, confounders, and IDWG	Model 4: Temperature, confounders, IDWG, and SBP
Temperature β	0.0689	0.0658	0.0674	0.0648
Indirect Effect	--	**0.0030 (0.0010, 0.0067)**	**0.0014 (0.0013, 0.0031)**	0.0041 (0.0027, 0.0119)
Percent Mediated	--	4.41%	2.11%	5.97%

Table S5-6. Effect size estimates and bootstrap-generated two-sided 95% confidence intervals for mediation effects of the association between daily maximum temperature and all-cause mortality (ACM) based on Lag 2 discrete-time model structure. Bold indicates statistically significant estimate at p<-0.05

Estimate	Model 1: Temperature and confounders only	Model 2: Temperature, confounders, and SBP	Model 3: Temperature, confounders, and IDWG	Model 4: Temperature, confounders, IDWG, and SBP
Temperature β	0.0792	0.0787	0.0809	0.0803
Indirect Effect	--	**0.0006 (0.0005, 0.0008)**	**-0.0017 (-0.0023, -0.0015)**	**-0.0011 (-0.0015, -0.0007)**
Percent Mediated	--	0.69%	-2.15%	-1.39%

Table S5-7. Effect size estimates and bootstrap-generated two-sided 95% confidence intervals for mediation effects of the association between daily maximum temperature and all-cause hospital admissions (ACHA) based on Lag 1 discrete-time model structure. Bold indicates statistically significant estimate at p<-0.05

Estimate	Model 1: Temperature and confounders only	Model 2: Temperature, confounders, and SBP	Model 3: Temperature, confounders, and IDWG	Model 4: Temperature, confounders, IDWG, and SBP
Temperature β	0.0849	0.0841	0.0887	0.0877
Indirect Effect	--	0.0008 (-0.0002, 0.0024)	**-0.0038 (-0.0051, -0.0010)**	**-0.0028 (-0.0037, -0.0015)**
Percent Mediated	--	0.93%	-4.51%	-3.27%

Table S5-8. Estimates and bootstrap-generated two-sided 95% confidence intervals for mediation effects of the association between daily maximum temperature and all-cause mortality (ACM) based on Lag 1 discrete-time model structure. Bold indicates statistically significant estimate at p<-0.05

	Model 1: unadjusted preSBP-only	Model 2: unadjusted IDWG-only	Model 3: adjusted preSBP-only	Model 4: adjusted IDWG-only	Model 5: adjusted preSBP + IDWG-only
preSBP (Lag2)	0.998 (0.995-1.000)		**0.997 (0.995-0.999)**		**0.997 (0.995-0.999)**
IDWG change (Lag2)		1.024 (0.988-1.061)		**1.022 (0.986-1.058)**	1.027 (0.991-1.065)

Table S5-9. Hazard ratio and 95% confidence intervals for the association of blood pressure (preSBP) and inter-dialytic weight gain (IDWG) percent change and all-cause hospital admissions (ACHA) based on Lag 2 discrete-time model structure. Adjusted models include age, race/ethnicity, treatment location, sex, and blood pressure medication use. Bold indicates statistically significant estimate at p<-0.05

	Model 1: unadjusted preSBP-only	Model 2: unadjusted IDWG-only	Model 3: adjusted preSBP-only	Model 4: adjusted IDWG-only	Model 5: adjusted preSBP + IDWG-only
preSBP (Lag2)	**0.984 (0.979-0.990)**		**0.988 (0.982-0.993)**		**0.988 (0.982-0.994)**
IDWG change (Lag2)		**0.890 (0.796-0.985)**		**0.902 (0.804-0.999)**	0.920 (0.835-1.014)

Table S5-10. Hazard ratio and 95% confidence intervals for the association of blood pressure (preSBP) and inter-dialytic weight gain (IDWG) percent change and all-cause mortality (ACM) based on Lag 2 discrete-time model structure. Adjusted models include age, race/ethnicity, treatment location, sex, and blood pressure medication use. Bold indicates statistically significant estimate at $p<0.05$

	Model 1: unadjusted preSBP-only	Model 2: unadjusted IDWG-only	Model 3: adjusted preSBP-only	Model 4: adjusted IDWG-only	Model 5: adjusted preSBP + IDWG-only
preSBP (Lag1)	0.998 (0.995-1.000)		**0.997 (0.995-0.999)**		**0.997 (0.995-0.999)**
IDWG change (Lag1)		**1.050 (1.018-1.081)**		**1.048 (1.017-1.078)**	**1.053 (1.022-1.084)**

Table S5-11. Hazard ratio and 95% confidence intervals for the association of blood pressure (preSBP) and inter-dialytic weight gain (IDWG) percent change and all-cause hospital admissions (ACHA) based on Lag 2 discrete-time model structure. Adjusted models include age, race/ethnicity, treatment location, sex, and blood pressure medication use. Bold indicates statistically significant estimate at $p<0.05$

	Model 1: unadjusted preSBP-only	Model 2: unadjusted IDWG-only	Model 3: adjusted preSBP-only	Model 4: adjusted IDWG-only	Model 5: adjusted preSBP + IDWG-only
preSBP (Lag1)	**0.993 (0.987-0.998)**		0.996 (0.991-1.002)		0.995 (0.990-1.001)
IDWG change (Lag1)		**1.131 (1.054-1.209)**		**1.159 (1.082-1.237)**	**1.168 (1.091-1.245)**

Table S5-12. Hazard ratio and 95% confidence intervals for the association of blood pressure (preSBP) and inter-dialytic weight gain (IDWG) percent change and all-cause mortality (ACM) based on Lag 1 discrete-time model structure. Adjusted models include age, race/ethnicity, treatment location, sex, and blood pressure medication use. Bold indicates statistically significant estimate at $p<0.05$

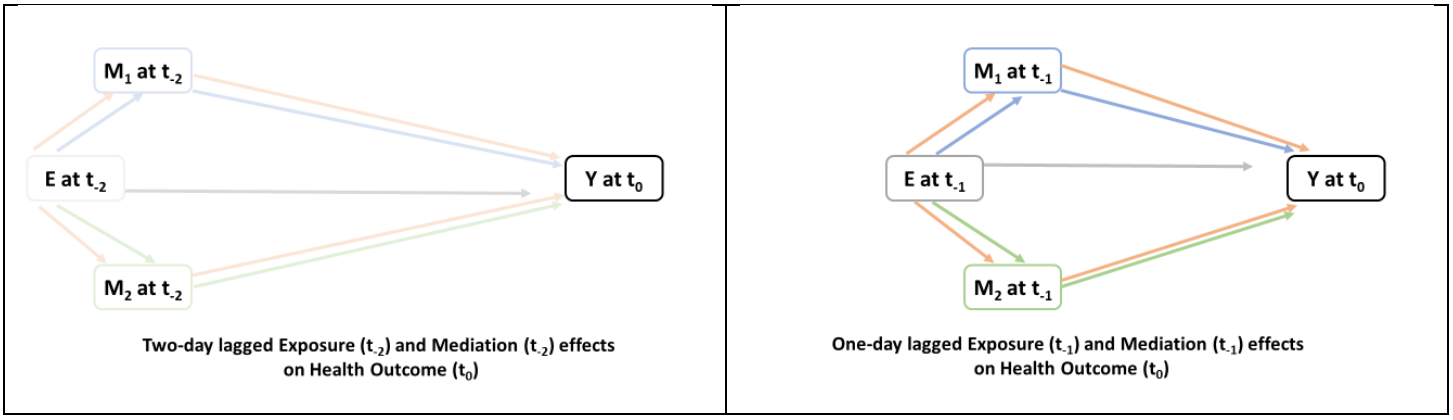


Figure S5-1. Directed acyclic graphs (DAGs) depicting mechanistic pathways between time-dependent extreme heat event exposures (E), and IDWG change (M_1) and preSBP (M_2) mediators. Lag 2 (left) and Lag 1(right) DAGs represents lag-specific pathways using t_{-2}, t_{-1}, and t_0 variables. Variables denote two-day, one-day, and same-day lags, respectively, that correspond to time-dependent measures before hospital admission or mortality events. Grey arrow represents total effect pathway; Single blue arrow represents an indirect pathway operating through M_1. Single green arrow represents an indirect pathway operating through M_2. And double orange arrows represent combined indirect pathways operating through M_1 and M_2.

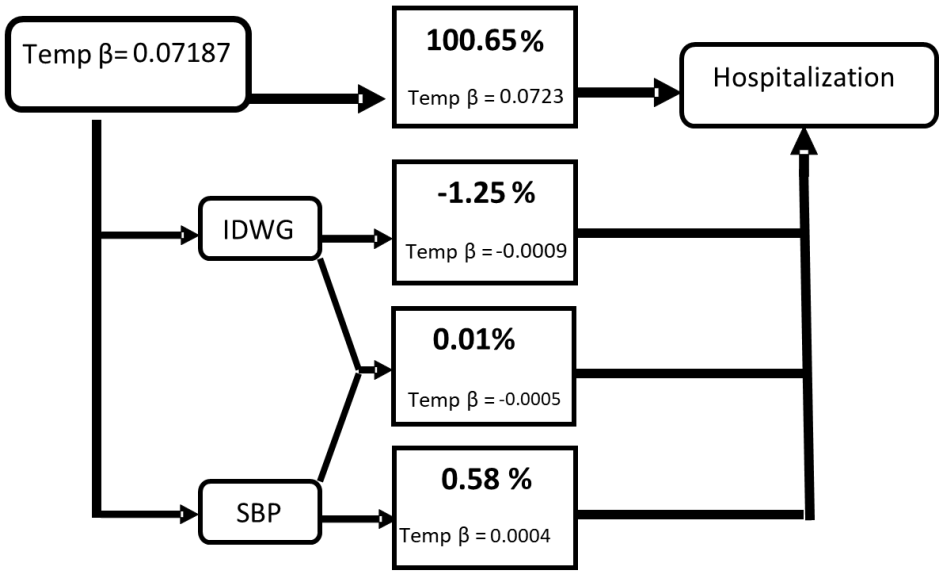


Figure S5-2. Combined pathway analysis of the association between daily maximum temperature and all-cause hospital admissions (ACHA) and mediating paths for combined mediators based on Lag 2 discrete-time model structure. For indirect paths: IDWG path is considered independent of preSBP, and preSBP indirect effect is independent of IDWG, and IDWG + preSBP path is independent of IDWG and preSBP indirect effects. Direct effects greater than 100% can occur when inconsistent mediation is present in one or more of the paths.

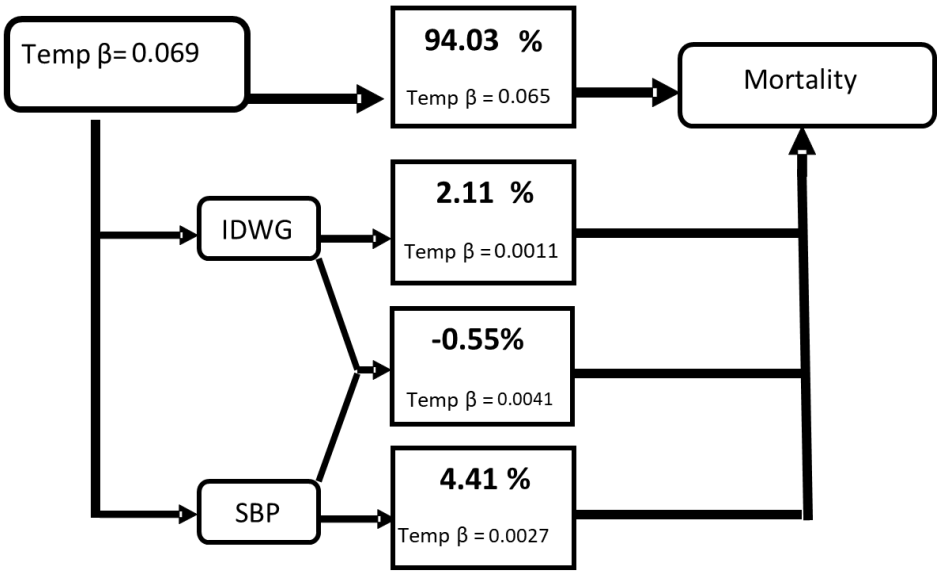


Figure S5-3. Combined pathway analysis of the association between daily maximum temperature and all-cause mortality (ACM) and mediating paths for combined mediators based on Lag 2 discrete-time model structure. For indirect paths: IDWG path is considered independent of preSBP, and preSBP indirect effect is independent of IDWG, and IDWG + preSBP path is independent of IDWG and preSBP indirect effects. Direct effects greater than 100% can occur when inconsistent mediation is present in one or more of the paths.

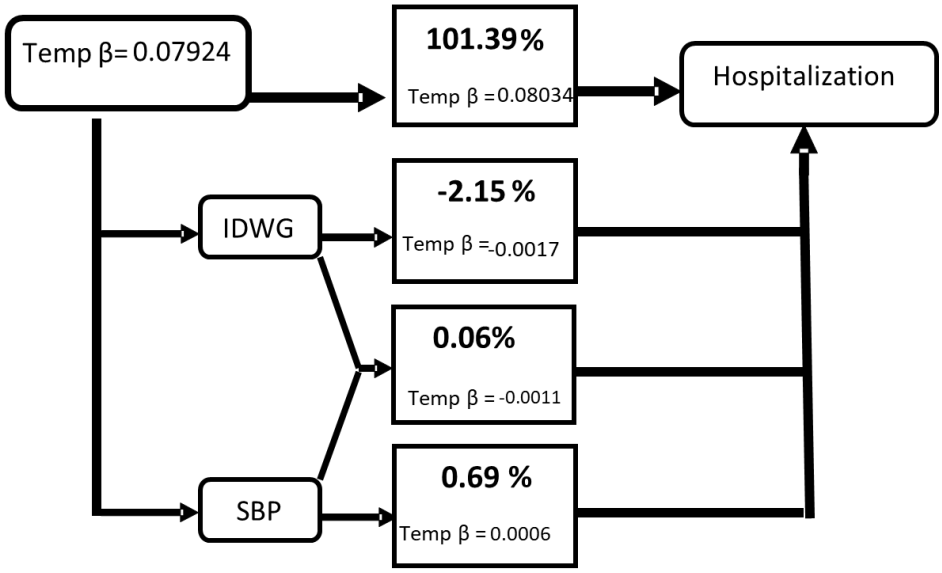


Figure S5-4. Combined pathway analysis of the association between daily maximum temperature and all-cause hospital admissions (ACHA) and mediating paths for combined mediators based on Lag 1 discrete-time model structure. For indirect paths: IDWG path is considered independent of preSBP, and preSBP indirect effect is independent of IDWG, and IDWG + preSBP path is independent of IDWG and preSBP indirect effects. Direct effects greater than 100% can occur when inconsistent mediation is present in one or more of the paths.

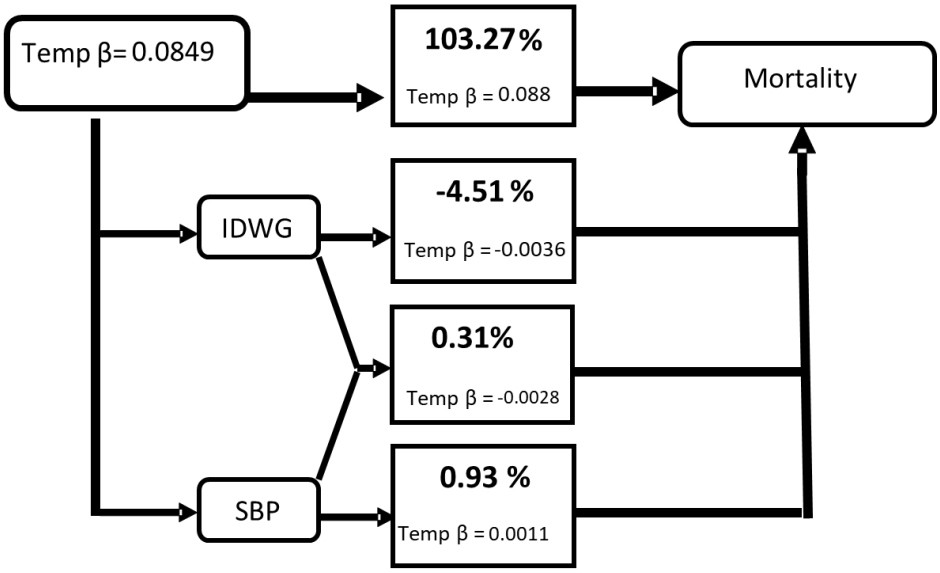


Figure S5-5. Combined pathway analysis of the association between daily maximum temperature and all-cause mortality (ACM) and mediating paths for combined mediators based on Lag 1 discrete-time model structure. For indirect paths: IDWG path is considered independent of preSBP, and preSBP indirect effect is independent of IDWG, and IDWG + preSBP path is independent of IDWG and preSBP indirect effects. Direct effects greater than 100% can occur when inconsistent mediation is present in one or more of the paths.

Bibliography

1. NOAA National Centers for Environmental Information. *Climate at a Glance: Global Time Series*. 2020 retrieved on 2021 January 03; Available from: https://www.ncdc.noaa.gov/cag/.
2. Wuebbles, D.J., D.W. Fahey, and K.A. Hibbard, *Climate science special report: fourth national climate assessment, volume I.* 2017.
3. Thoman, R.L., J. Richter-Menge, and M. L. Druckenmiller, *Arctic Report Card 2020.* 2020.
4. Jansen, E., et al., *Past perspectives on the present era of abrupt Arctic climate change.* Nature Climate Change, 2020. **10**(8): p. 714-721.
5. Hulley, G.C., B. Dousset, and B.H. Kahn, *Rising Trends in Heatwave Metrics Across Southern California.* Earth's Future, 2020. **8**(7).
6. Hersher, R. and L. Sommer, *2020 May Be The Hottest Year On Record. Here's The Damage It Did*, in *National Public Radio*. 2020.
7. Goss, M., et al., *Climate change is increasing the likelihood of extreme autumn wildfire conditions across California.* Environmental Research Letters, 2020. **15**(9): p. 094016.
8. Russell, B.T., et al., *Investigating the association between late spring Gulf of Mexico sea surface temperatures and U.S. Gulf Coast precipitation extremes with focus on Hurricane Harvey.* Environmetrics, 2020. **31**(2).
9. Thompson, A. and A. Montanez, *In 2020, Record-Breaking Hurricanes Arrived Early—and Often: A record 30 storms have formed, compared to the previous high of 28; almost all were the earliest on record*, in *Scientific American*. 2020.
10. Reidmiller, D.R., et al., *Impacts, Risks, and Adaptation in the United States: Fourth National Climate Assessment, Volume II.* 2017.
11. Birch, E.L., *A Review of "Climate Change 2014: Impacts, Adaptation, and Vulnerability" and "Climate Change 2014: Mitigation of Climate Change".* Journal of the American Planning Association, 2014. **80**(2): p. 184-185.
12. Ebi, K., et al., *Chapter 14: Human Health. Impacts, Risks, and Adaptation in the United States: The Fourth National Climate Assessment, Volume II*. 2018, US Global Change Research Program Washington, DC.
13. Li, M., et al., *Heat waves and morbidity: current knowledge and further direction-a comprehensive literature review.* Int J Environ Res Public Health, 2015. **12**(5): p. 5256-83.
14. Guo, Y., et al., *Global variation in the effects of ambient temperature on mortality: a systematic evaluation.* Epidemiology (Cambridge, Mass.), 2014. **25**(6): p. 781-789.
15. Guo, Y., et al., *The impact of temperature on mortality in Tianjin, China: a case-crossover design with a distributed lag nonlinear model.* Environmental health perspectives, 2011. **119**(12): p. 1719-1725.
16. Smoyer, K.E., D.G. Rainham, and J.N. Hewko, *Heat-stress-related mortality in five cities in Southern Ontario: 1980–1996.* International Journal of Biometeorology, 2000. **44**(4): p. 190-197.

17. Armstrong, B., *Models for the relationship between ambient temperature and daily mortality.* Epidemiology, 2006: p. 624-631.
18. Fisher, J.A., et al., *Summertime extreme heat events and increased risk of acute myocardial infarction hospitalizations.* J Expo Sci Environ Epidemiol, 2017. **27**(3): p. 276-280.
19. Soneja, S., et al., *Exposure to extreme heat and precipitation events associated with increased risk of hospitalization for asthma in Maryland, U.S.A.* Environmental Health, 2016. **15**: p. 57.
20. Upperman, C.R., et al., *Exposure to extreme heat events is associated with increased hay fever prevalence among nationally representative sample of US adults: 1997-2013.* The Journal of Allergy and Clinical Immunology: In Practice, 2017. **5**(2): p. 435-441. e2.
21. Jiang, C., et al., *Climate change, extreme events and increased risk of salmonellosis in Maryland, USA: Evidence for coastal vulnerability.* Environment International, 2015. **83**: p. 58-62.
22. Knowlton, K., et al., *The 2006 California Heat Wave: Impacts on Hospitalizations and Emergency Department Visits.* Environmental Health Perspectives, 2009. **117**(1): p. 61-67.
23. Tasian, G.E., et al., *Daily mean temperature and clinical kidney stone presentation in five US metropolitan areas: a time-series analysis.* Environmental health perspectives, 2014. **122**(10): p. 1081-1087.
24. Bobb, J.F., et al., *Cause-specific risk of hospital admission related to extreme heat in older adults.* JAMA, 2014. **312**(24): p. 2659-67.
25. Borg, M., et al., *The impact of daily temperature on renal disease incidence: an ecological study.* Environmental Health, 2017. **16**: p. 114.
26. Crandall, C.G. and T.E. Wilson, *Human Cardiovascular Responses to Passive Heat Stress.* Comprehensive Physiology, 2014: p. 17-43.
27. Romeo Upperman, C., et al., *Frequency of Extreme Heat Event as a Surrogate Exposure Metric for Examining the Human Health Effects of Climate Change.* PLOS ONE, 2015. **10**(12): p. e0144202.
28. The Renal Association. *CKD Stages*. 2018 2 May 2018; Available from: https://renal.org/information-resources/the-uk-eckd-guide/ckd-stages/.
29. Hallan, S.I., et al., *Combining GFR and Albuminuria to Classify CKD Improves Prediction of ESRD.* Journal of the American Society of Nephrology, 2009. **20**(5): p. 1069-1077.
30. United States Renal Data System, *2020 USRDS Annual Data Report: Epidemiology of kidney disease in the United States*. 2020, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases: Bethesda, MD.
31. Saran, R., et al., *US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States.* American journal of kidney diseases: the official journal of the National Kidney Foundation, 2020. **75**(1S1): p. A6.
32. National Institute of Diabetes and Digestivev and Kidney Diseases. *Hemodialysis*. 2018 [cited 2018 6 July 2018]; Available from:

https://www.niddk.nih.gov/health-information/kidney-disease/kidney-failure/hemodialysis.
33. Iseki, K., et al., *Low diastolic blood pressure, hypoalbuminemia, and risk of death in a cohort of chronic hemodialysis patients.* Kidney Int, 1997. **51**(4): p. 1212-7.
34. Port, F.K., et al., *Predialysis blood pressure and mortality risk in a national sample of maintenance hemodialysis patients.* Am J Kidney Dis, 1999. **33**(3): p. 507-17.
35. Klassen, P.S., et al., *Association between pulse pressure and mortality in patients undergoing maintenance hemodialysis.* Jama, 2002. **287**(12): p. 1548-55.
36. Raimann, J.G., et al., *Blood pressure stability in hemodialysis patients confers a survival advantage: results from a large retrospective cohort study.* Kidney Int, 2012. **81**(6): p. 548-58.
37. Zager, P.G., et al., *"U" curve association of blood pressure and mortality in hemodialysis patients.* Kidney International, 1998. **54**(2): p. 561-569.
38. Kalantar-Zadeh, K., et al., *Fluid retention is associated with cardiovascular mortality in patients undergoing long-term hemodialysis.* Circulation, 2009. **119**(5): p. 671-9.
39. Wong, M.M., et al., *Interdialytic Weight Gain: Trends, Predictors, and Associated Outcomes in the International Dialysis Outcomes and Practice Patterns Study (DOPPS).* Am J Kidney Dis, 2017. **69**(3): p. 367-379.
40. Wang, Q., et al., *Environmental ambient temperature and blood pressure in adults: A systematic review and meta-analysis.* Sci Total Environ, 2017. **575**: p. 276-286.
41. Gronlund, C.J., et al., *Vulnerability to the Cardiovascular Effects of Ambient Heat in Six US Cities: Results from the Multi-Ethnic Study of Atherosclerosis (MESA).* Epidemiology, 2018. **29**(6): p. 756-764.
42. Cheung, A.K., et al., *Seasonal variations in clinical and laboratory variables among chronic hemodialysis patients.* J Am Soc Nephrol, 2002. **13**(9): p. 2345-52.
43. Guinsburg, A.M., et al., *Seasonal variations in mortality and clinical indicators in international hemodialysis populations from the MONDO registry.* BMC Nephrol, 2015. **16**: p. 139.
44. Usvyat, L.A., et al., *Seasonal variations in mortality, clinical, and laboratory parameters in hemodialysis patients: a 5-year cohort study.* Clin J Am Soc Nephrol, 2012. **7**(1): p. 108-15.
45. Wu, M.-Y., et al., *Association between air pollutants and development of chronic kidney disease: A systematic review and meta-analysis.* Science of The Total Environment, 2020. **706**: p. 135522.
46. Bowe, B., et al., *Particulate Matter Air Pollution and the Risk of Incident CKD and Progression to ESRD.* J Am Soc Nephrol, 2018. **29**(1): p. 218-230.
47. Wu, M.Y., et al., *Association between air pollutants and development of chronic kidney disease: A systematic review and meta-analysis.* Sci Total Environ, 2020. **706**: p. 135522.

48. Chuang, K.-J., et al., *Associations between submicrometer particles exposures and blood pressure and heart rate in patients with lung function impairments.* Journal of occupational and environmental medicine, 2005. **47**(11): p. 1093-1098.
49. Jeong, S.M., et al., *Effects of abdominal obesity on the association between air pollution and kidney function.* Int J Obes (Lond), 2020.
50. Pope, C.A., et al., *Exposure to Fine Particulate Air Pollution Is Associated With Endothelial Injury and Systemic Inflammation.* Circulation Research, 2016. **119**(11): p. 1204-1214.
51. Nemmar, A., et al., *Diesel exhaust particles in the lung aggravate experimental acute renal failure.* Toxicol Sci, 2010. **113**(1): p. 267-77.
52. Wang, H.H., et al., *Combined toxicity of outdoor air pollution on kidney function among adult women in Mianyang City, southwest China.* Chemosphere, 2020. **238**: p. 124603.
53. Reid, C.E., et al., *Associations between respiratory health and ozone and fine particulate matter during a wildfire event.* Environ Int, 2019. **129**: p. 291-298.
54. Peng, R.D., et al., *Acute effects of ambient ozone on mortality in Europe and North America: results from the APHENA study.* Air Quality, Atmosphere & Health, 2013. **6**(2): p. 445-453.
55. Hou, P. and S. Wu, *Long-term Changes in Extreme Air Pollution Meteorology and the Implications for Air Quality.* Scientific Reports, 2016. **6**(1): p. 23792.
56. Remigio, R.V., et al., *Association of Extreme Heat Events With Hospital Admission or Mortality Among Patients With End-Stage Renal Disease.* JAMA Network Open, 2019. **2**(8): p. e198904-e198904.
57. Remigio, R.V., et al. *Impact of Extreme Heat on End-Stage Renal Disease Patients in the Northeast US Using Selected Clinical Outcomes*. in *ISEE Conference Abstracts*. 2018.
58. Patz, J.A., et al., *Climate change: challenges and opportunities for global health.* JAMA, 2014. **312**(15): p. 1565-80.
59. US Global Change Research Program, *The Impacts of Climate Change on Human Health in the United States: A Scientific Assessment*. 2016, Taylor & Francis: Washington, DC:. p. 312.
60. Stocker, T., et al., *IPCC, 2013: Summary for policymakers in climate change 2013: the physical science basis, contribution of working group I to the fifth assessment report of the intergovernmental panel on climate change*. 2013, Cambridge University Press, Cambridge, New York, USA.
61. Madrigano, J., et al., *A Case-Only Study of Vulnerability to Heat Wave-Related Mortality in New York City (2000-2011).* Environmental Health Perspectives, 2015. **123**(7): p. 672-8.
62. Petkova, E.P., et al., *Towards More Comprehensive Projections of Urban Heat-Related Mortality: Estimates for New York City under Multiple Population, Adaptation, and Climate Scenarios.* Environmental Health Perspectives, 2017. **125**(1): p. 47-55.
63. Semenza, J.C., et al., *Excess hospital admissions during the July 1995 heat wave in Chicago.* American Journal of Preventive Medicine, 1999. **16**.

64. Mendez-Lazaro, P.A., et al., *Climate change, heat, and mortality in the tropical urban area of San Juan, Puerto Rico.* International Journal of Biometeorology, 2016.
65. Wong, M.S., et al., *Spatially Analyzing the Inequity of the Hong Kong Urban Heat Island by Socio-Demographic Characteristics.* International Journal of Environmental Research and Public Health, 2016. **13**(3).
66. Quinn, A., P. Kinney, and J. Shaman, *Predictors of summertime heat index levels in New York City apartments.* Indoor Air, 2017.
67. Nguyen, J.L., J. Schwartz, and D.W. Dockery, *The relationship between indoor and outdoor temperature, apparent temperature, relative humidity, and absolute humidity.* Indoor air, 2014. **24**(1): p. 103-112.
68. Tamerius, J.D., et al., *Socioeconomic and Outdoor Meteorological Determinants of Indoor Temperature and Humidity in New York City Dwellings.* Weather, Climate, and Society, 2013. **5**(2): p. 168-179.
69. Xu, Z., et al., *The impact of heat waves on children's health: a systematic review.* International Journal of Biometeorology, 2014. **58**(2): p. 239-47.
70. Zhang, Y., et al., *The Short-Term Effect of Ambient Temperature on Mortality in Wuhan, China: A Time-Series Study Using a Distributed Lag Non-Linear Model.* International Journal of Environmental Research and Public Health, 2016. **13**(7).
71. Schmeltz, M.T., et al., *Identifying Individual Risk Factors and Documenting the Pattern of Heat-Related Illness through Analyses of Hospitalization and Patterns of Household Cooling.* PLoS ONE, 2015. **10**(3): p. e0118958.
72. Anderson, B.G. and M.L. Bell, *Weather-related mortality: how heat, cold, and heat waves affect mortality in the United States.* Epidemiology, 2009. **20**(2): p. 205-13.
73. Mastrangelo, G., et al., *Pattern and determinants of hospitalization during heat waves: an ecologic study.* BMC Public Health, 2007. **7**(1): p. 200.
74. Wang, Y., et al., *Heat stroke admissions during heat waves in 1,916 US counties for the period from 1999 to 2010 and their effect modifiers.* Environ Health, 2016. **15**(1): p. 83.
75. Wang, X.Y., et al., *Increased risk of emergency hospital admissions for children with renal diseases during heatwaves in Brisbane, Australia.* World Journal of Pediatrics, 2014. **10**(4): p. 330-5.
76. Kloppenburg, W.D., et al., *Assessing dialysis adequacy and dietary intake in the individual hemodialysis patient.* Kidney Int, 1999. **55**(5): p. 1961-9.
77. United States Renal Data System, *2017 USRDS annual data report: Epidemiology of kidney disease in the United States*. 2017, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases Bethesda, MD.
78. McTavish, R.K., et al., *Association Between High Environmental Heat and Risk of Acute Kidney Injury Among Older Adults in a Northern Climate: A Matched Case-Control Study.* American Journal of Kidney Diseases, 2017.
79. Kahle, D. and H. Wickham, *ggmap: spatial visualization with ggplot2.* R Journal, 2013. **5**(1).

80. National Kidney Foundation. *Insurance Options for People on Dialysis or With a Kidney Transplant*. 2019 February 14, 2017 June 1, 2019].
81. R Core Team, *R: A language and environment for statistical computing.* R Foundation for Statistical Computing, 2016.
82. Turner, H. and D. Firth, *Generalized nonlinear models in R: An overview of the gnm package*. 2018.
83. Jaakkola, J.J.K., *Case-crossover design in air pollution epidemiology.* European Respiratory Journal, 2003. **21**(40 suppl): p. 81s-85s.
84. Greenland, S., *Confounding and exposure trends in case-crossover and case-time-control designs.* Epidemiology, 1996. **7**(3): p. 231-9.
85. Janes, H., L. Sheppard, and T. Lumley, *Case-crossover analyses of air pollution exposure data: referent selection strategies and their implications for bias.* Epidemiology, 2005. **16**(6): p. 717-26.
86. Maclure, M., *The case-crossover design: a method for studying transient effects on the risk of acute events.* Am J Epidemiol, 1991. **133**(2): p. 144-53.
87. Armstrong, B.G., A. Gasparrini, and A. Tobias, *Conditional Poisson models: a flexible alternative to conditional logistic case cross-over analysis.* BMC Medical Research Methodology, 2014. **14**(1): p. 122.
88. Steinbach, R., et al., *The effect of reduced street lighting on road casualties and crime in England and Wales: controlled interrupted time series analysis.* J Epidemiol Community Health, 2015. **69**(11): p. 1118-1124.
89. Milojevic, A., et al., *Methods to Estimate Acclimatization to Urban Heat Island Effects on Heat- and Cold-Related Mortality.* Environ Health Perspect, 2016. **124**(7): p. 1016-22.
90. Oudin, A., et al., *The association between daily concentrations of air pollution and visits to a psychiatric emergency unit: a case-crossover study.* Environmental Health, 2018. **17**(1): p. 4.
91. Ferreri, J.M., et al., *The January 2013 Beijing "Airpocalypse" and its acute effects on emergency and outpatient visits at a Beijing hospital.* Air Quality, Atmosphere & Health, 2018. **11**(3): p. 301-309.
92. Zanobetti, A., et al., *A national case-crossover analysis of the short-term effect of PM2.5 on hospitalizations and mortality in subjects with diabetes and neurological disorders.* Environ Health, 2014. **13**(1): p. 38.
93. Schenker, N. and J. Gentleman, *On judging the significance of differences by examining the overlap between confidence intervals.* The American Statistician, 2001. **55**(3): p. 182-186.
94. Weinberger, K.R., et al., *Projected Changes in Temperature-related Morbidity and Mortality in Southern New England.* Epidemiology, 2018. **29**(4): p. 473-481.
95. Petkova, E.P., et al., *Heat-Related Mortality in a Warming Climate: Projections for 12 U.S. Cities.* International Journal of Environmental Research and Public Health, 2014. **11**(11): p. 11371-11383.
96. Wang, Y., et al., *Heat stroke admissions during heat waves in 1,916 US counties for the period from 1999 to 2010 and their effect modifiers.* Environmental Health, 2016. **15**(1): p. 83.

97. Zhou, L., et al., *Heat and mortality for ischemic and hemorrhagic stroke in 12 cities of Jiangsu Province, China.* Sci Total Environ, 2017. **601-602**: p. 271-277.
98. Kenny, G.P., et al., *Heat stress in older individuals and patients with common chronic diseases.* Canadian Medical Association Journal, 2010. **182**(10): p. 1053-60.
99. Lai, C.C., et al., *The association between COPD and outcomes of patients with advanced chronic kidney disease.* Int J Chron Obstruct Pulmon Dis, 2018. **13**: p. 2899-2905.
100. Navaneethan, S.D., et al., *Mortality Outcomes of Patients with Chronic Kidney Disease and Chronic Obstructive Pulmonary Disease.* Am J Nephrol, 2016. **43**(1): p. 39-46.
101. Reid, C.E., et al., *Mapping Community Determinants of Heat Vulnerability.* Environmental Health Perspectives, 2009. **117**(11): p. 1730-1736.
102. Zanobetti, A., et al., *Summer temperature variability and long-term survival among elderly people with chronic disease.* Proceedings of the National Academy of Sciences of the United States of America, 2012. **109**(17): p. 6608-6613.
103. Klein Rosenthal, J., P.L. Kinney, and K.B. Metzger, *Intra-urban vulnerability to heat-related mortality in New York City, 1997-2006.* Health Place, 2014. **30**: p. 45-60.
104. Uejio, C.K., et al., *Intra-urban societal vulnerability to extreme heat: the role of heat exposure and the built environment, socioeconomics, and neighborhood stability.* Health Place, 2011. **17**(2): p. 498-507.
105. Gronlund, C.J., *Racial and socioeconomic disparities in heat-related health effects and their mechanisms: a review.* Curr Epidemiol Rep, 2014. **1**(3): p. 165-173.
106. Gubernot, D.M., G.B. Anderson, and K.L. Hunting, *Characterizing occupational heat-related mortality in the United States, 2000–2010: An analysis using the census of fatal occupational injuries database.* American Journal of Industrial Medicine, 2015. **58**(2): p. 203-211.
107. Noe, R.S., J.O. Jin, and A.F. Wolkin, *Exposure to natural cold and heat: hypothermia and hyperthermia Medicare claims, United States, 2004-2005.* Am J Public Health, 2012. **102**(4): p. e11-8.
108. Quinn, A., et al., *Predicting Indoor Heat Exposure Risk during Extreme Heat Events.* The Science of the total environment, 2014. **490**: p. 686-693.
109. Lee, A.C.K. and R. Maheswaran, *The health benefits of urban green spaces: a review of the evidence.* Journal of Public Health, 2011. **33**(2): p. 212-222.
110. Burkart, K., et al., *Modification of Heat-Related Mortality in an Elderly Urban Population by Vegetation (Urban Green) and Proximity to Water (Urban Blue): Evidence from Lisbon, Portugal.* Environ Health Perspect, 2016. **124**(7): p. 927-34.
111. Habeeb, D., J. Vargo, and B. Stone, *Rising heat wave trends in large US cities.* Natural Hazards, 2015. **76**(3): p. 1651-1665.

112. Weisskopf, M.G. and T.F. Webster, *Trade-offs of Personal Versus More Proxy Exposure Measures in Environmental Epidemiology.* Epidemiology, 2017. **28**(5): p. 635-643.
113. Rothman, K.J., S. Greenland, and T.L. Lash, *Modern epidemiology*. Vol. 3. 2008: Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia.
114. Mendez-Lazaro, P.A., et al., *Climate change, heat, and mortality in the tropical urban area of San Juan, Puerto Rico.* Int J Biometeorol, 2016.
115. Wong, M.S., et al., *Spatially Analyzing the Inequity of the Hong Kong Urban Heat Island by Socio-Demographic Characteristics.* Int J Environ Res Public Health, 2016. **13**(3).
116. Watts, N., et al., *The 2019 report of The Lancet Countdown on health and climate change: ensuring that the health of a child born today is not defined by a changing climate.* The Lancet, 2019. **394**(10211): p. 1836-1878.
117. Vargo, J., et al., *The social and spatial distribution of temperature-related health impacts from urban heat island reduction policies.* 2016. **66**: p. 366-374.
118. Weinberger, K.R., et al., *Effectiveness of National Weather Service heat alerts in preventing mortality in 20 US cities.* Environment International, 2018. **116**: p. 30-38.
119. Benmarhnia, T., et al., *A difference-in-differences approach to assess the effect of a heat action plan on heat-related mortality, and differences in effectiveness according to sex, age, and socioeconomic status (Montreal, Quebec).* Environmental health perspectives, 2016. **124**(11): p. 1694-1699.
120. Hayhoe, K., et al., *Regional climate change projections for the Northeast USA.* 2008. **13**(5-6): p. 425-436.
121. Li, T., R.M. Horton, and P.L. Kinney, *Projections of seasonal patterns in temperature- related deaths for Manhattan, New York.* Nature Climate Change, 2013. **3**(8): p. 717-721.
122. Petkova, E., et al., *Projected Heat-Related Mortality in the U.S. Urban Northeast.* International Journal of Environmental Research and Public Health, 2013. **10**(12): p. 6734-6747.
123. Xi, Y., et al., *Mortality in US Hemodialysis Patients Following Exposure to Wildfire Smoke.* Journal of the American Society of Nephrology, 2020. **31**(8): p. 1824-1835.
124. Azhar, G.S., et al., *Heat-Related Mortality in India: Excess All-Cause Mortality Associated with the 2010 Ahmedabad Heat Wave.* PLoS ONE, 2014. **9**(3): p. e91831.
125. Desai, R.J., et al., *Bias Implications of Outcome Misclassification in Observational Studies Evaluating Association Between Treatments and All-Cause or Cardiovascular Mortality Using Administrative Claims.* Journal of the American Heart Association, 2020. **9**(17).
126. NOAA National Centers for Environmental Information, *Climate Data Online Data Tools.* 2020.
127. Mostofsky, E., B.A. Coull, and M.A. Mittleman, *Analysis of Observational Self-matched Data to Examine Acute Triggers of Outcome Events with Abrupt Onset.* Epidemiology, 2018. **29**(6): p. 804-816.

128. R Core Team, *R: A language and environment for statistical computing*. 2019.
129. Turner, H. and D. Firth, *Generalized nonlinear models in R: An overview of the gnm package.(R package version 1.1-1)*. 2020, Warwick, UK: University of Warwick.
130. Wickham, H., R. François, and L. Henry, *dplyr: A Grammar of Data Manipulation, R Package Version 0.8.3*. 2019.
131. Quinn, A., et al., *Predicting indoor heat exposure risk during extreme heat events.* Science of The Total Environment, 2014. **490**: p. 686-693.
132. Anderson, G.B., M.L. Bell, and R.D. Peng, *Methods to Calculate the Heat Index as an Exposure Metric in Environmental Health Research.* Environmental Health Perspectives, 2013. **121**(10): p. 1111-1119.
133. NWS (National Weather Service). *Meteorological Conversions and Calculations : Heat Index Calculator*. 2016; Available from: http://www.wpc.ncep.noaa.gov/html/heatindex.shtml.
134. Steadman, R.G., *The Assessment of Sultriness. Part I: A Temperature-Humidity Index Based on Human Physiology and Clothing Science.* Journal of applied meteorology, 1979. **18**(7): p. 861-873.
135. Anderson, G.B., M.L. Bell, and R.D. Peng, *Methods to calculate the heat index as an exposure metric in environmental health research.* Environ Health Perspect, 2013. **121**(10): p. 1111-9.
136. Soneja, S., et al., *Extreme precipitation events and increased risk of campylobacteriosis in Maryland, U.S.A.* Environmental Research, 2016. **149**: p. 216-221.
137. Weinberger, K.R., et al., *Comparison of temperature-mortality associations estimated with different exposure metrics.* Environmental Epidemiology, 2019. **3**(5): p. e072.
138. *US Renal Data System 2019 Annual Data Report: Epidemiology of Kidney Disease in the United States.* Am J Kidney Dis, 2019.
139. Yang, C.Y. and M.T. Lin, *Oxidative stress in rats with heatstroke-induced cerebral ischemia.* Stroke, 2002. **33**(3): p. 790-4.
140. Lavados, P.M., V.V. Olavarría, and L. Hoffmeister, *Ambient Temperature and Stroke Risk.* Stroke, 2018. **49**(1): p. 255-261.
141. Zhang, Y., et al., *The effects of ambient temperature on cerebrovascular mortality: an epidemiologic study in four climatic zones in China.* Environmental Health, 2014. **13**(1): p. 24.
142. Hawkins, M.D., V. Brown, and J. Ferrell, *Assessment of NOAA National Weather Service Methods to Warn for Extreme Heat Events.* Weather, Climate, and Society, 2017. **9**(1): p. 5-13.
143. Bikbov, B., et al., *Global, regional, and national burden of chronic kidney disease, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017.* The Lancet, 2020. **395**(10225): p. 709-733.
144. Chan, K.E., R.I. Thadhani, and F.W. Maddux, *Adherence Barriers to Chronic Dialysis in the United States.* Journal of the American Society of Nephrology, 2014. **25**(11): p. 2642-2648.
145. Heft-Neal, S., et al., *Robust relationship between air quality and infant mortality in Africa.* Nature, 2018. **559**(7713): p. 254-258.

146. Shang, Y., et al., *Systematic review of Chinese studies of short-term exposure to air pollution and daily mortality.* Environment international, 2013. **54**: p. 100-111.
147. Wellenius, G.A., J. Schwartz, and M.A. Mittleman, *Particulate air pollution and hospital admissions for congestive heart failure in seven United States cities.* The American journal of cardiology, 2006. **97**(3): p. 404-408.
148. Nemmar, A., et al., *Prolonged Pulmonary Exposure to Diesel Exhaust Particles Exacerbates Renal Oxidative Stress, Inflammation and DNA Damage in Mice with Adenine-Induced Chronic Renal Failure.* Cellular Physiology and Biochemistry, 2016. **38**(5): p. 1703-1713.
149. Huang, X., et al., *PM2.5 exposure induced renal injury via the activation of the autophagic pathway in the rat and HK-2 cell.* Environmental Sciences Europe, 2020. **32**(1).
150. Bowe, B., et al., *Estimates of the 2016 global burden of kidney disease attributable to ambient fine particulate matter air pollution.* BMJ Open, 2019. **9**(5): p. e022450.
151. Mills, N.L., et al., *Combustion-derived nanoparticulate induces the adverse vascular effects of diesel exhaust inhalation.* European heart journal, 2011. **32**(21): p. 2660-2671.
152. Bowe, B., et al., *Associations of ambient coarse particulate matter, nitrogen dioxide, and carbon monoxide with the risk of kidney disease: a cohort study.* The Lancet Planetary Health, 2017. **1**(7): p. e267-e276.
153. Blum, M.F., et al., *Particulate matter and albuminuria, glomerular filtration rate, and incident CKD.* Clinical Journal of the American Society of Nephrology, 2020. **15**(3): p. 311-319.
154. Bowe, B., et al., *Particulate matter air pollution and the risk of incident CKD and progression to ESRD.* Journal of the American Society of Nephrology, 2018. **29**(1): p. 218-230.
155. Chan, T.-C., et al., *Long-Term Exposure to Ambient Fine Particulate Matter and Chronic Kidney Disease: A Cohort Study.* Environmental Health Perspectives, 2018. **126**(10): p. 107002.
156. Hendryx, M., *Mortality from heart, respiratory, and kidney disease in coal mining areas of Appalachia.* International archives of occupational and environmental health, 2009. **82**(2): p. 243-249.
157. Mehta, A.J., et al., *Long-Term Exposure to Ambient Fine Particulate Matter and Renal Function in Older Men: The Veterans Administration Normative Aging Study.* Environmental Health Perspectives, 2016. **124**(9): p. 1353-1360.
158. Wyatt, L., et al. *Mortality in US Hemodialysis Patients Following Exposure to Wildfire Smoke*. in *AGU Fall Meeting 2019*. 2019. AGU.
159. Crimmins, A., et al., *The impacts of climate change on human health in the United States: a scientific assessment.* J Global Change Research Program: Washington, DC, USA, 2016.
160. Hou, P. and S. Wu, *Long-term changes in extreme air pollution meteorology and the implications for air quality.* Scientific reports, 2016. **6**: p. 23792.

161. Peterson, T.C., et al., *Changes in weather and climate extremes: State of knowledge relevant to air and water quality in the United States.* Journal of the Air & Waste Management Association, 2014. **64**(2): p. 184-197.
162. Seltzer, K.M., et al., *Evaluation of near surface ozone and particulate matter in air quality simulations driven by dynamically downscaled historical meteorological fields.* Atmospheric Environment, 2016. **138**: p. 42-54.
163. Tao, Z., et al., *Impact of Fire Emissions on US Air Quality from 1997 to 2016–A Modeling Study in the Satellite Era.* Remote Sensing, 2020. **12**(6): p. 913.
164. United States Environmental Protection Agency. *NAAQS Table*. Criteria Air Pollutants 2020 [cited 2020 1 April 2020]; Available from: https://www.epa.gov/criteria-air-pollutants/naaqs-table#3.
165. Lu, Y. and S.L. Zeger, *On the equivalence of case-crossover and time series methods in environmental epidemiology.* Biostatistics, 2007. **8**(2): p. 337-44.
166. Bateson, T.F. and J. Schwartz, *Control for Seasonal Variation and Time Trend in Case-Crossover Studies of Acute Effects of Environmental Exposures.* Epidemiology, 1999. **10**(5): p. 539-544.
167. Gasparrini, A., *Distributed Lag Linear and Non-Linear Models in R: The Package dlnm.* J Stat Softw, 2011. **43**(8): p. 1-20.
168. Ren, C., G.M. Williams, and S. Tong, *Does Particulate Matter Modify the Association between Temperature and Cardiorespiratory Diseases?* Environmental Health Perspectives, 2006. **114**(11): p. 1690-1696.
169. Li, L., et al., *Particulate matter modifies the magnitude and time course of the non-linear temperature-mortality association.* Environmental Pollution, 2015. **196**: p. 423-430.
170. Breitner, S., et al., *Short-term effects of air temperature on mortality and effect modification by air pollution in three cities of Bavaria, Germany: a time-series analysis.* Science of the Total Environment, 2014. **485**: p. 49-61.
171. Iranpour, S., et al., *Modification of the effect of ambient air temperature on cardiovascular and respiratory mortality by air pollution in Ahvaz, Iran.* Epidemiology and Health, 2020: p. e2020053.
172. Gasparrini, A. and B. Armstrong, *Reducing and meta-analysing estimates from distributed lag non-linear models.* BMC Med Res Methodol, 2013. **13**: p. 1.
173. Gasparrini, A., B. Armstrong, and M.G. Kenward, *Distributed lag non-linear models.* Stat Med, 2010. **29**(21): p. 2224-34.
174. Chen, K., et al., *Two-way effect modifications of air pollution and air temperature on total natural and cardiovascular mortality in eight European urban areas.* Environ Int, 2018. **116**: p. 186-196.
175. Kim, S.E., Y.-H. Lim, and H. Kim, *Temperature modifies the association between particulate air pollution and mortality: A multi-city study in South Korea.* Science of The Total Environment, 2015. **524-525**: p. 376-383.
176. Stafoggia, M., et al., *Does temperature modify the association between air pollution and mortality? A multicity case-crossover analysis in Italy.* American journal of epidemiology, 2008. **167**(12): p. 1476-1485.

177. Chen, K., et al., *Future ozone-related acute excess mortality under climate and population change scenarios in China: A modeling study.* PLOS Medicine, 2018. **15**(7): p. e1002598.
178. Lippmann, M., *HEALTH EFFECTS OF OZONE A Critical Review.* JAPCA, 1989. **39**(5): p. 672-695.
179. Lovasi, G.S., et al., *Urban tree canopy and asthma, wheeze, rhinitis, and allergic sensitization to tree pollen in a New York City birth cohort.* Environmental health perspectives, 2013. **121**(4): p. 494-500.
180. Sapkota, A., et al., *Association Between Changes in Timing of Spring Onset and Asthma Hospitalization in Maryland.* JAMA Network Open, 2020. **3**(7): p. e207551.
181. Zoccali, C., et al., *Lung Congestion as a Risk Factor in End-Stage Renal Disease.* Blood Purification, 2013. **36**(3-4): p. 184-191.
182. Fisher, J.A., et al., *Case-crossover analysis of short-term particulate matter exposures and stroke in the health professionals follow-up study.* Environ Int, 2019. **124**: p. 153-160.
183. US Environmental Protection Agency. *Air Quality System Data Mart*. November, 2018]; Available from: http://www.epa.gov/ttn/airs/aqsdatamart.
184. Girguis, M.S., et al., *Exposure measurement error in air pollution studies: the impact of shared, multiplicative measurement error on epidemiological health risk estimates.* Air Quality, Atmosphere & Health, 2020. **13**(6): p. 631-643.
185. Travis, K.R., et al., *Why do models overestimate surface ozone in the Southeast United States?* Atmospheric Chemistry and Physics, 2016. **16**(21): p. 13561-13577.
186. Shmool, J.L.C., et al., *Area-level socioeconomic deprivation, nitrogen dioxide exposure, and term birth weight in New York City.* 2015. **142**: p. 624-632.
187. Hansen, A.L., et al., *The effect of heat waves on hospital admissions for renal disease in a temperate city of Australia.* International Journal of Epidemiology, 2008. **37**(6): p. 1359-1365.
188. Raimann, J.G., et al., *Blood pressure stability in hemodialysis patients confers a survival advantage: results from a large retrospective cohort study.* Kidney international, 2012. **81**(6): p. 548-558.
189. Inrig, J.K., et al., *Relationship Between Interdialytic Weight Gain and Blood Pressure Among Prevalent Hemodialysis Patients.* American Journal of Kidney Diseases, 2007. **50**(1): p. 108-118.e4.
190. Lertdumrongluk, P., et al., *Changes in Pulse Pressure during Hemodialysis Treatment and Survival in Maintenance Dialysis Patients.* Clinical Journal of the American Society of Nephrology, 2015. **10**(7): p. 1179-1191.
191. Kalantar-Zadeh, K., et al., *Fluid Retention Is Associated With Cardiovascular Mortality in Patients Undergoing Long-Term Hemodialysis.* Circulation, 2009. **119**(5): p. 671-679.
192. Boyle, S.M., et al., *Neighborhood context and kidney disease in Philadelphia.* SSM-population health, 2020. **12**: p. 100646.
193. Bellavia, A. and L. Valeri, *Decomposition of the Total Effect in the Presence of Multiple Mediators and Interactions.* Am J Epidemiol, 2018. **187**(6): p. 1311-1318.

194. Chamberlain, S., *rnoaa:'NOAA'Weather Data from R. R package version 1.1. 0.* https://cran. r-project.org/web/packages/rnoaa/, 2020.
195. Mange, K.C., *Blood Pressure and the Survival of Renal Allografts from Living Donors.* Journal of the American Society of Nephrology, 2004. **15**(1): p. 187-193.
196. Hägg-Holmberg, S., et al., *The role of blood pressure in risk of ischemic and hemorrhagic stroke in type 1 diabetes.* Cardiovascular Diabetology, 2019. **18**(1).
197. Peters, A., et al., Epidemiologic Perspectives & Innovations, 2006. **3**(1): p. 10.
198. Andersen, P.K. and R.D. Gill, *Cox's regression model for counting processes: a large sample study.* The annals of statistics, 1982: p. 1100-1120.
199. Amorim, L.D. and J. Cai, *Modelling recurrent events: a tutorial for analysis in epidemiology.* International Journal of Epidemiology, 2015. **44**(1): p. 324-333.
200. Mills, M., *Introducing survival and event history analysis*. 2010: Sage.
201. Harel, Z., et al., *Rehospitalizations and Emergency Department Visits after Hospital Discharge in Patients Receiving Maintenance Hemodialysis.* Journal of the American Society of Nephrology, 2015. **26**(12): p. 3141-3150.
202. Chan, K.E., et al., *Association between repeat hospitalization and early intervention in dialysis patients following hospital discharge.* Kidney International, 2009. **76**(3): p. 331-341.
203. Go, A.S., et al., *Chronic Kidney Disease and the Risks of Death, Cardiovascular Events, and Hospitalization.* New England Journal of Medicine, 2004. **351**(13): p. 1296-1305.
204. Ratcliffe, S.J., W. Guo, and T.R. Ten Have, *Joint Modeling of Longitudinal and Survival Data via a Common Frailty.* Biometrics, 2004. **60**(4): p. 892-899.
205. Balan, T.A. and H. Putter, *A tutorial on frailty models.* Statistical Methods in Medical Research, 2020. **29**(11): p. 3424-3454.
206. Therneau, T., *A Package for Survival Analysis in R*. 2020.
207. Twisk, J.W.R., *Applied analysis of recurrent events: a practical overview.* Journal of Epidemiology & Community Health, 2005. **59**(8): p. 706-710.
208. VanderWeele, T.J., *Mediation Analysis: A Practitioner's Guide.* Annu Rev Public Health, 2016. **37**: p. 17-32.
209. Burgos Ochoa, L., et al., *Performance of methods to conduct mediation analysis with time-to-event outcomes.* Statistica Neerlandica, 2020. **74**(1): p. 72-91.
210. MacKinnon, D.P., J.L. Krull, and C.M. Lockwood, *Equivalence of the mediation, confounding and suppression effect.* Prevention science, 2000. **1**(4): p. 173-181.
211. Tan, F.E., S. Jolani, and H. Verbeek, *Guidelines for multiple imputations in repeated measurements with time-dependent covariates: A case study.* Journal of clinical epidemiology, 2018. **102**: p. 107-114.
212. Murad, H., et al., *Imputing missing time-dependent covariate values for the discrete time Cox model.* Statistical methods in medical research, 2020. **29**(8): p. 2074-2086.

213. Carroll, O.U., T.P. Morris, and R.H. Keogh, *How are missing data in covariates handled in observational time-to-event studies in oncology? A systematic review.* BMC Medical Research Methodology, 2020. **20**: p. 1-15.
214. Marshall, A., D.G. Altman, and R.L. Holder, *Comparison of imputation methods for handling missing covariate data when fitting a Cox proportional hazards model: a resampling study.* BMC medical research methodology, 2010. **10**(1): p. 112.
215. Van Buuren, S. and K. Groothuis-Oudshoorn, *Multivariate imputation by chained equations.* J Stat Softw, 2011. **45**(3): p. 1-67.
216. Shrout, P.E. and N. Bolger, *Mediation in experimental and nonexperimental studies: new procedures and recommendations.* Psychological methods, 2002. **7**(4): p. 422.
217. Tchetgen Tchetgen Eric, J., *On Causal Mediation Analysis with a Survival Outcome*, in *The International Journal of Biostatistics*. 2011. p. 1.
218. Pazzagli, L., et al., *Methods for time-varying exposure related problems in pharmacoepidemiology: An overview.* Pharmacoepidemiol Drug Saf, 2018. **27**(2): p. 148-160.
219. Quinn, A. and J. Shaman, *Health symptoms in relation to temperature, humidity, and self-reported perceptions of climate in New York City residential environments.* International Journal of Biometeorology, 2017. **61**(7): p. 1209-1220.
220. Waugh, D.W., et al., *Indoor heat exposure in Baltimore: does outdoor temperature matter?* International Journal of Biometeorology, 2020.
221. Sera, F., et al., *Air Conditioning and Heat-related Mortality: A Multi-country Longitudinal Study.* Epidemiology, 2020. **31**(6): p. 779-787.
222. Wright, M.K., et al., *Social and behavioral determinants of indoor temperatures in air-conditioned homes.* Building and Environment, 2020. **183**: p. 107187.
223. Camalier, L., W. Cox, and P. Dolwick, *The effects of meteorology on ozone in urban areas and their use in assessing ozone trends.* Atmospheric Environment, 2007. **41**(33): p. 7127-7137.
224. Quinn, A., et al., *Predicting indoor heat exposure risk during extreme heat events.* Sci Total Environ, 2014. **490**: p. 686-93.
225. Sheridan, S.C., *A survey of public perception and response to heat warnings across four North American cities: an evaluation of municipal effectiveness.* International Journal of Biometeorology, 2007. **52**(1): p. 3-15.
226. Bleyer, A.J., et al., *An international study of patient compliance with hemodialysis.* Jama, 1999. **281**(13): p. 1211-3.
227. Phend, C., *Dialysis Crisis in Texas: 'Catastrophic'*, in *MedPage Today*. 2021.
228. Gasparrini, A., et al., *Projections of temperature-related excess mortality under climate change scenarios.* The Lancet Planetary Health, 2017. **1**(9): p. e360-e367.
229. Li, T., R.M. Horton, and P.L. Kinney, *Projections of seasonal patterns in temperature-related deaths for Manhattan, New York.* Nature climate change, 2013. **3**(8): p. 717-721.

230. Schwartz, J.D., et al., *Projections of temperature-attributable premature deaths in 209 U.S. cities using a cluster-based Poisson approach.* Environmental Health, 2015. **14**(1).
231. Lopez Bernal, J., S. Cummins, and A. Gasparrini, *Interrupted time series regression for the evaluation of public health interventions: a tutorial.* International Journal of Epidemiology, 2016: p. dyw098.
232. Cho, S.H. and Y.T. Huang, *Mediation analysis with causally ordered mediators using Cox proportional hazards model.* Statistics in Medicine, 2019. **38**(9): p. 1566-1581.
233. Park, J., et al., *A comparative effectiveness research study of the change in blood pressure during hemodialysis treatment and survival.* Kidney international, 2013. **84**(4): p. 795-802.
234. Knafl, G.J., et al., *Incorporating nonlinearity into mediation analyses.* BMC Medical Research Methodology, 2017. **17**(1).
235. Valeri, L. and T.J. VanderWeele, *Mediation analysis allowing for exposure–mediator interactions and causal interpretation: theoretical assumptions and implementation with SAS and SPSS macros.* Psychological methods, 2013. **18**(2): p. 137.
236. Vansteelandt, S., et al., *Mediation analysis of time-to-event endpoints accounting for repeatedly measured mediators subject to time-varying confounding.* Statistics in Medicine, 2019. **38**(24): p. 4828-4840.