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Environmental exposures and human health challenges: Evidence-based insights from health surveillance systems

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by

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Dedicated to

My grandmother (Late. Raghavamma Dharanikota), family (Rama Mohana Rao Puvvula, Satya sayamma Puvvula, and Pavan Kumar Puvvula) and friends (Vijay Krishna Reddy Vuyyuru, Santosh Kumar Sunki, Venkata Srinivas Ronanki, Raghavendra Gupta, and Ravindranath Tagore) for their overall support.

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Abstract

Human exposure to environmental hazards is associated with a variety of preventable adverse health outcomes. As the environmental health risks result from the complex interaction between hazard, exposure, and susceptibility, these exposure-outcome associations are heterogeneous across the population. Improving environmental health literacy by advocating evidence-based environmental risk communication could play a role in reinforcing protective behavior against environmental hazards. The use of public health surveillance systems to assess the exposure-response associations is one of the effective ways to quantify the environmental health risks. However, there are several gaps in effectively quantifying environmental health risks. This dissertation aims to address a few gaps in the context of climate change, heat waves, and air pollution, using public health surveillance systems.

This dissertation quantified the acute and direct health outcomes associated with environmental exposures (outdoor temperature and air quality) using syndromic surveillance and health care utilization databases. The environmental exposures in this dissertation are ascertained using ambient measurements. We followed intermittent time series (controlled and uncontrolled) design to assess the exposure-outcome associations to minimize potential systematic bias. We applied this strategy in three use cases: 1. Climate change, 2. Heat waves, and 3. Air pollution.

In the first use case, we quantified the rate of heat-related illness (HRI) morbidity risk attributable to current and future climate change. Following this, the

second use case compared the sensitivity of heat wave definitions that could be effective in minimizing HRI emergency department visits. The third use case estimated the joint association between ambient air pollutant mixtures and pediatric asthma exacerbations. Additionally, in the third use case, we identified specific air pollutants that contributed to higher weights associated with pediatric asthma exacerbations. The findings from this dissertation using public health surveillance systems are aimed to support environmental health literacy among communities and public health policy change. Our results do not imply causal relationships due to the study design and unmeasured biases that influenced our results. Further studies that consider confounding due to susceptibility factors and robust exposure measurements are needed to advocate to build a strong case for environmental health policy changes.

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LIST OF ABBREVIATIONS

AIC	Akaike Information Criterion
AQS	Air Quality System
CCSM	Community Climate System Model
CDC	Center for Disease Control
CI	Confidence Interval
CITS	Controlled Interrupted Time Series
CM	Clinical Modification
CMIP	Climate Model Intercomparison Project
DAMIP	Detection and Attribution Model Intercomparison Project
df	Degree of freedom
DLNM	Distributive Lag Nonlinear Model
DOW	Day of Week
ED	Emergency Department
EHF	Excess Heat Factor
eHRA	Environmental Health Risk Assessment
EU	European Union
GAM	Generalized Additive Model
GFDL	Geophysical Fluid Dynamics Laboratory
GHCNd	Global Historical Climatology Network-daily
GLM	Generalized Linear Model
GHG	Green House Gases
gWQS	Generalized Weighted Quantile Sum
HI	Heat Index
HRI	Heat Related Illness
HW	Heat Wave
ICD	International Classification of Diseases
ILM	Wilmington, NC

IPCC	Intergovernmental Panel on Climate Change
ITS	Interrupted Time Series
IQR	Inter Quartile Range
LOCA	Localized Constructed Analogs
MAT	Maximum Apparent Temperature
MHX	New Port/Morehead City, NC
NASA	National Aeronautics and Space Administration
NC	North Carolina
NE	Nebraska
NOAA	National Oceanic and Atmospheric Administration
NC-DETECT	North Carolina Disease Event Tracking and Epidemiologic Collection Tool
NC-DHHS	North Carolina Department of Health and Human Services
NC-DPH	North Carolina Division of Public Health
NHA	Nebraska Hospital Association
NHIS	Nebraska Hospital Information System
NWS	National Weather Service
PM	Particulate Matter
PPCA	Probabilistic Principal Component Analysis
PRISM	Parameter Elevation Regressions on Independent Slope Model
RAH	Raleigh, NC
RCP	Representative Concentration Pathway
RMSPE	Root Mean Square Percentage Error
SD	Standard Deviation
TDI	Therman Discomfort Index
US	United States
USEPA	United States Environmental Protection Agency

USGCRP	United States Global Change Research Program
UITS	Uncontrolled Interrupted Time Series
WFO	Weather Forecast Office
WHO	World Health Organization
WMA	World Meteorological Association

CHAPTER 1: BACKGROUND

ENVIRONMENTAL RISK FACTORS AND HUMAN HEALTH BURDEN

Environmental hazards are the elements from the public environment (ex: ambient air quality), personal environment (ex: nutrition), individual lifestyle choices (ex: physical activity), and workplace (ex: occupational-related) that can affect human health (Ayres et al., 2010; Liverman, 2001). Human exposure to environmental hazards is hereafter referred to as environmental exposures. Environmental exposures are a collective of "all the physical, chemical and biological factors external to a person, and all related behaviors, but excluding those natural environments that cannot reasonably be modified" (Frumkin, 2005; Prüss-Ustün et al., 2018). Environmental exposures often occur as complex mixtures, and the intensity of exposure may vary over time (Ayres et al., 2010). Exposure to environmental hazards begins as early as preconception when the Oocyst, Spermatid, and Blastocyst have been exposed to the paternal and maternal biological environment (Louis & Platt, 2011). These early-life exposures could result in a spectrum of outcomes ranging from in-utero, postnatal, or later onset events (Louis & Platt, 2011). Life-course environmental exposures often play a crucial role in mediating the susceptibility to environmental hazards (Kuh et al., 2003).

The environmental risks are conceptualized as an interaction between the environmental exposures and human factors (vulnerability and resilience) that moderates the likelihood of an adverse event (Bonadonna et al., 2021; Cardona et al., 2012; Liverman, 2001). Environmental risks are typically presented as quantitative measurements to express the health burden attributable to environmental exposures (Liverman, 2001). This document focuses on the public environment among the four environmental exposures.

In 2012, the World Health Organization (WHO) estimated that 22% [95% Confidence Interval (CI): 16-38%] of the global deaths and disabilities are attributable

to environmental exposures (Prüss-Ustün et al., 2018). Over a previous decade (2002 - 2012), the number of global deaths attributable to environmental factors declined by 5.4% (13.3 to 12.6 million deaths per year) (Prüss-Ustün et al., 2018). In 2012, the fraction of deaths attributable to environmental risk factors was higher among African countries (23%) and lower in the Americas (Canada, Chile, Trinidad, and Tobago, United States of America, 11%) (Prüss-Ustün et al., 2018). Most of the global population (99%) is exposed to air pollutants above the WHO standards, and 85% are exposed to hazards attributable to anthropogenic climate change (Callaghan et al., 2021; WHO, 2022a, 2022b).

Additionally, air pollution and anthropogenic climate change go hand in hand. Anthropogenic activities are the primary sources of criteria pollutants (except ozone) in the atmosphere (von Schneidemesser et al., 2015). Criteria pollutants that interact with the atmospheric chemistry could directly or indirectly affect radiative forcing, otherwise known as anthropogenic climate change (Myhre et al., 2013; von Schneidemesser et al., 2015). Climate change extends its effects on aeroallergen counts, season, allergenicity (pollen and mold) mediated via warm temperatures, and extreme events such as thunderstorms (Beggs, 2004). We assumed the feedback mechanism between air pollutants and climate change as mentioned in Figure 1. As air pollution and climate change are interconnected, and environmental exposures cover most of the population, we narrowed this document from the physical environment to anthropogenic climate change and air pollution.

Anthropogenic activities, global warming, and climate change

Human activities such as industrial processes, energy production, prescribed burns, and processing waste are the primary sources of air pollution (Mallik, 2019). Among the primary air pollutants released by human activities, sulfur dioxide is from the combustion of coal and oil; nitrogen oxides from vehicle exhaust; carbon monoxide from the combustion of carbon-based fuel; carbon dioxide from the combustion of fossil fuels and the cement industry; methane from landfills, oil and

gas industry and agricultural activities (Mallik, 2019; United States Environmental Protection Agency (USEPA), 2022b). Additionally, particulate matter is a mixture of minerals, organic and inorganic salts produced from agricultural burning, construction, road dust, combustion of fossil fuel, and industrial emissions (Mallik, 2019). Unlike the primary pollutants, ozone is a secondary pollutant formed due to the photochemical reaction between nitrogen oxides and volatile organic compounds in the troposphere (Mallik, 2019).

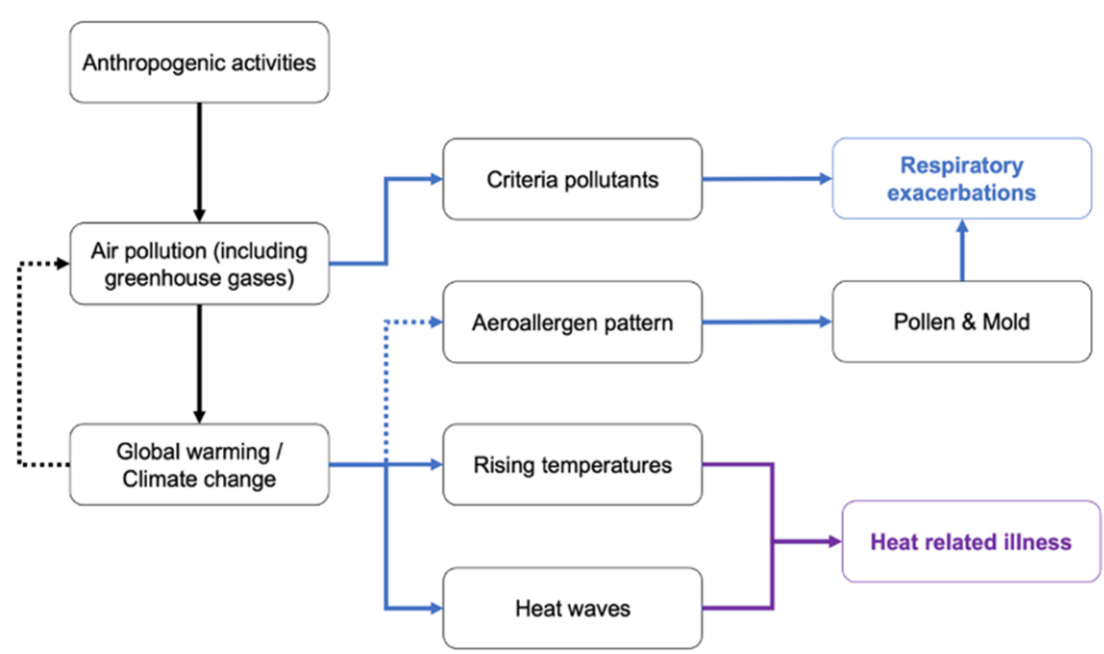

Figure 1. Conceptualization of the feedback mechanism between climate change.

These air pollutants were associated with adverse human health outcomes (Kulshreshtha, 2019), whereas the air pollutants categorized as greenhouse gases (GHG), carbon dioxide and methane, are known to trap the heat energy generated via infrared radiation in the earth's atmosphere (Tiwari & Mishra, 2019; Vavrus et al., 2015). According to the National Aeronautics and Space Administration (NASA), global warming is defined as the "Long-term heating of the earth's climate system observed since the pre-industrial period (between 1850 and 1900) due to human activities, primarily fossil fuel burning, which increase heat trapping GHG levels in

Earth's atmosphere" (NASA, 2022). Similarly, climate change is defined as "a long-term change in the average weather patterns that have come to define Earth's local, regional and global climates" (NASA, 2022).

Climate change in the United States (US) is associated with extreme weather events (Balbus et al., 2016). Extreme weather events include rising temperature, heat waves, wildfires, extreme precipitation, floods, hurricanes, and drought (Balbus et al., 2016). Over the period 2004 to 2013, heat waves had the highest human health burden among the extreme weather events (Bell et al., 2016). Additionally, altered weather conditions were found to impact air quality (carbon dioxide, particulate matter, and ozone) and aid the release of aeroallergens (Fann et al., 2016).

Rising temperatures

According to the Intergovernmental Panel on Climate Change (IPCC), the current (2010-2019) global mean surface temperature increased by 0.8-1.3°C due to human activities than during the pre-industrial period (1850-1900) (IPCC, 2018, 2021b). Assuming constant greenhouse gas emissions as of the current period, the global warming trend is projected to increase by 0.2°C per decade (IPCC, 2018). Since 1990, carbon dioxide has contributed 59-64% of the global net anthropogenic greenhouse gas emissions (IPCC, 2022). In 2019, carbon dioxide emissions were estimated to be increased by 167% compared to 1990 (IPCC, 2022). Over the last 15 decades (1850-2019), the North American region ranked as the highest (23% of global emissions) emitter of carbon dioxide into the atmosphere associated with human activities (IPCC, 2022). Consistent increase in the global greenhouse gas emissions indicates an overall decrease in the frequency of cold days and nights and an increase in warm nights and days (IPCC, 2012; Smith et al., 2014). Anthropogenic climate change was associated with an increase in the frequency of hot extremes globally, except in the Central and Eastern regions of North America (IPCC, 2021b).

In comparison, the Central and Eastern North American regions observed an increase in heavy precipitation events driven by climate change (IPCC, 2021b).

In the US, the annual mean surface temperature increased by 1°C relative to the pre-industrial period and is estimated to increase by 1.6-6.6°C over the next few decades (Hayhoe et al., 2018). Within the US, the annual mean surface temperature is projected to increase over this century, with a higher magnitude at higher latitudes (Great Plains North, Alaska, Southwest, Northwest, and Northeast) than the contiguous US average (Vose et al., 2017).

In the Southeastern region of the US, the frequency of warm nights (24°C) increased by three times during the previous decade compared to the 1970s (Carter et al., 2018). In the context of heat waves, Raleigh, North Carolina, is one of the five large cities with a warming trend above the national average (Carter et al., 2018). These findings from the fourth national climate assessment report are the major drivers for our focus in this dissertation, quantifying the human health risks attributable to the current and future anthropogenic climate change (Carter et al., 2018).

Heat waves

A heat wave is an episode of abnormally hot weather that could last from days to weeks (USGCRP, 2022). There are several strategies across the globe to define heat waves. According to the World Meteorological Association (WMA), a heat wave is a period of 5 or more consecutive days with an ambient temperature greater than the long-term (1961-1990) mean temperature (Basu, 2015). In the US, heat waves are defined using the criteria developed by the regional NOAA Weather Forecast Offices (Ferrell et al., 2017). Since 1950, the frequency, intensity, and duration of heat waves have increased globally and are projected to worsen due to global warming (Perkins-Kirkpatrick & Lewis, 2020). The number of heat waves per decade in the US increased by three times (2 heat waves in the 1960s compared to 6 in the 2010s) (EPA, 2021). Additionally, the annual average length of the heat

wave (daily minimum apparent temperature ≥ 85th percentile of summer (July-August) historic threshold (1981-2010)) season increased by 3.2 times in the 2010s compared to the 1960s (USEPA, 2021). These increases in heat waves were observed in the eastern region of the US (USEPA, 2021).

Historically, heat waves (1966-St. Louis, MO & New York, NY; 1980: St. Louis, Kansas City, MO, & Memphis, TN; 1993: Philadelphia; 1995: Chicago, IL) were highlighted in the context of mortality (Applegate et al., 1981; Henschel et al., 1969; Jones et al., 1982; Schuman, 1972; Semenza et al., 1996). Several researchers compared the association between mortality and a wide variety of heat wave definitions (Anderson & Bell, 2011; Barnett et al., 2012; Guo et al., 2017; McElroy et al., 2020; Vaidyanathan et al., 2016). These studies evaluated associations at several geographic scales, including administrative boundaries and climate regions. However, there was a limited emphasis on the acute outcome, such as heat-related illness (HRI) associated with heat waves. This dissertation compared the association between HRI and multiple heat waves.

Air quality

"Climate change can impact air quality and, conversely, air quality can impact climate change" (USEPA, 2022). Weather conditions such as temperature, wind (direction, speed), cloud cover and precipitation, and anthropogenic air pollutants and natural sources released into the atmosphere affect air quality (Nolte et al., 2018). On the other hand, greenhouse gases emitted into the atmosphere due to anthropogenic activities feed into global warming (IPCC, 2021b).

Exposure to air pollutants is a known risk factor associated with several adverse human health outcomes (Anenberg et al., 2020; Dominski et al., 2021). These associations were not limited to respiratory diseases but extended to cardiovascular, cardio-respiratory, pregnancy, mental health, cancer, and other chronic conditions (Dominski et al., 2021). Recent studies systematically reviewed the association between air quality and health outcomes and reported that long-term

exposure to a lower concentration of air pollutants (below regulatory limits) could result in adverse health outcomes (Beelen et al., 2014; Chen & Hoek, 2020). As a result of the recent findings on associations between low concentration of air pollutants and adverse health outcomes, the WHO revised ambient air quality guidelines (WHO, 2021). Along the same lines, the European Commission initiated the Inception Impact Assessment to possibly revise the ambient air quality directives (European Commission (EC), 2020).

Among the ambient air pollutants, criteria pollutants (ozone, particulate matter, carbon monoxide, lead, sulfur dioxide, and nitrogen dioxide) received the most attention due to the US EPA's Clean Air Act that regulates the nation's air quality (USEPA, 2022a). However, the association between climate change and air quality is not limited to criteria pollutants but impacts aeroallergens (Nolte et al., 2018). Climate change (ambient temperature, precipitation, and carbon dioxide) was identified as a participant in altering the intensity and duration of aeroallergens (pollen and mold spores) (Manangan et al., 2021; Nolte et al., 2018; Paudel et al., 2021; Poole et al., 2019).

EXPOSURE ASSESSMENT

The exposure measurements in this dissertation were from ambient sources, commonly used in weather-related and air pollution studies. Basu et al. (2002) reported similar temperature measurements while comparing personal ambient temperature exposures with the ambient temperature measurements monitored at the city airport (Basu & Samet, 2002). Similarly, strong correlations were reported between ambient and personal exposure to air pollutants (Janssen et al., 2005; Sarnat et al., 2000; Williams et al., 2000). Approximating the ambient measurements as personal exposures could introduce systematic bias. To minimize the exposure misclassification bias in this dissertation, we adapted sub-regional spatial delineations.

HEALTH OUTCOME ASSESSMENT

The health outcome data in the chapters discussing HRI-related emergency department visits was obtained from a syndromic surveillance system, the North Carolina (NC) Disease Event Tracking and Epidemiologic Collection Tool (DETECT), established by the North Carolina Department of Health and Human Services (NC DHHS). In comparison, the health outcome data in the chapter discussing pediatric asthma-related emergency department visits was obtained from a Healthcare Utilization Database, the Nebraska Hospital Information System (NHIS), maintained by the Nebraska Hospital Association. The use of health outcomes from these public health surveillance systems was suitable for the use case in this dissertation, where we aim to quantify the acute exposure-outcome associations.

Syndromic surveillance

Syndromic surveillance is a method to monitor public health risks typically conducted at a population scale (Huybrechts & Schneeweiss, 2021). The data is harvested from emergency department records, hospital admissions, medical prescriptions, calls to healthcare hotlines, internet queries, and social media mentions (Huybrechts & Schneeweiss, 2021). The primary purpose of the NC DETECT database is to conduct real-time surveillance of summertime (May-August) HRI-related emergency department visits and promote heat mitigation strategies and heat health education that support minimizing HRI emergencies in North Carolina. This dissertation considered the syndromic surveillance data to perform a secondary analysis that supports the dissertation objectives.

Healthcare Utilization Databases

Healthcare Utilization Databases are the data harvested from insurance claims from private companies, Medicare, and Medicaid (Huybrechts & Schneeweiss, 2021). They contain patient-level information, including payer-billing codes related to patient diagnosis, procedures, medications, and physician services (Huybrechts &

Schneeweiss, 2021). The NHIS database contains health outcomes data harvested from the administrative health insurance claims submitted from the care provider to the payer.

In this dissertation, we observed the characteristics of the health outcome data from the above sources, and the health data is used for secondary analysis. The datasets we received from the NC DETECT and the NHIS followed a similar format and were considered for quantifying environmental health risks. Hereafter, the NC-DETECT and NHIS data are referred to as public health surveillance data.

ENVIRONMENTAL HEALTH RISK ASSESSMENT

Environmental Health Risk Assessment (eHRA) is a quantitative process of estimating the human health risks associated with environmental exposures (Fjeld et al., 2007; Vohra & Hurley, 2010). According to this dissertation's objectives, we adapted and modified the risk assessment framework (illustrated in Figure 2) developed by the WHO (WHO, 2016). The US-EPA and European Environmental Agency developed several tools based on this framework to evaluate associations between outdoor air pollutants and adverse health outcomes (Hassan Bhat et al., 2021). The eHRA in this dissertation was assessed using the interrupted time series (ITS) study design, a sub-type of quasi-experimental (non-randomized) approaches (Harris et al., 2006; J. Lopez-Bernal et al., 2018). The ITS design is a conventional approach as an alternative to randomized controlled trials to assess population-level exposure-response associations (Hudson et al., 2019; Kontopantelis et al., 2015; James Lopez-Bernal et al., 2018). This dissertation relied on ambient measurements for exposures and outcomes ascertained using public health surveillance databases.

We focused on environmental hazards (ambient temperature and air pollutants) established in the literature (USGCRP, 2016b). Our contribution to the literature is by contextualizing environmental risk factors in estimating the human health risk attributable to anthropogenic climate change (current and future), comparing the sensitivity of heat wave definitions associated with acute heat-related emergencies,

and evaluating the joint association between ambient air pollutants and asthma emergencies. As the dissertation objectives focus on assessing associations between ambient environmental exposures and relevant acute health outcomes, we relied on the ITS study design. As this dissertation is based on ITS with time-period as a control group, we focused on acute associations. We used data at a daily scale temporal resolution to strengthen the findings. Even though the ITS design has several limitations in drawing causal inference, it is an ideal substitute for an RCT in evaluating acute exposure-outcomes associations (Celentano & Szklo, 2019; James Lopez-Bernal et al., 2018).

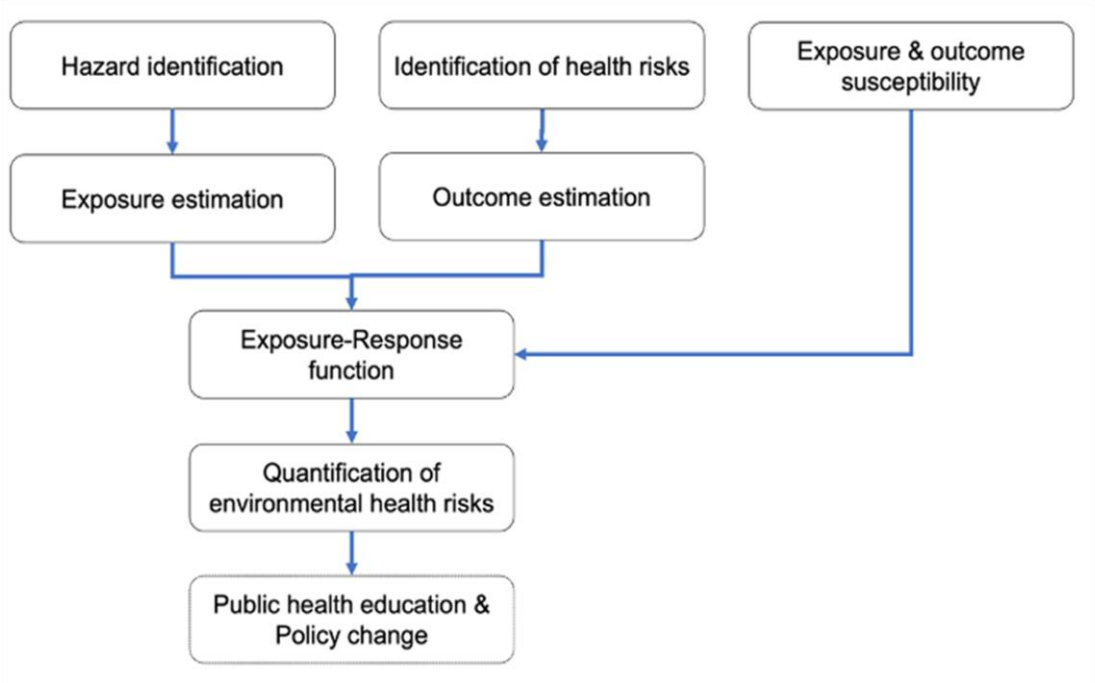

Figure 2. Environmental Health Risk Assessment framework.
Adapted and modified from the WHO, Health Risk Assessment for air pollution

OBJECTIVES

This dissertation aims to develop public health insights that support environmental risk communication to the communities and policymakers using public health surveillance systems. Exposure to environmental hazards is associated with various adverse health outcomes that could play a role in an increased rate of preventable health conditions and an increased burden on society. Quantifying and

communicating the risks associated with environmental hazards will help communities and public health policymakers to develop environmental risk mitigation strategies. Additionally, this dissertation could strengthen the framework for practicing environmental epidemiologic research based on public health surveillance data.

STUDY MOTIVATION

Over the life course, humans are exposed to a mixture of environmental hazards daily. The interaction between environmental exposures and human susceptibility factors results in adverse health outcomes. Factors such as mistrust and disagreements of risk assessment, degree of belief in science and institutions, social stigma, political dynamics, and social polarization play a role in environmental risk perception. To overcome the shifts in environmental risk perception, we would require a scientifically standardized framework for quantifying the associations between environmental risk factors and adverse health outcomes. In this dissertation, we attempted to develop evidence-based environmental health insights that support community health education and policy change.

STUDY INNOVATION

As the three studies discuss unique themes in quantifying environmental health risks, we will highlight the innovative contributions of each objective. We quantified the human health risks attributable to current and future climate change for the first objective, using acute health outcomes stratified by physiographic regions. Recent literature in this area was focused on mortality, and the attributable outcomes were estimated using political boundaries. Additionally, the hybrid approach between the ideas from ITS design and mixture analysis to evaluate the association between ambient air pollutants and pediatric asthma exacerbations was an innovative contribution to the literature. Applying the ITS study design as an alternative to randomized control trials in quantifying environmental health risks could substantially

minimize systematic bias than the cross-sectional design (Fretheim et al., 2015; St.Clair et al., 2016). Additionally, considering acute health emergencies as the outcomes in this dissertation further strengthened our findings by minimizing uncertainty while quantifying environmental health risks.

SPECIFIC AIMS

Study 1

Evaluating the burden of heat-related illness morbidity attributable to anthropogenic climate change in North Carolina.

Aim 1: Developing exposure-response function to estimate the rate of heat-related illness emergency department visits.

Hypothesis: There is a non-linear association between heat metrics and heat-related emergency department visits.

Aim 2: Quantifying the heat-related illness burden attributable to current climate change.

Hypothesis: The rate of heat-related illness is lower during the natural simulations (simulated heat metrics without industrial revolution) than in the actual observations.

Aim 3: Quantifying the heat-related illness burden associated with the future climate projections under two greenhouse gas emission scenarios.

Hypothesis 1: The rate of heat-related illness will increase over the future periods compared to the study baseline.

Hypothesis 2: The rate of heat-related illness is higher during the higher greenhouse gas emission scenario than in the lower greenhouse gas emission scenario.

This study is based on a controlled interrupted time series design (CITS), considering emission scenarios and baseline period as the control group for attributing the HRI morbidity associated with climate change (James Lopez-Bernal et

al., 2018). The goal of the first study is to quantify the heat-related illness risk attributable to non-anthropogenic climate change. Although several studies demonstrated climate change as a human health risk using mortality as an outcome, there is a greater chance for uncertainty as many individuals exposed to extreme temperatures may not manifest death. The findings from this study will help understand the acute and direct human health risks (heat-related emergencies) attributable to climate change.

Study 2

Evaluating the sensitivity of heat wave definitions among the North Carolina physiographic divisions.

Aim 1: Identifying a heat wave definition with the best model fit to estimate the rate of heat-related illness.

Hypothesis: There is heterogeneity in the model fit among the heat wave definitions included in this study.

Aim 2: Comparing the heat wave definition identified in this study with the National Weather Service warnings.

Hypothesis: Significant differences exist between the heat wave days from this study compared to the National Weather Service warnings.

This study follows CITS with a fraction of the period (non-heat wave days) as the control group to estimate HRI morbidity associated with heat waves (Lopez-Bernal et al., 2018). The goal of the second study is to identify a heat wave definition with the best model fit to estimate heat-related emergencies. Several studies compared the effectiveness of heat wave definitions using mortality and to identify extreme heat warnings; this study focuses on moderate and frequently occurring heat waves in the context of heat-related emergencies. These findings could support public health education to minimize heat-related emergencies and recalibrate the National Weather Service warnings.

Study 3

Joint association between ambient air pollutant mixture and pediatric asthma exacerbations.

Aim 1: To estimate the joint association between ambient air pollutant exposure and pediatric asthma exacerbations.

Hypothesis: Compound exposure to ambient air pollutants is associated with pediatric asthma exacerbation-related emergencies.

This study follows the uncontrolled interrupted time series (UITS) design. We aim to evaluate the joint association between the ambient air pollutant mixture and pediatric asthma exacerbations to account for concurrent events across time. We anticipate our results will highlight the key pollutants in the atmosphere associated with pediatric asthma exacerbations.

CHAPTER 2: ESTIMATING THE BURDEN OF HEAT RELATED ILLNESS MORBIDITY ATTRIBUTABLE TO ANTHROPOGENIC CLIMATE CHANGE IN NORTH CAROLINA

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ABSTRACT

Climate change is known to increase the frequency and intensity of hot days (daily maximum temperature ≥ 30°C), both globally and locally. Exposure to extreme heat is associated with numerous adverse human health outcomes. This study estimated the burden of heat-related illness (HRI) attributable to anthropogenic climate change in North Carolina physiographic divisions (Coastal and Piedmont) during the summer months from 2011-2016. Additionally, assuming intermediate and high greenhouse gas emission scenarios, future HRI morbidity burden attributable to climate change was estimated. The association between daily maximum temperature and the rate of HRI was evaluated using the Generalized Additive Model. The rate of HRI assuming natural simulations (i.e., absence of greenhouse gas emissions) and future greenhouse gas emission scenarios was predicted to estimate the HRI attributable to climate change. Over four years (2011, 2012, 2014, and 2015), we observed a significant decrease in the rate of HRI assuming natural simulations compared to the observed. About 3 out of 20 HRI visits are attributable to anthropogenic climate change in the Coastal (13.40% (IQR: -34.90,95.52)) and Piedmont (16.39% (IQR: -35.18,148.26)) regions. During the future periods, the median rate of HRI was significantly higher (78.65%: Coastal, and 65.85%: Piedmont), assuming a higher emission scenario than the intermediate emission scenario. We observed significant associations between anthropogenic climate change and adverse human health outcomes. Our findings indicate the need for evidence-based public health interventions to protect human health from climate-related exposures, like extreme heat, while minimizing greenhouse gas emissions.

Keywords: Climate change, climate attribution, climate projections, heat related illness, morbidity

INTRODUCTION

Since the mid-20th century, the frequency and duration of hot days have increased globally due to anthropogenic climate change (Hoegh-Guldberg et al., 2018). Global temperature is very likely to increase up to 1.5-1.6°C during 2021-2040, 1.6-2.4°C during 2041-2060, and 1.4-4.4°C during 2081-2100, relative to1850-1900 (IPCC, 2021b). These increases in temperature since the mid-20th century are primarily the result of anthropogenic greenhouse gas emissions (IPCC, 2021b). Mora et al., (2017) estimate that roughly 30 percent of the current global population is exposed to extreme heat conditions; this number is expected to increase to 50-75% by 2100.

Exposure to extreme heat leads to heat-related morbidity and mortality. Extreme heat outcomes can be characterized as direct (e.g., heat-related illness (HRI)), or indirect (e.g., exacerbation of cardiovascular, respiratory, renal, endocrine, and mental health conditions) (Bell et al., 2018; Ebi et al., 2021; Sarofim et al., 2016). Failure to acclimatize during extreme heat conditions can result in HRI ranging from muscle cramps, heat exhaustion, and heat stroke (Danzl, 2018). HRI, if untreated, can lead to life-threatening conditions (LoVecchio, 2016; Nemer & Juarez, 2019). In the United States (US), heat-related fatalities are more common than deaths due to other natural disasters (NOAA, 2019). In the US, there are an average of 702 heat-related deaths per year (Vaidyanathan et al., 2020). There is a potential imbalance between heat-related mortality and morbidity, posing an exponentially higher number of heat-related emergencies. For example, during a four-day heat wave event in North Carolina, there were 556 HRI emergencies compared to 1 heat-related death (NC-DHHS, 2016). The magnitude of the HRI emergencies compared to mortality demonstrate the need to focus on morbidity rather than mortality.

Climate change has been associated with the increasing trend of heat-related mortality and morbidity (Bell et al., 2018; Christidis et al., 2019; Ebi et al., 2021a). Evidence-based climate detection and attribution play a key role in characterizing the

changes in natural climate variability that are attributable to human activities (Ebi et al., 2020; Ebi et al., 2017). There is strong evidence supporting the association between future climate change and mortality (Conlon et al., 2016; Gosling et al., 2017; Guo et al., 2018; Lay et al., 2018). At the same time, attribution of human health risk to anthropogenic climate change has been limited to considering mortality as a health outcome (Mitchell et al., 2016; Vicedo-Cabrera et al., 2021).

It is common for attribution analyses to investigate heat-related mortality, providing insight into the magnitude of extreme heat events on the most serious health outcomes. Based on the contrast between the frequency of heat-related mortality and morbidity in North Carolina, we hypothesized that using heat-related mortality would be an underestimate to quantify human health risks associated with climate change. We investigated heat-related morbidity to better understand the scope of human health burden associated with climate change. This study estimated the HRI attributable to anthropogenic climate change. Additionally, future HRI burden attributable to climate change was estimated using the climate projections driven by representative concentration pathways (RCPs). The RCPs are greenhouse gas concentration trajectories adopted by the IPCC that are used for climate modeling (IPCC, 2014). Future climate change is typically represented using four RCP scenarios, RCP2.6 is a stringent mitigation scenario, RCP4.5 and RCP6.0 are intermediate scenarios, and RCP8.5 is a scenario with very high greenhouse gas emissions (IPCC, 2014). This study includes two of the four RCP scenarios, comparing the intermediate emission scenario (RCP4.5) and higher emission scenario (RCP8.5).

This study aimed to evaluate the association between heat metrics and HRI morbidity to estimate the HRI morbidity attributable to climate change. The analysis was conducted by estimating the HRI attributable to the current (2011, 2012, 2014, & 2015) levels of anthropogenic climate change and by estimating the HRI associated with future climate change under two greenhouse gas emission scenarios (RCPs).

MATERIALS AND METHODS

This study includes three analytic components: 1) Modeling and optimization of an epidemiologic model to estimate the rate of HRI emergency department visits, 2) Estimating the HRI burden attributable to current anthropogenic climate change, and 3) Quantifying the HRI burden associated with future climate change.

Study area: North Carolina has three physiographic regions with distinct climatological profiles: Coastal, Piedmont, and Mountain regions (Figure 3). The Coastal region includes 41 counties, Piedmont consists of 34 counties, and the Mountain contains 25 counties. Due to distinct weather conditions experienced by the population living in these physiographic regions, most of the heat-related research has been conducted using these sub-divisions (NC-DHHS, 2015). The study period included summer months (May 01-September 30) over five years from 2011 to 2016. Data for 2013 was unavailable and is excluded from the analysis.

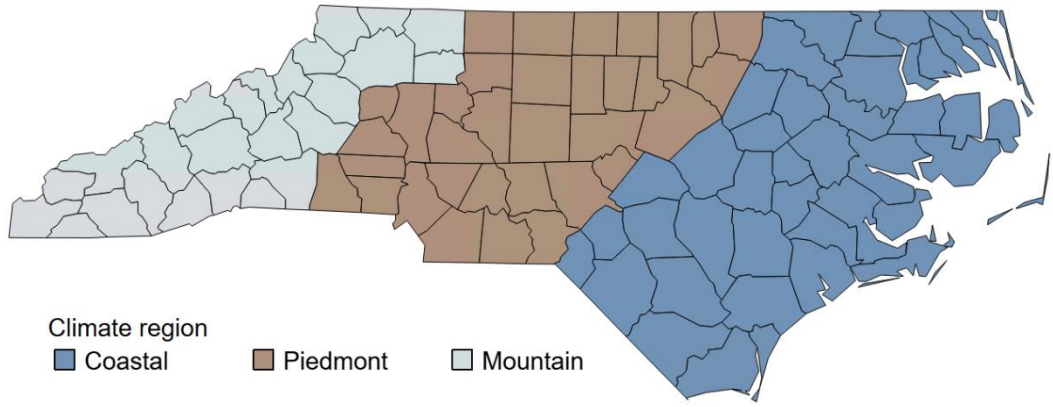


Figure 3. North Carolina physiographic regions.
North Carolina counties are represented using black boundaries and physiographic regions with similar climate profile are clustered and represented using three colors (blue-Coastal, brown-Piedmont and grey-Mountains).

HRI morbidity data

The HRI data was obtained from the North Carolina Department of Health and Human Services (NC-DHHS) that has partnered with 124 hospitals to collect statewide emergency department (ED) visit data to provide real-time, electronic

public health surveillance, which is stored in the North Carolina Disease Tracking and Epidemiologic Collection Tool (NC-DETECT, 2021). Heat-related illnesses were identified using ICD-9 CM codes with E992/E900.0/E900.0/E900; ICD-10 CM codes within T67/X30/X32; and various keywords from the chief complaint and triage notes (Morano & Waller, 2017; NC-DETECT, 2021). We obtained daily aggregated counts of HRI ED visits. Days with fewer than five HRI cases were suppressed to maintain the confidentiality of patient identifiable information.

Decennial census population data at the county level from 2010 were aggregated to the three regions in North Carolina. Equation (1) was used to estimate the rate of HRI morbidity per study region.

$$\text{HRI morbidity rate} = \frac{\text{Count HRI emergency department visits}}{\text{Population at risk}} * 100{,}000 \ldots\ldots\ldots \text{Equation 1}$$

Observed meteorological data

Daily temperature data (mean (t_{mean}), minimum (t_{min}), and maximum (t_{max})) from the Global Historical Climatology Network-Daily (GHCN-D) database was extracted and aggregated by region. The GHCN-D dataset contains daily temperature measurements based on approximately five stations per region (Houston et al., 2012). Daily temperature measurements were homogenized to account for instrumentation and processing station observations (Rennie et al., 2019). Dew point data was obtained from the Parameter-elevation Regressions on Independent Slopes Model (PRISM) dataset (PRISM, 2019). The relative humidity (RH), maximum apparent temperature (MAT), US NWS/Steadman's heat index (NWS_HI & Steadmans_HI), humidex, thermal discomfort index (TDI), and Excess Heat Factor (EHF) were computed by study region (Anderson et al., 2013; Baccini et al., 2008; Castelhano & Laboclima, 2017; Langlois et al., 2013).

Natural simulations

The natural simulations are an estimate of daily maximum temperature ($t_{max\text{-}NS}$) in the absence of human-caused greenhouse gas emissions. The natural

simulations are based on greenhouse gas emissions similar to the pre-industrial period (1980s) and not adjusted for stratospheric aerosol burden or solar luminosity (Stone et al., 2019). The daily maximum temperature observations assuming absence of human-caused greenhouse gas emissions (similar to pre-industrial period) were obtained from the dataset developed by the Climate of the 20th Century Plus Detection and Attribution (C20C+D&A) Project (Stone et al., 2019). The C20C+D&A project is built on an ensemble of multiple dynamic models based on the atmosphere-land system. Due to lack of data, we excluded the year 2013 and 2016 in the analysis. We extracted daily maximum temperatures during the summer seasons of 2011, 2012, 2014, and 2015.

Climate projections

Localized and bias-corrected climate projections were obtained from the Localized Constructed Analogs (LOCA) database (Pierce et al., 2014). The LOCA dataset was statistically downscaled from the Climate Model Intercomparison Project 5 (CMIP5) and corrected for bias using constructed analogs (Pierce et al., 2014). The current study was based on study regions, amounting to more coarse geographies. The use of LOCA data with 1/16º resolution allowed us to assign localized temperature projections to finer geographies. We focused on the Community Climate System Model version-4.0 (CCSM4) and Geophysical Fluid Dynamics Laboratory (GFDL) model outputs as these models outperformed other climate models in the Southeastern United States (Zhang et al., 2013).

The climate projection dataset contained maximum temperature aggregated for three time periods: 1. Baseline (2011-2016), 2. Mid-century (2036-2065), and 3. Late century (2070-2099). The maximum temperature ($t_{max\text{-}FS}$) was estimated for each period, assuming intermediate (RCP4.5) and high-emission (RCP8.5) scenarios.

Analysis

The analytic dataset contained the rate of HRI, t_{mean}, t_{min}, t_{max}, RH, MAT, NWS_HI, Steadman_HI, humidex, TDI, and EHF at a daily scale (Table 1). Additionally, we created a nominal variable to describe seven days of the week (DOW), a binary variable to identify weekend or weekday (Wday), as well as a nominal variable representing month and year.

Table 1. Variables and data sources.

Variables	**Source**
Temperature (t_{max}, t_{min}, t_{mean})	GHCN-D
Dew point	PRISM
Relative humidity	Calculated using daily maximum temperature and dew point.
Humidex/Heat Index	Calculated using daily maximum temperature and relative humidity
Thermal Discomfort index	Calculated using daily maximum temperature and relative humidity
Excess Heat Factor	Calculated using the daily maximum temperature
Natural simulations	C20C+D&A
Future climate projections	LOCA
HRI emergency department visits	NC DETECT
Total population	US Census Bureau

All the variables below (except total population) were measured at a daily scale by the physiographic region

Evaluating the relationship between climate metrics and HRI morbidity

Spearman correlations were run to determine temperature metrics to include in further analysis. Five of ten variables (t_{max}, t_{mean}, NWS_HI, Steadmans_HI, and MAT) had a correlation coefficient greater than 55% and these metrics were considered for evaluating association with HRI (Figure 4). The exploratory analysis suggested a nonlinear relationship between the rate of HRI and heat metrics.

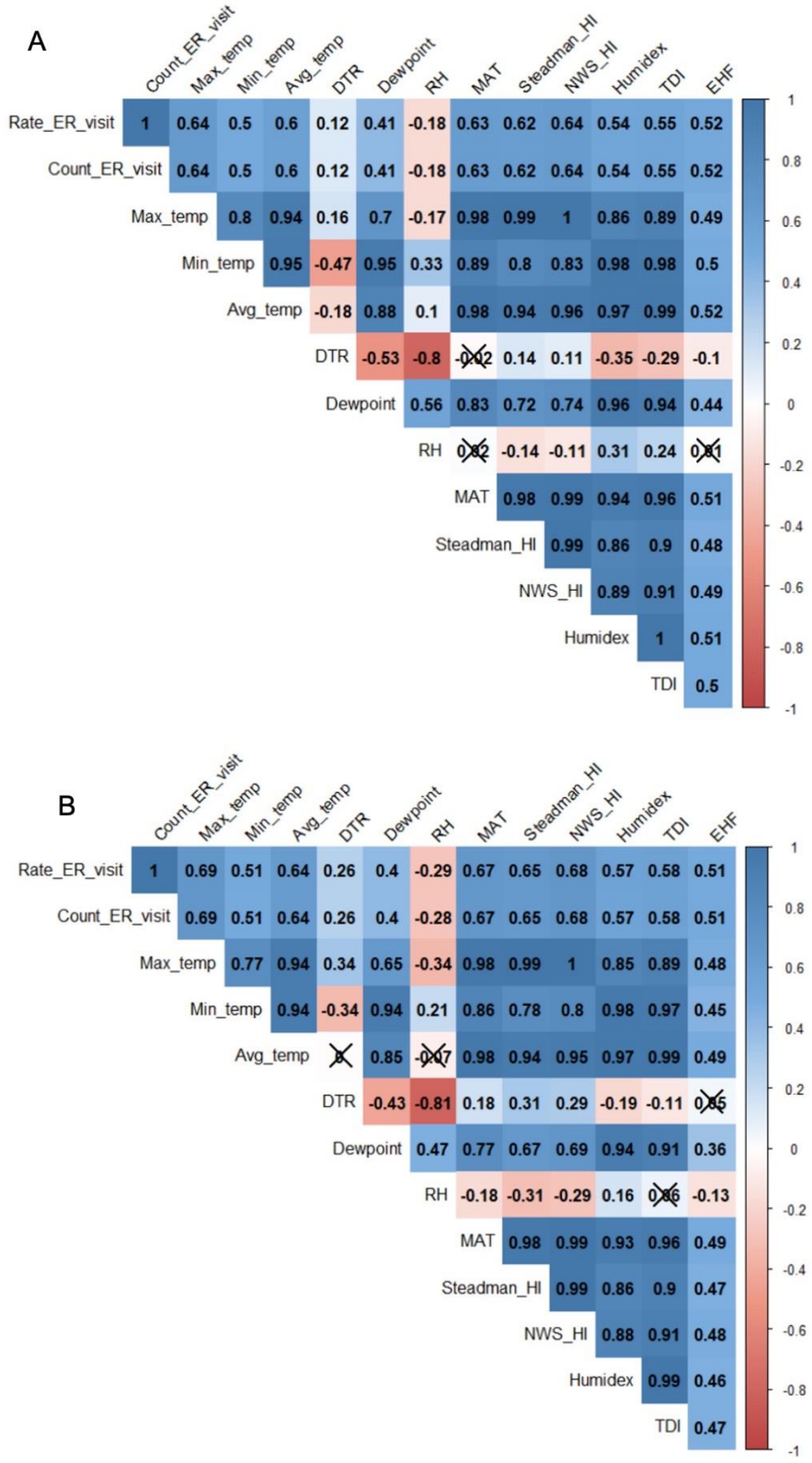


Figure 4. Correlation between meteorological variables/heat indices and HRI morbidity.
A-Coastal & B-Piedmont. The numeric values corresponding to the color legend (blue-positive association and red-negative association) are the Spearman correlation coefficients that describe the association between two variables. The non-significant ($P<0.05$) correlation coefficient values were stricken off.

The nonlinear relationship between the HRI rate and heat metrics was evaluated using the Generalized Additive Model (GAM) - 'mgcv' package version 1.8-34 (Wood, 2021) and distributed lag nonlinear model (DLNM) approach (the 'dlnm' R package version 2.4.5, Gasparrini et al. 2021).

GAM is a semi-parametric framework to address non-linearity using smoothing splines (Dominici & Peng, 2008). The smoothing term was considered for the heat metric using cubic regression bases, with up to 5 knots (Wood, 2017b). The number of smoothing parameters for heat metrics was estimation using Generalized Cross Validation (GCV) method (Wood, 2017b). The associations were evaluated assuming gamma distribution and log link (Wood, 2017a). Additionally, we included day of week, month, and year, as covariates to adjust for potential temporal autocorrelation. To identify a heat metric as a predictor in our nested model with a smaller residual sum of squares, we compared the Akaike Information Criterion (AIC) and R-squared values. The statistical model using t_{max} outperformed to estimate the rate of HRI compared to other heat metrics (Equation 2).

$$\log(\mathbb{E}[\text{HRI morbidity}]) = \sum_{j=1}^{n} b_j\,(t_{max})\beta_j + \text{wDay} + \text{Month} + \text{Year} + \varepsilon \quad \text{... Equation 2}$$

The distributive effect of heat metrics on HRI was estimated using DLNM (Gasparrini, 2011). The DLNM follows an interrupted time-series approach, where daily HRI ED visits were assumed to follow the Poisson distribution and were fit using the GAM, controlling for seasonal effect. We smoothed the heat metric exposure variable using cubic splines with 5 knots at equally spaced heat metric values. Using the ‘crossbasis’ function, we create a basis matrix between the heat metric and 5-lag days to model the association in each dimension. The association between heat metrics and HRI was evaluated for up to 5 lag days. DLNM was implemented using the ‘gam’ function, with daily HRI count as the outcome and the heat metric cross-basis matrix. The DLNM approach was implemented using ‘dlnm’ package version 2.4.5, and dependencies using ‘spline’, ‘mgcv’ packages (Gasparrini et al., 2021).

We then estimated the relative risk to daily maximum temperature by 0-5 lag days using the 'crosspred' function. The risk estimates for daily maximum temperature were predicted using the 70th percentile value (32ºC) as a reference.

Attributing the burden of HRI morbidity to current anthropogenic climate change

The statistical model was trained by physiographic regions (Equation 2.) using t_{max}, time-series variables to estimate the rate of HRI. The model performance metrics were optimum while using three cubic regression splines for t_{max} for the Coastal region and four for Piedmont. The daily rate of HRI was estimated corresponding to the daily $t_{max\text{-}NS}$ values. The percentage difference between the observed and estimated HRI rates assuming natural simulation was considered as the burden of HRI attributable to climate change. The mean difference between the daily rate of HRI between observed and natural simulation was tested using the paired t-test. Additionally, the frequency of hot days between natural simulations and actual observations was compared using the chi-square test. The percent of HRI attributable to anthropogenic climate change is expressed as median percent per year and interquartile range (IQR).

Projecting HRI morbidity under future climate change scenarios

Using t_{max} as a predictor, we trained a statistical model (Equation 3) by physiographic regions to estimate the rate of HRI. Future HRI was estimated over three different 30-year periods (baseline, mid-century, and late century), focusing on RCP4.5 and RCP8.5 scenarios. The difference between HRI across two emission scenarios was evaluated using the paired t-test and the differences between HRI across the three time periods were assessed using Analysis of Variance.

$$\log(\mathbb{E}[\text{HRI morbidity}]) = \sum_{j=1}^{n} b_j\,(t_{max})\beta_j + \varepsilon \quad \text{... Equation 3}$$

RESULTS

During the study period, 28.81% (219) of Coastal and 28.94% (220) of Piedmont regional observations were suppressed. The suppressed data were

imputed with the median value (3) of the suppressed range. The Mountain region was excluded from the study due to poor data quality [50.13% (381) suppressed].

The mean HRI rate was 54.52 per 100,000 and 34.27 in the Coastal and Piedmont regions respectively. The annual HRI rate was consistently higher in the Coastal region than in Piedmont. In both study regions, the rate of HRI was higher (Coastal:40.94% higher; Piedmont: 28.47% higher) during the summer of 2015, compared to the study period (Table 2). The increase in the rate of HRI in 2015 could be due to a 14-day heat event with tmax exceeding 32°C, from June 13th-June 27th, 2015.

Table 2. Rate of HRI morbidity per 100,000 persons.

	2011	2012	2014	2015	2016	Study period
Coastal	57.71	50.05	35.46	82.59	72.96	54.52
Piedmont	39.12	33.66	19.00	45.69	45.22	34.27

The population at risk was estimated using 2010 decennial population estimates per physiographic region in North Carolina.

Association between daily maximum temperature and HRI

The nonlinear association between HRI and t_{max} was established using the GAM (Figure 5). From the model diagnostics, we observed that about 80% of the deviance in HRI could be explained by equation 2 (Table. 3). Due to a higher number of observations with t_{max} between 26.7-35°C, there is a narrow residual confidence interval that reflects lower prediction uncertainty.

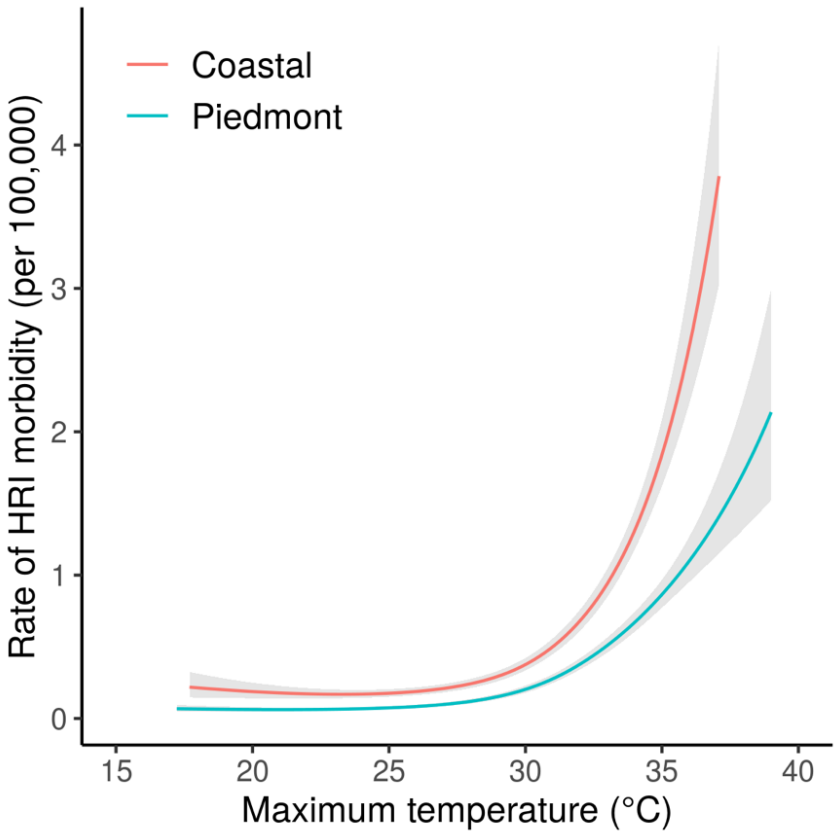


Figure 5. Association between daily maximum temperature and HRI morbidity rate.
The nonlinear association was estimated using the GAM framework, using spline terms for temperature and temporal variables (day of week, month, and year) to decompose the temporal trend. The x-axis represents the daily maximum temperature on the centigrade scale, and the y-axis represents the rate of HRI morbidity per 100,000 per day. The solid red and cyan line represent the effect of daily maximum temperature on HRI morbidity for the Coastal and Piedmont regions, respectively. The grey shaded area represents 95% confidence interval. The estimated degree of freedom for Coastal (s=3): 2.86; Piedmont (s=4):3.60.

Table 3. Generalized additive model - diagnostics.

	Coastal		Piedmont	
	a	b	a	b
AIC	189	-783	-1779	-1586
Deviance explained (%)	76.6	70.1	79.6	74.2
R-squared (%)	77.3	54.9	76.7	69.1

a- based on equation 2; b- based on equation 3.

The results from the DLNM suggest that the risk of HRI significantly increased with t_{max} of more than 35°C. The HRI risk was higher during the day of exposure than the following days (Figure 6). When the t_{max} was recorded as 35°C, the HRI risk

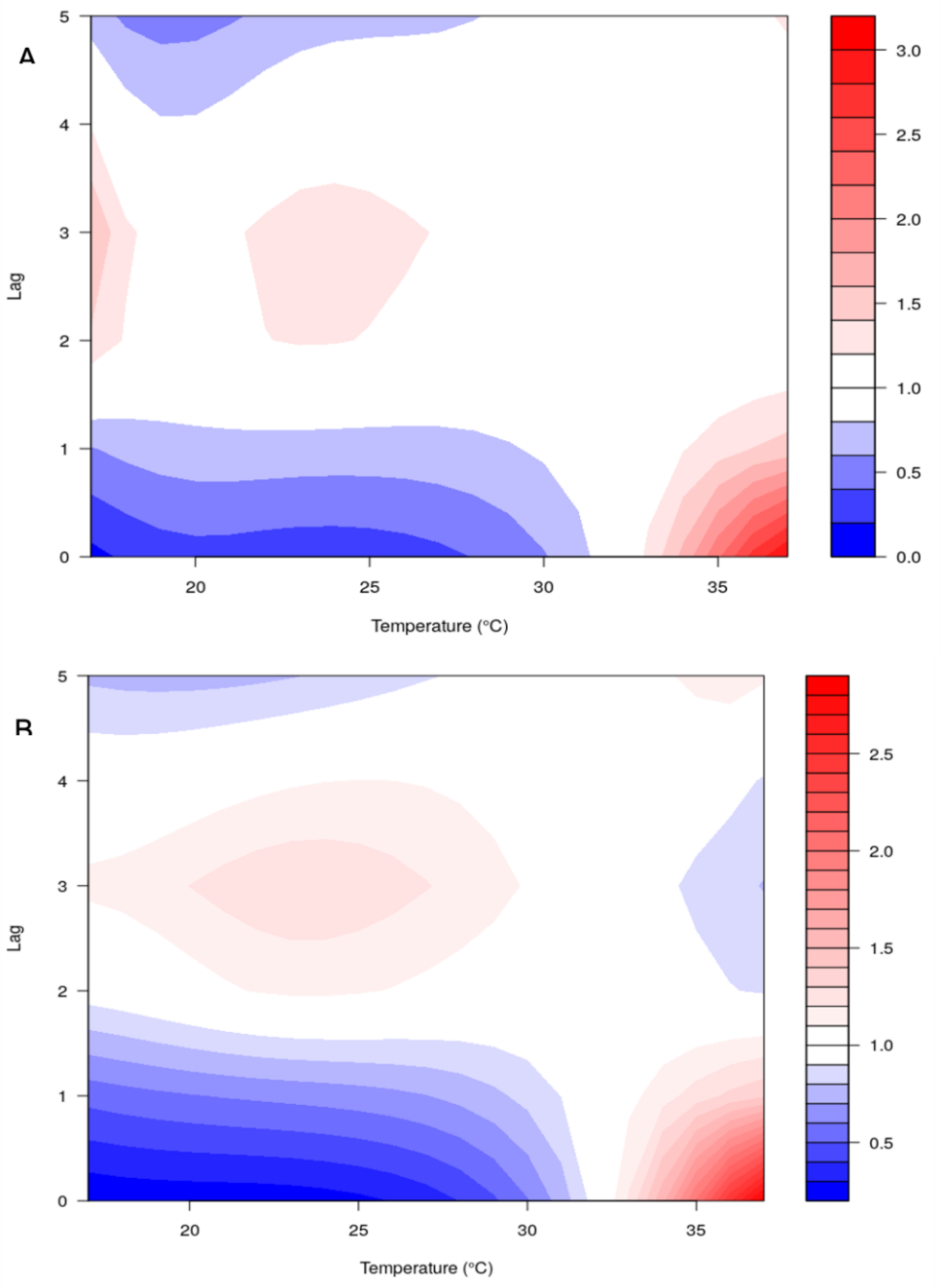


Figure 6. Distributive HRI ED visit risk associated with daily maximum temperature.
A-Coastal & B-Piedmont. The color gradient represents risk ratio, blue – protective effect, and red – adverse effect. The x-axis represents lag values corresponding to the distributive effect (lag 0: same-day effect and lag 5: risk distributed by 5 days of exposure). The risk ratio values were generated using the DLNM framework.

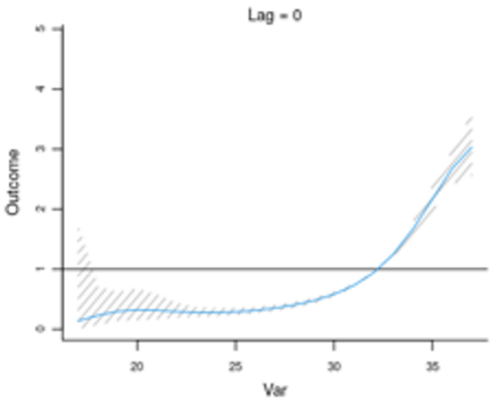
declined from about 2 to 1.2 from the day of exposure to the following day, potentially indicating a harvesting – or displacement – effect. It showed non-significant results during lag 2-5 days in the Coastal and Piedmont regions (Figure 7). The results from the DLNM suggest a negligible distributive effect of daily maximum temperature exposure on HRI morbidity.

As the HRI risk was higher during the day of exposure than in the latent period, further analysis is based on the same-day exposure-outcome relationship. As the primary goal of the current work was to build a prediction model rather effect estimation, the GAM (Equations 2, 3) was used to estimate the rate of HRI.

Burden of HRI attributable to anthropogenic climate change

Over the four years studied (2011, 2012, 2014, and 2015), the frequency of hot days was about 30% higher during the actual observations than natural simulations in both the Coastal and Piedmont regions, (p-value < 0.001) (Figure 8). We observed a significant reduction in the daily mean rate of HRI morbidity in the Coastal (estimated assuming natural simulation: 0.32 per 100,000, observed: 0.40 per 100,000; p-value < 0.001) and Piedmont (estimated assuming natural simulation: 0.19 per 100,000, observed: 0.24 per 100,000; p-value < 0.001) assuming natural scenario rather than actual observations. In the Coastal region, 13.40% (IQR: -34.90,95.52) of the HRI morbidity is attributable to anthropogenic climate change and 16.39% (IQR: -35.18,148.26) in the Piedmont region (Figure 9). Based on our attribution analysis, about 83 HRI ED visits per summer season (152 days) in the Coastal region and 85 in Piedmont could be attributed to anthropogenic climate change.

7A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Outcome
Var
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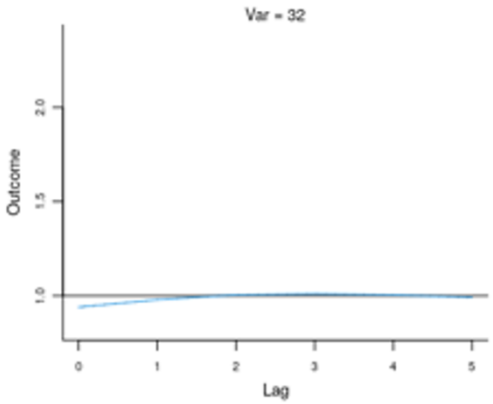
25
30
35

7B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Outcome
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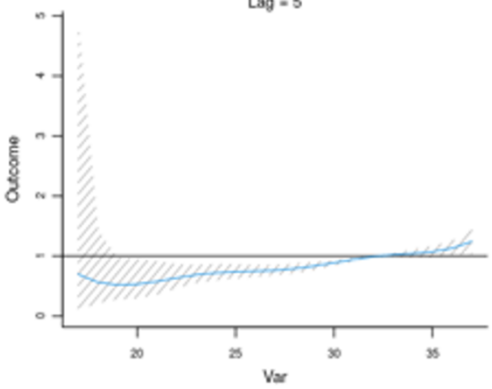
7C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Outcome
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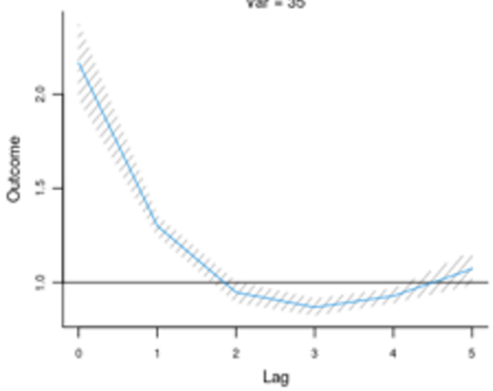
7D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Outcome
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2
3
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5

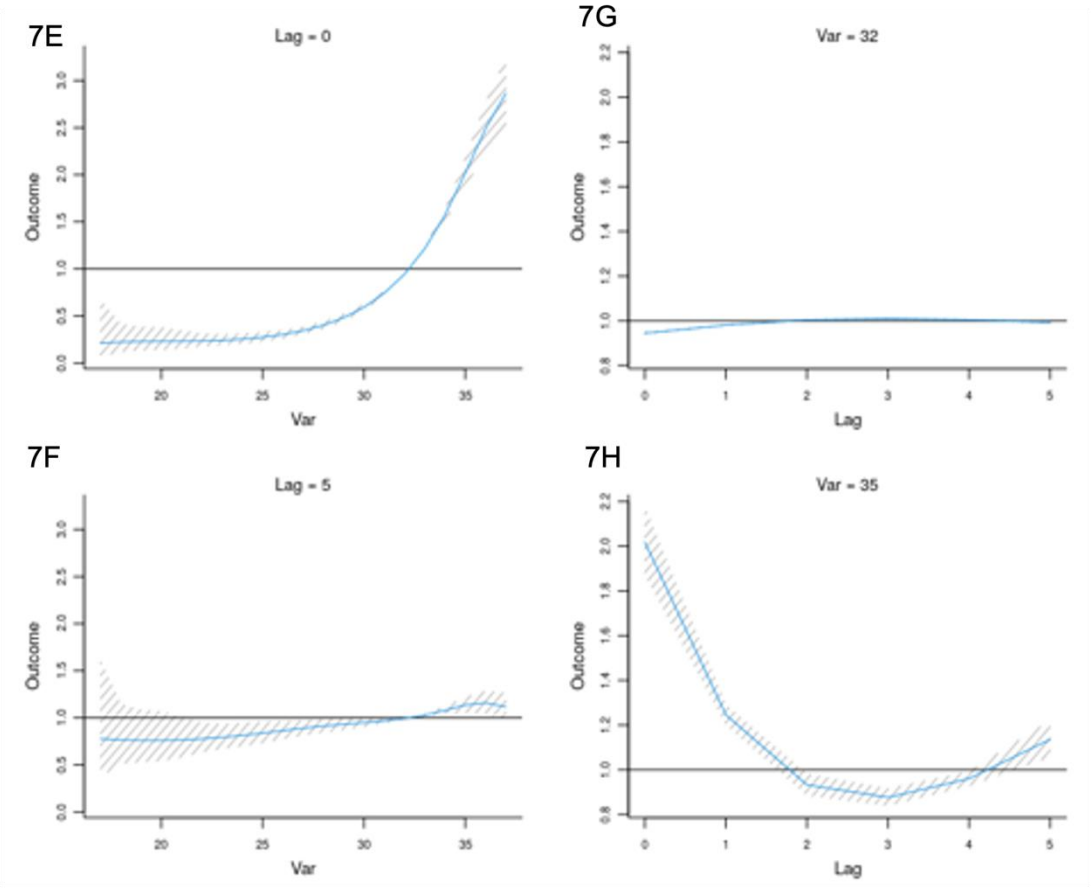

Figure 7. Distributive HRI morbidity risk associated with daily maximum temperature exposure.
This figure was generated using DLNM. Panels A-D are the results for Coastal region and E-H are for Piedmont region. The plots A, B, E, & F show the association between daily maximum temperature (on x-axis) and HRI morbidity risk (on y-axis). A & E were plotted by holding lag at 0 days (same day exposure-response association). B & F were plotted to show the distributive association between temperature and HRI morbidity at lag 5th day. The panels C, D, G, & H are plotted to show the distributive associations across lag 0-5 days (on x-axis) and HRI morbidity risk (on y-axis). C & G were plotted by holding daily maximum temperature at 32ºC, whereas D & H were plotted by holding daily maximum temperature at 35ºC.

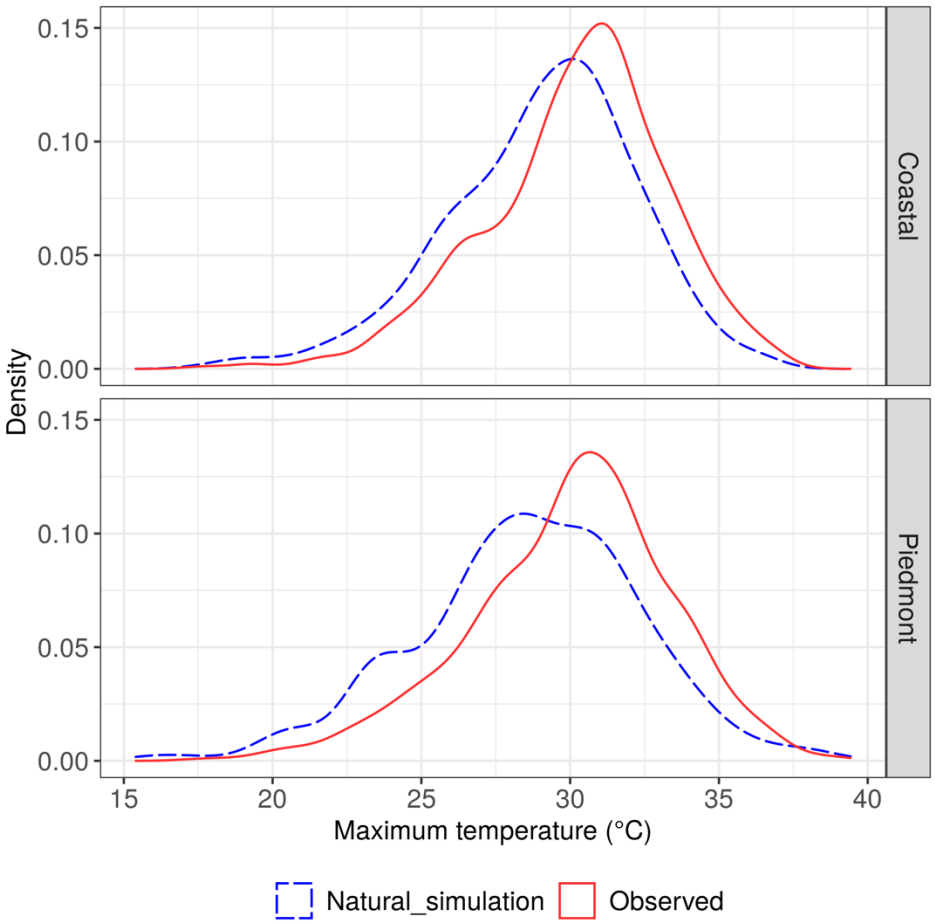

Figure 8. Comparison of the daily maximum temperature (actual observations vs. natural scenario).
Observed data was obtained from the GHCN-D database. Simulated daily temperature data assuming without anthropogenic climate change (natural simulation) was obtained from the Climate of the 20th Century Plus Detection and Attribution (C20C+D&A) Project.

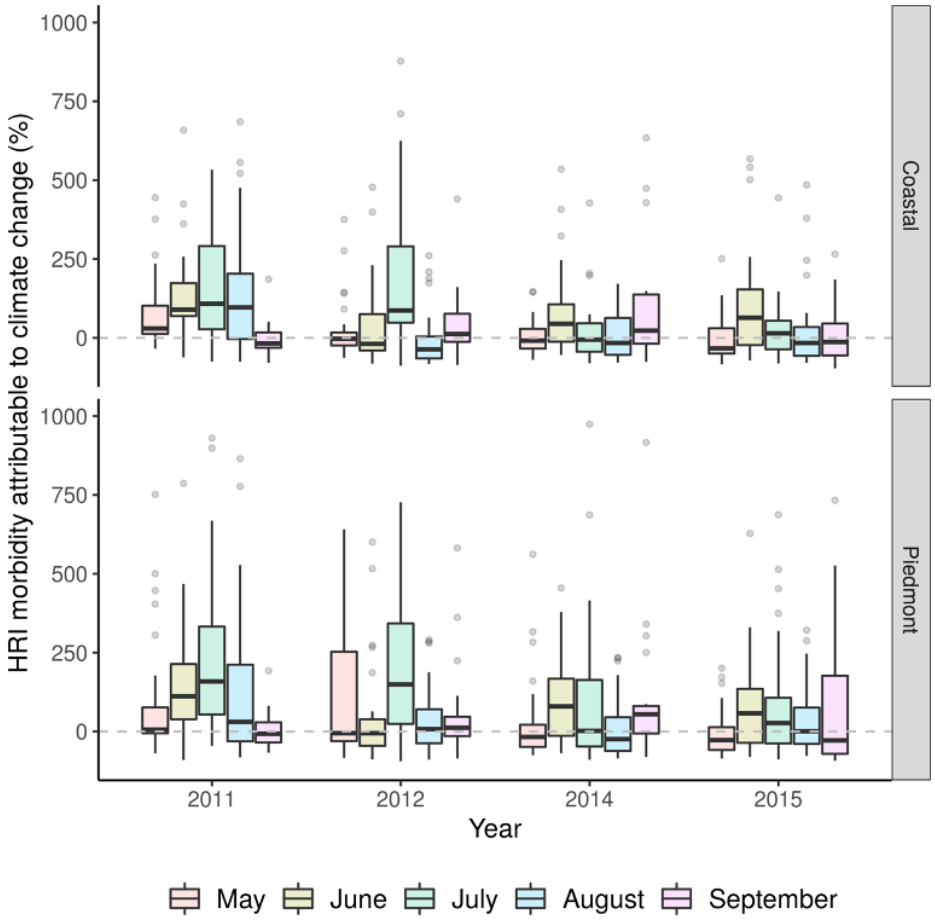

Figure 9. HRI morbidity attributable to anthropogenic climate change. Box plots are color coded by summer months and grouped by year. The boxplots show the median and interquartile range (25-75% range), outliers were represented using grey dots. The proportion of the box plot above the horizontal dashed line represent percent increase in HRI morbidity attributable to climate change.

The burden of HRI morbidity in the context of future climate change

Aggregate t_{max} values for the baseline, mid-century, and late-century were estimated assuming intermediate emission (RCP4.5) and higher emission (RCP8.5) scenarios using the CCSM4 and GFDL-ESM2M model outputs. In both the Coastal and Piedmont regions, we observed a significant increase in the frequency of hot days (Figure 10).

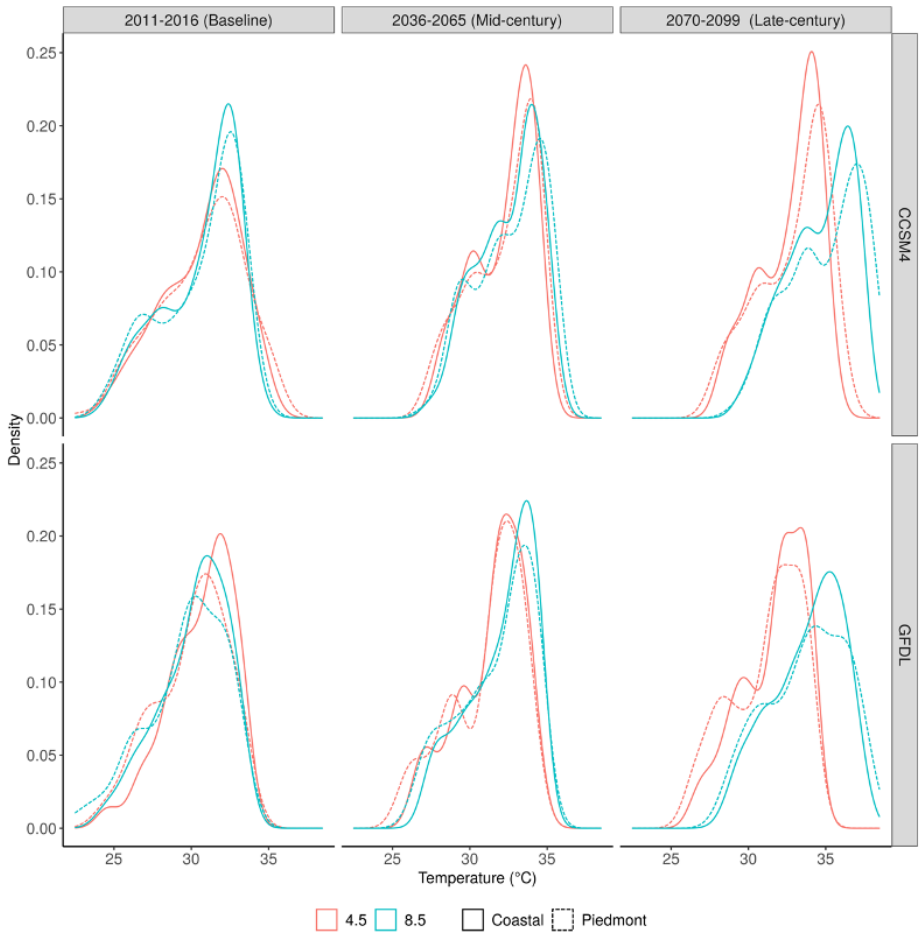

Figure 10. Projected maximum temperature using CCSM4 and GFDL model simulations.
Climate projection data was obtained from the Localized Constructed Analogs database at 1/16º resolution. Among the 32 CIMP5 model runs, we included CCSM4 and GFDL simulations in this study. The x-axis represents temperature on a centigrade scale and y-axis represents probability of distribution.

In the Coastal region, during the mid-century, we observed up to 31.45% increase in the median HRI, assuming a higher emission scenario compared to intermediate (p-value < 0.001). In the late century, the median HRI increased up to 78.65%, assuming higher emission scenario, compared to the intermediate scenario (p-value < 0.001). Additionally, assuming the intermediate emission scenario, the median HRI increased up to 53.01% during the mid-century and up to 67.98% in the late century, compared to the baseline period (p-value < 0.001). Similarly, assuming a higher emission scenario, the median HRI increased up to 68.77% during the mid-century and up to 116.31% in the late century, compared to the baseline (p-value < 0.001).

In the Piedmont region, during the mid-century, the median HRI increased up to 24.17% assuming higher emission, compared to intermediate (p-value < 0.001). In the late century, the median HRI increased up to 65.85% assuming higher emissions, compared to intermediate emission scenario (p-value < 0.001). Additionally, assuming intermediate emissions, the median HRI increased up to 55.89% during the mid-century and up to 75.59% in late century, compared to the baseline (p-value < 0.001). Assuming higher emission scenario, the median HRI increased up to 77.28% during mid-century and up to 110.35% in late century, compared to the base line (p-value < 0.001) (Figure 11).

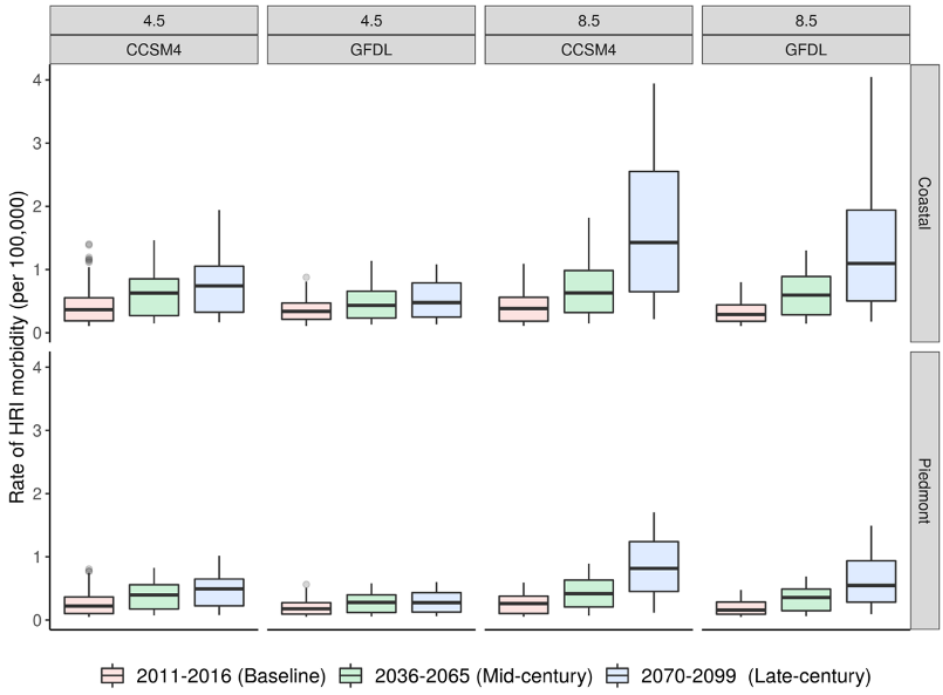

Figure 11. Estimated HRI morbidity rate in context of climate change. The box plots are color coded by time-period and grouped by climate scenario/climate model. The box plot shows median and interquartile range (25-75%), with outliers using grey dots. CCSM4 – Community Climate System Model (version. 4) & GFDL – Geophysical Fluid Dynamics Laboratory.

DISCUSSION

To our knowledge, this is the first study to identify a significant increase in HRI associated with current and future anthropogenic climate change. We identified that anthropogenic climate change attributed to higher frequency of hot days in North Carolina over a four-year period from 2011-2016. During the four-year study period, our findings suggest about 3 out of 20 HRI emergency department visits in North Carolina were attributable to anthropogenic climate change. In addition, future projections of climate change showed a continued increase in HRI over the next century.

Our findings are similar to other studies that have found an increase in heat-related mortality attributable to anthropogenic climate change. However, this is the first study to focus on morbidity. Unlike studies focused on mortality, morbidity better

captures the total human health burden associated with climate change. Other studies focused on health outcomes associated with climate-related events show that mortality often underestimates the total impacts on health and the associated healthcare costs. Based on our results in two regions in North Carolina, we estimate that 13.4% and 16.4% of HRI emergency room visits from 2011-2016 occurred because of anthropogenic climate change. The HRI attributable to anthropogenic climate change could be translated to an average of up to 85 HRI emergency department visits per physiographic region per summer season. Similarly, Vicedo-Cabrera et al. (2021) reported an average of about 23 heat-related deaths per year in 6 major cities in North Carolina attributable to anthropogenic climate change (Vicedo-Cabrera et al., 2021). Our results suggest that heat-related morbidity is 3.69 times higher than the heat-related mortality rate reported by Vicedo-Cabrera et al. (2021). The higher number of HRI could be due to the difference in the total number of cities included in our study (all the area covered under Coastal and Piedmont regions) compared to Vicedo-Cabrera et al., 2021, which included 6 major cities in North Carolina. It is also natural that morbidity should be higher than estimates of mortality, as not every heat-related illness result in a death. In North Carolina, the annual mean heat-related mortality rate is about 200 times less than the rate of heat-related ED visits [0.11 (1997-2001) versus 22.2 (2007-2012) per 100,000 persons] (Mirabelli & Richardson, 2005; Sugg et al., 2016). Additionally, the natural simulation data used in this study is from the C20C+D&A project (Stone et al., 2019a), whereas their simulation runs were obtained from the Detection and Attribution Model Intercomparison Project (DAMIP). The natural simulations from C20C+D&A were based on a dynamical ocean model (ocean surface and sea ice conditions) and are hypothesized to have minimal bias compared to the simulations from DAMIP that are based on prescribed sea surface conditions (Stone et al., 2019). The use of exposure data in our study from the C20C+D&A project versus DAMIP data being used by Vicedo-Cabrera et al., 2021, could introduce heterogeneity in ambient heat

exposure assessment. We observed a significant decline in the frequency of hot days assuming natural simulations than the actual observations, similar to Mitchell et al. (2016) and Vicedo-Cabrera et al. (2021). The HRI rate was significantly higher during the actual observations than in natural simulations. Further studies need to explore the current attributable impacts on morbidity associated anthropogenic climate change.

Along with the current climate risk attribution, we estimated the HRI associated with future climate change. This study discussed the burden of HRI associated with climate change by comparing the HRI rate assuming intermediate and high emission scenarios. We observed a significant increase (up to 78.65% in Coastal and 65.85% in Piedmont regions) in HRI assuming a higher emission scenario (RCP8.5) compared to the intermediate emission scenario (RCP4.5). Additionally, the median rate of HRI significantly increased during the mid (up to 68.77% in Coastal and 77.28% in Piedmont) and late century (up to 116.31% in Coastal and 110.35% in Piedmont) compared to the baseline during both the emission scenarios. Similar results were reported by Lay et al. (2018), who estimated an increase in HRI emergencies by 32% in 2050 and 79% in 2090, assuming RCP8.5 compared to the RCP4.5 scenario. Kingsley et al. (2016) reported a 20% increase in HRI in Rhode Island assuming the RCP8.5 scenario and attributable to climate change. Our results (up to 31.45% increase in HRI during mid-century and 78.65% in the late century) are similar to the HRI changes reported by Lay et al. (2018) and Kingsley et al. (2016). The heterogeneity in the findings from our study compared to the literature could be explained by the climate variability and human vulnerability to natural hazards across geographies (Ebi, 2018). The findings from the fourth national climate assessment suggest that the population living in the Southeastern US are exposed to extreme temperatures more than in the other parts of the US (Carter, 2018). Similarly, variability in vulnerability characteristics across geographies that interact with natural hazards such as extreme heat could result in

differential exposure-response associations by geographic areas (Berke et al., 2015; Cutter & Finch, 2008). Transitioning to the presentation of the HRI burden associated with anthropogenic climate change, we discussed our findings using the percent increase in HRI morbidity. Lay et al. (2018) estimated the attributable cost of heat on morbidity using employer-based health insurance claims database of people under the age of 65. Discussing HRI in terms of cost often provides compelling insights that would effectively advocate policy change but were associated with limitations. The health data being used by Lay et al. (2018) excluded the most vulnerable population groups, such as the unemployed and elderly. In contrast, our study did not restrict vulnerable population groups from North Carolina.

The evidence-based findings from our study discussing HRI attributable to climate change play a key role in public health education and preparedness that are relevant to extreme temperature exposure. Translating our results into public health action by developing community scale risk mitigation plans could substantially minimize the HRI risk. In addition, this study could support actuarial approaches as a framework to assess the human health risks associated with extreme events driven by climate change. Unlike the existing literature, our methodology contextualized both current and future HRI morbidity attributable to climate change. Our comprehensive methodologic approach in quantifying HRI morbidity associated with climate change using the acute (GAM) and distributive (DLNM) associations would allow direct comparison of effect estimates from two statistical approaches that are commonly practiced in climate attribution studies. Additionally, population vulnerabilities, such as age, gender, comorbidities, household type, income, nature of the employment and daily activity, are known to interact or mediate with temperature exposure in exacerbating HRI risk (Ebi et al., 2021b). Along with population vulnerabilities, community build characteristics could mediate the HRI risk associated with climate change. Certain phenomenon, such as the urban heat island and heat dome effect, were identified to be driving factors associated with extreme

heat exposure disparities by geography (Henderson et al., 2022; Tuholske et al., 2021). These phenomena are typically driven by neighborhood characteristics, such as land use and land cover (Fard et al., 2021). Further studies discussing human health risks attributable to the current and future climate change, by considering population vulnerabilities and neighborhood characteristics could address these gaps in the research. As we observed strong correlation with daily maximum temperature, compared to the heat metrics based on temperature and humidity during the study period, the statistical model based on temperature was trained to predict HRI morbidity attributable to current and future climate change. According to the 2017 National Climate Assessment, there is a minimal change in summer precipitation associated with climate change in the Southeastern region, compared to the other regions in the US (Easterling, 2017). However, the future changes in precipitation trends could influence the HRI morbidity estimates.

In this study, the future projections of HRI were estimated using static population (2010 decennial census). The objective of this study is to estimate the percent change in HRI over time, rather than presenting an absolute count of future HRI ED visits. Few studies adjusted for future population growth (Lay et al., 2018; Martinez et al., 2016) to describe the results based on absolute counts to estimate the cost associated with hospitalizations and ED visits. Estimation of the future population growth would be essential to translate estimated number of HRI morbidity or mortality from the current period to project future HRI. In this study, we discussed the human health burden associated with future climate change using the percent change in the rate of HRI, which do not require population growth estimation. Due to data limitations, we did not calculate the excess number of morbidities associated with future climate change, which is essential for the cost estimation. Additionally, changes in population characteristics across North Carolina physiographic divisions could influence our study results.

CONCLUSION

This work adds strong evidence quantifying the human health risk associated with current and future climate change in the Southeastern United States. This study estimated about 3 out of 20 emergency room visits associated with HRI in North Carolina during the study period is attributable to anthropogenic climate change. Additionally, a substantial increase in HRI assumed a high emission scenario compared to an intermediate emission scenario. Our findings suggest that anthropogenic climate change is already having a significant effect on human health and will continue to have impacts in the future. Our findings suggest that adaptation interventions, along with greenhouse gas mitigation, are needed to reduce the health impacts of climate change. As current climate change is already causing increases in hospitalization, public health interventions should be implemented now to reduce the current and future health burden. By using best knowledge and practices, the health impacts associated with climate change can be addressed.

CHAPTER 3: EVALUATING THE SENSITIVITY OF HEAT WAVE DEFINITIONS AMONG NORTH CAROLINA PHYSIOGRAPHIC REGIONS

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ABSTRACT

Exposure to extreme heat is a known risk factor that is associated with increased heat-related illness (HRI) morbidity and mortality. The relevance of heat wave definitions could change across the health conditions and geographies due to the heterogenous climate profile. This study compared the sensitivity of 28 heat wave definitions associated with HRI emergency department visits over five summer seasons (2011-2016), stratified by two physiographic regions (Coastal and Piedmont) in North Carolina. The HRI rate ratios associated with heat waves were estimated using the generalized linear regression framework assuming a negative binomial distribution. We compared the Akaike Information Criterion (AIC) values across the heat wave definitions to identify an optimal heat wave definition. In the Coastal region, heat wave definition based on daily maximum temperature with a threshold >90th percentile for two or more consecutive days had the optimal model fit. In the Piedmont region, heat wave definition based on the daily minimum temperature with a threshold value >90th percentile for two or more consecutive days was optimal. Additionally, we observed that the optimal heat wave definitions from this study captured the moderate and frequent heat episodes better than the National Weather Service (NWS) heat products that worked best for extreme heat episodes. In this study, we compared the HRI morbidity risk associated with epidemiologic based heat wave definitions and with NWS heat products. Our findings could be used for public health education and suggest recalibration of NWS heat products.

INTRODUCTION

A heat wave is often described as an acute episode of one or more consecutive days with temperatures or heat indices exceeding a threshold value (Mazdiyasni & AghaKouchak, 2015). However, there is no standard definition to identify heat waves (USGCRP, 2016a). Heat waves are typically classified using a synoptic (e.g., air mass, temperature-humidity index), physiologic (e.g., Environmental Stress Index, Wet Bulb Global Temperature), or epidemiologic

approach (Hajat et al., 2010). Hajat et al. (2010) reported that epidemiologic-based algorithms (temperature-mortality relationship) identified the days with higher heat related mortality.

Heat waves are associated with an increased risk of HRI outcomes (Knowlton et al., 2009). In the United States (US), roughly 700 heat-related deaths per year are attributable to ambient temperature exposure (Vaidyanathan et al., 2020). The frequency and intensity of heat waves have been on the rise since the industrial revolution and are likely to increase in the future due to climate change (IPCC, 2021a; Rennie et al., 2019). In Philadelphia, heat-related risk communication, along with the NWS warnings, played a crucial role by minimizing up to 3 heat related deaths per day that are associated with extreme heat exposure (Ebi et al., 2004; Kalkstein et al., 1995). In the US, public health departments rely on heat products (e.g., excessive heat watch, heat advisory, and excessive heat warning) from the local National Weather Service Weather Forecast Office (NWS-WFO) to communicate heat-health risks. According to Weinberger et al., (2018), the NWS heat products moderately reduced the impact of extreme heat on human health, but the human health risk associated with ambient temperature is not a resolved issue.

Despite the early heat warnings, the average annual percentage of HRI emergency department visits in North Carolina has increased by 19% over the last decade (CDC n.d.; NCDHHS n.d.). The rise in HRI risk could be due to various factors ranging from population vulnerabilities and higher thresholds for temperature and humidity set by NWS for issuing heat alerts (Wellenius et al., 2017). There are multiple attempts in characterizing human health risks associated with heat wave definitions (Anderson & Bell, 2011; Hajat et al., 2010; Vaidyanathan et al., 2016; Vaidyanathan et al., 2019; Xu et al., 2016). To evaluate heat wave definitions, most of these studies focused on extreme events in the context of minimizing heat-related deaths. Epidemiologic studies evaluating the association between outdoor temperature exposure (e.g., heat waves or ambient temperature) and human health

are generally focused on extreme events, where the human health outcome is typically measured as cause-specific or all-cause mortality (Song et al., 2017; Xu et al., 2016). A meta-analysis on heat wave definition evaluation studies summarized that the studies included in this review generalized the warnings to a larger geographic area, such as a state or a group of states (Xu et al., 2016). Generalizing heat warning systems over larger geography may not be ideal due heterogeneity in exposures, population vulnerability, and exposure-outcome associations (Reid et al., 2009). Physiographic or sub-regional scale heat warning systems that account for meteorological heterogeneity and specific to health conditions were found to play a role in minimizing the human health risks associated with heat waves (Ebi et al., 2004; Fechter-Leggett et al., 2016; McElroy et al., 2020; Vaidyanathan et al., 2019).

This study assessed the association between frequent and moderate heat waves and HRI emergencies in North Carolina physiographic regions. The objective of this study was to compare the statistical model performance of heat wave definitions and assess their association with HRI emergency visits in North Carolina. Additionally, we aim to compare the heat wave definition with the best model performance from our study with the NWS extreme heat alerts.

MATERIALS AND METHODS

This study was focused on five summer seasons (May 01-September 30) from 2011 to 2016 among the three physiographic regions (Coastal, Piedmont & Mountain) in North Carolina. The year 2013 was excluded in this study due to data availability constraints.

Data

Heat metrics

Daily mean, minimum, and maximum temperatures were obtained from the Global Historical Climate Network – Daily (GHCN-D) database (NCEI n.d.; Rennie et al., 2019). Dew point data was obtained from the Parameter-elevation Regression on

Independent Slopes Model (PRISM) database (PRISM n.d.). The station-based temperature measurements and gridded dew point data were aggregated by physiographic regions. The daily maximum apparent temperature and relative humidity were estimated using daily maximum temperature and dew point using “heat.index.function” and “dewpoint.to.humidity” functions available from the weathermetrics package in R (Anderson et al., 2016).

Heat Wave definitions

Twenty-eight heat wave definitions (Table 4) associated with human health outcomes were adopted from the existing literature and were included in this study (Anderson & Bell, 2011; Kent et al., 2014; Smith et al., 2013; Vaidyanathan et al., 2016). These heat wave definitions were classified based on four factors: 1) a heat metric (daily mean, minimum, maximum, and apparent temperatures), 2) duration (number of days), 3) threshold type (relative/absolute), and 4) threshold intensity. Among the two threshold types, relative threshold-based definitions account for cumulative heat exposure (2+ or 3+ consecutive days), and definitions based on absolute threshold are based on single heat day exposure. The heat wave definitions based on daily temperature as metric and a relative threshold were classified using four percentile values (99, 98, 95, 90) as threshold intensity. The percentile threshold values were calculated using historic observations over the summer season from 1895-2016. The definitions based on the apparent temperature as metric and a relative threshold were classified using three percentile threshold values (95, 90, 85) as threshold intensity.

Among the 28 heat wave definitions (HW_01 to HW_28) included in this study, 24 are based on relative threshold values, and four heat wave definitions use an absolute threshold value. Three of the 27 heat wave definitions using relative threshold values were based on maximum apparent temperature as the heat metric. The remaining 24 heat wave definitions were based on the daily mean (HW_01-HW_08), maximum (HW_09-HW_16), and minimum (HW_18-HW_25) temperature

values as the heat metric. Additionally, one heat wave definition using absolute threshold value is based on daily maximum temperature as the heat metric (Table 4). Using the 28 heat wave definitions, we categorized the summer days during the study period as heat waves and non-heat wave days using a binary variable to indicate heat waves.

National Weather Service – Heat products

The heat products released by the NWS during the study period were retrieved from the Iowa Environmental Mesonet (IEM n.d.). During the study period, the NWS heat products (heat advisories and excessive heat warnings) released by the three NWS-WFOs (ILM-Wilmington; MHX-Newport/Morehead city; and RAH-Raleigh) located in North Carolina were included in this study. The WFOs ILM and MHX cover most of the Coastal region, and RAH covers the Piedmont region (NWS-WFO n.d.). Among the three WFOs, heat products released by the ILM and MHX follow the NWS procedural directive. The RAH WFO is the only center in North Carolina that collaborated with health partners to revise the heat products (Ferrell et al., 2017). The heat products from RAH are based on local conditions such as maximum temperature instead heat index, sunlight, nighttime temperature, heterogeneity between rural and urban temperatures, and knowledge from historical weather conditions (Ferrell et al., 2017). The heat products used in the three WFOs located in North Carolina are based on the following criteria. A heat advisory is released during the days when the daytime heat index value is between 100-105°F (NC-DPS, 2022). An excessive heat warning is released if the daytime heat index forecast value is between 105-110°F (NC-DPS, 2022).

We extracted the start and end dates and county information from the Iowa Environmental Mesonet heat product archives. The county information was aggregated to the North Carolina physiographic region scale to match the spatial resolution of the health data included in this study. The NWS heat products were

represented using a binary variable (NWS_HW) to identify the days with NWS alerts on a daily scale by physiographic region.

Heat-related illness

Daily HRI-related emergency department visit data were obtained as an aggregate count per day per physiographic region from the North Carolina Disease Event Tracking and Epidemiologic Collection Tool (NC DETECT) surveillance program maintained by the North Carolina Division of Public Health (NC DPH) (NC-DETECT, 2021). Heat-related illnesses were defined using ICD-9 CM codes with E992/E900.0/E900.0/E900; ICD-10 CM codes within T67/X30/X32; and various keywords from the chief compliant/triage notes (Morano & Waller, 2017; NC-DETECT, 2021). The days with HRI emergency department visits fewer than five were censored, amounting to 28.81% (219) of observations from the Coastal and 28.94% (220) in the Piedmont region. The days with censored HRI emergency visits in the Coastal and Piedmont regions were imputed by the median value of 3 visits per day. The Mountain region was excluded from the analysis as 50.13% of the data was censored due to low HRI emergencies.

Statistical analysis

The sensitivity of 28 heat wave definitions was compared using the Akaike Information Criterion (AIC) value corresponding to the model fit (Hibble, 2014; Peng, 2008) evaluating the HRI morbidity rate associated with heatwaves included in this study. AIC is a metric that is a balance between model accuracy and penalty due to complexity, commonly used to measure the optimal model fit (Equation *4*) (Kamo et al., 2013). A smaller the AIC value (close to -∞) represents an optimal fit (Dunn & Smyth, 2018).

$$\mathrm{AIC} = \mathrm{goodness\ of\ fit} + \mathrm{penalty} \quad \text{... Equation 4}$$

The HRI rate ratios corresponding to the 28 heat wave definitions included in this study were estimated using the Generalized Linear Model (GLM) and assuming

negative binomial distribution to account for outcome overdispersion. To compare the HRI risk across physiographic regions, the regression model was adjusted for population density by using the 2010 decennial population by region as an offset term (USCB n.d.). To estimate the direct effect of heat wave definitions, the statistical models using heat wave definitions based on temperature as a heat metric were adjusted for relative humidity and NWS heat wave alert days were added as covariates to adjust for potential confounding effects and effect modification. Similarly, the statistical models with heat wave definitions using apparent temperature as a heat metric were adjusted for NWS heat alerts. Additionally, to account for temporal autocorrelation, we adjusted the statistical models mentioned above for the day of the week (weekday/weekend (binary)), month (factor), and year (factor) (Figure 12 and Equation *5*). In equation 5, HW is a binary variable represents heat wave definitions, RH represents relative humidity, NWS-HW represents NWS heat wave alerts, and TS represents the time series variables (day of week, month, and year).

$$log\left(\frac{E(HRI\ count)}{population}\right) = \beta_0 + \beta_{HW} + \beta_{RH} + \beta_{NWS\_HW} + \beta_{TS} + \varepsilon$$ ...Equation 5

We processed 28 statistical models stratified by physiographic region to obtain the rate ratio (RR) and 95% confidence intervals. The sensitivity of heat wave definitions was evaluated by comparing the AIC values across heat wave definitions by physiographic region that were generated from the GLM output. The statistical model with the lowest AIC value among the 28 heat wave definitions was considered the optimal heat wave definition. We then compared the overlap between the days considered as heat waves from this study and the NWS heat products using the Chi-Square test (Walker, 2010). The analysis was conducted using R version 4.0.3 and MASS package version 7.3 (Ripley et al., 2013).

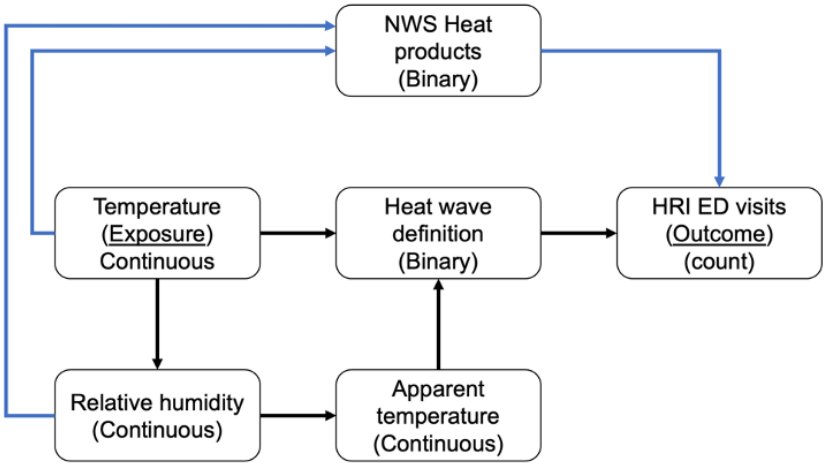

Figure 12. Conceptualization of evaluating the direct effect of temperature or apparent temperature on HRI ED visits.
We assumed that the association between temperature and HRI is mediated through NWS heat products. Additionally, relative humidity is influenced by temperature. To evaluate the association between heat wave definitions based on temperature and HRI, we adjusted for relative humidity and NWS heat products. We adjusted for NWS heat products while evaluating the association between heat wave definitions based on apparent temperature and HRI ED visits.

RESULTS

Heat wave definition – Sensitivity

Among the 28-heat metrics included in this study, the heat wave definition using maximum temperature had the best fit with HRI morbidity in the Coastal region and mean temperature for the Piedmont region. The heat wave definitions based on a moderate (90^{th}) percentile threshold for Coastal and Piedmont regions had an optimal model fit than the heat wave definitions based on extreme threshold (99^{th}, 98^{th}, and 95^{th} percentile) values.

In the Coastal region, the heat wave definition based on daily maximum temperature as a heat metric with a threshold value > 90^{th} percentile for two or more consecutive days (HW_15) had the optimal model fit (lowest AIC value) to estimate the HRI morbidity compared to the heat wave definitions included in this study. We

did not observe a similar result for the Piedmont region. In the Piedmont region, the heat wave definition based on daily mean temperature as a heat metric with a threshold value > 90th percentile for two or more consecutive days (HW_07) had the optimal model fit to estimate the HRI morbidity. In the Coastal region, the heat wave definition HW_15 is associated with 2.75 (95% CI 2.40-3.08) times higher HRI morbidity rate during heat wave days than the non-heat wave days. In the Piedmont region, the heat wave definition HW_07 is associated with a 2.72 (95% CI 2.46-3.01) times higher HRI morbidity rate compared to the non-heat wave days (Figure 13; Table 4).

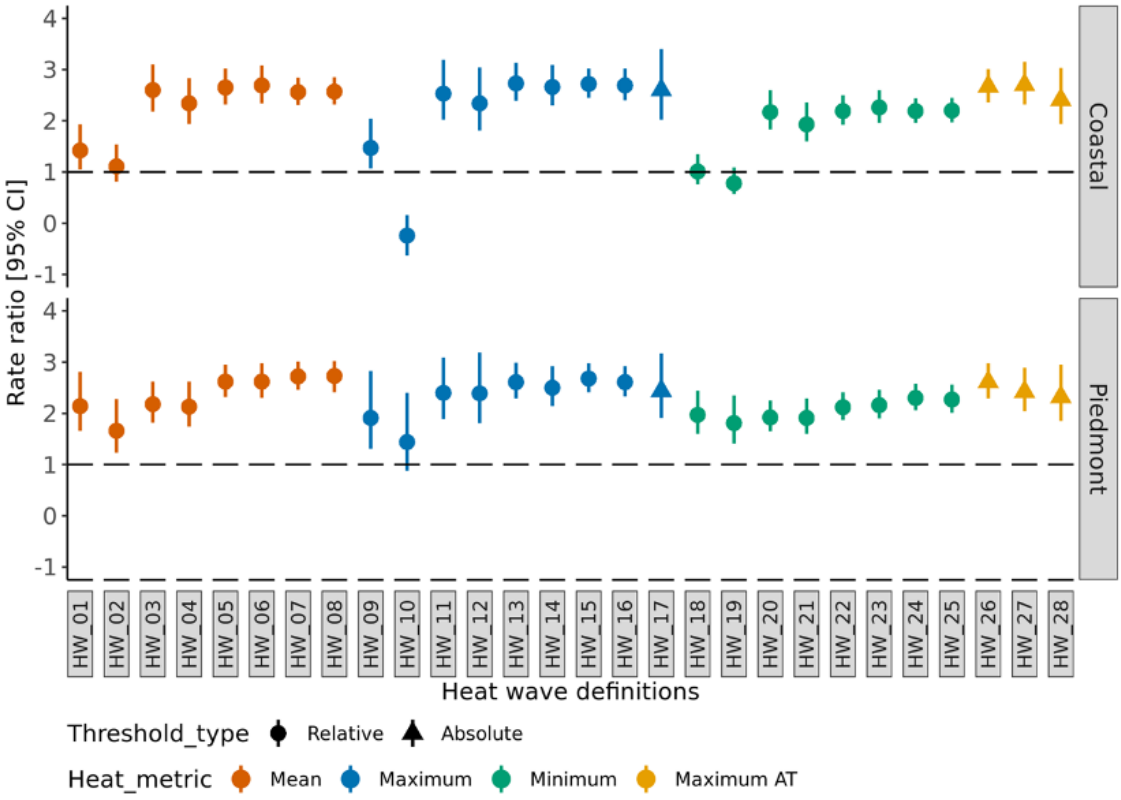

Figure 13. HRI rate ratio corresponding to heat wave definitions.
The rate ratios and the corresponding 95% confidence intervals were generated using the generalized linear model (GLM), assuming a negative binomial distribution. The X-axis represents distinct heat wave definitions, stratified by North Carolina physiographic regions, and grouped by metric and threshold type. The Y-axis represents the HRI morbidity rate ratio, which could be interpreted as an increase/decrease in HRI morbidity rate during a heat wave day compared to a non-heat wave day.

Table 4. Description of heat wave definitions

Definition	Heat metric	Duration (No. of days)	Threshold type	Threshold intensity	Coastal			Piedmont		
					Threshold (°C)	HW days	AIC	Threshold (°C)	HW days	AIC
HW_01	Mean temperature	2+consecutive	Relative	>99th percentile	29.16	33	4475.7	28.40	29	4817.9
HW_02		3+consecutive	Relative	>99th percentile		25	4480.7		21	4843.0
HW_03		2+consecutive	Relative	>98th percentile	28.57	58	4362.9	27.66	61	4778.4
HW_04		3+consecutive	Relative	>98th percentile		46	4396.7		49	4796.9
HW_05		2+consecutive	Relative	>95th percentile	27.65	105	4287.3	26.70	136	4629.7
HW_06		3+consecutive	Relative	>95th percentile		97	4293.5		118	4656.9
HW_07		2+consecutive	Relative	>90th percentile	26.65	217	4216.2	25.63	241	4547.9
HW_08		3+consecutive	Relative	>90th percentile		195	4211.8		227	4551.8
HW_09	Maximum temperature	2+consecutive	Relative	>99th percentile	35.04	22	4475.4	35.52	20	4842.6
HW_10		3+consecutive	Relative	>99th percentile		16	4479.7		14	4852.4
HW_11		2+consecutive	Relative	>98th percentile	34.31	38	4413.7	34.69	38	4799.8
HW_12		3+consecutive	Relative	>98th percentile		30	4435.3		32	4813.2
HW_13		2+consecutive	Relative	>95th percentile	33.13	98	4283.5	33.30	109	4665.9
HW_14		3+consecutive	Relative	>95th percentile		80	4318.0		85	4716.0
HW_15		2+consecutive	Relative	>90th percentile	31.97	190	4192.6	31.94	194	4583.4
HW_16		3+consecutive	Relative	>90th percentile		168	4234.4		180	4615.9
HW_17		1-day	Absolute	> 35°C	35.00	26	4423.1	35.00	34	4801
HW_18	Minimum temperature	2+consecutive	Relative	>99th percentile	23.86	29	4488.1	21.86	45	4810.3
HW_19		3+consecutive	Relative	>99th percentile		25	4479.1		31	4831.9
HW_20		2+consecutive	Relative	>98th percentile	23.36	56	4401.1	21.40	83	4783.6
HW_21		3+consecutive	Relative	>98th percentile		46	4433.5		65	4799.5
HW_22		2+consecutive	Relative	>95th percentile	22.57	108	4352.0	20.63	156	4722.0
HW_23		3+consecutive	Relative	>95th percentile		94	4353.0		136	4722.6
HW_24		2+consecutive	Relative	>90th percentile	21.64	223	4305.5	19.72	265	4670.3
HW_25		3+consecutive	Relative	>90th percentile		199	4303.0		235	4693.7
HW_26	Maximum apparent temperature	1-day	Absolute	>95th percentile	37.21	36	4254.0	35.26	27	4659.0
HW_27		1-day	Absolute	>90th percentile	36.20	71	4319.9	35.92	58	4749.8
HW_28		1-day	Absolute	>85th	35.47	106	4415.7	36.95	98	4799.1

HW (Heat wave) days per Coastal and Piedmont region represent the cumulative number of days during the study period that are categorized as heat wave days corresponding to the heat wave definitions.

Using the HW_15 definition, 27% (190/704) of the days in the Coastal and using the HW_07 heat wave definition, 34% (241/719) of the days in the Piedmont region were flagged as heat wave days during the study period (Table 5). There are an average of 6 HRI ED visits per day in the Coastal region during the heat wave days based on HW_15 and an average of 8 HRI ED visits per day during the heat wave days based on HW_07 in the Piedmont region (Table 5). The frequency of heat wave days in the Piedmont region using the HW_07 definition was 24% higher than in the Coastal region using the HW_15 definition. About 72% of the heat wave days from the Coastal region matched with the Piedmont region. During the study period,

we observed a lower number of heat wave days during the summer of 2014. The frequency of heat wave days was higher in July than in other summer months, based on the epidemiologic relationship-based heat wave definition (Coastal: HW_15; Piedmont: HW_07).

Table 5. Frequency of heat wave days and HRI ED visits in North Carolina physiographic regions.

		Month									
		May		Jun		Jul		Aug		Sep	
		a	b	a	b	a	b	a	b	a	b
2011	HW	3	1	21	14	22	25	10	15	0	0
	ED	65	37	309	334	225	417	195	302	0	0
2012	HW	0	0	5	6	23	27	0	8	2	6
	ED	0	0	45	95	306	520	0	112	35	52
2014	HW	0	0	6	7	7	11	0	5	5	6
	ED	0	0	101	141	103	149	0	55	68	92
2015	HW	0	0	15	16	14	19	5	9	2	3
	ED	0	0	817	897	306	569	117	177	25	54
2016	HW	0	0	5	8	24	26	19	24	2	5
	ED	0	0	80	204	721	950	366	499	30	106

a-Coastal; b-Piedmont; HW- number of heat wave days using the definition from this study [Coastal: HW_15; Piedmont: HW_07] and excluding the days that overlapped with the heat wave days flagged by the NWS; ED-number of HRI emergency department visits corresponding to the heat wave days.

Comparing epidemiologic-based heat wave definition and NWS heat products

During the study period, NWS flagged 26 days in the Coastal and 18 days in the Piedmont regions as heat waves. The NWS heat wave days overlapped with the optimal heat wave definition identified in this study (HW_15 for Coastal and HW_07 for Piedmont). In the Coastal region, there were a significantly higher (6-times) number of heat wave days based on HW_15 than the NWS heat alerts (McNemar χ^2=158.15, df=1; P<0.05). Similarly, the Piedmont region had a significantly higher (13 times) number of heat waves based on HW_07 than the NWS heat alerts (McNemar χ^2=219.04, df=1, P<0.05) (Figure. 14).

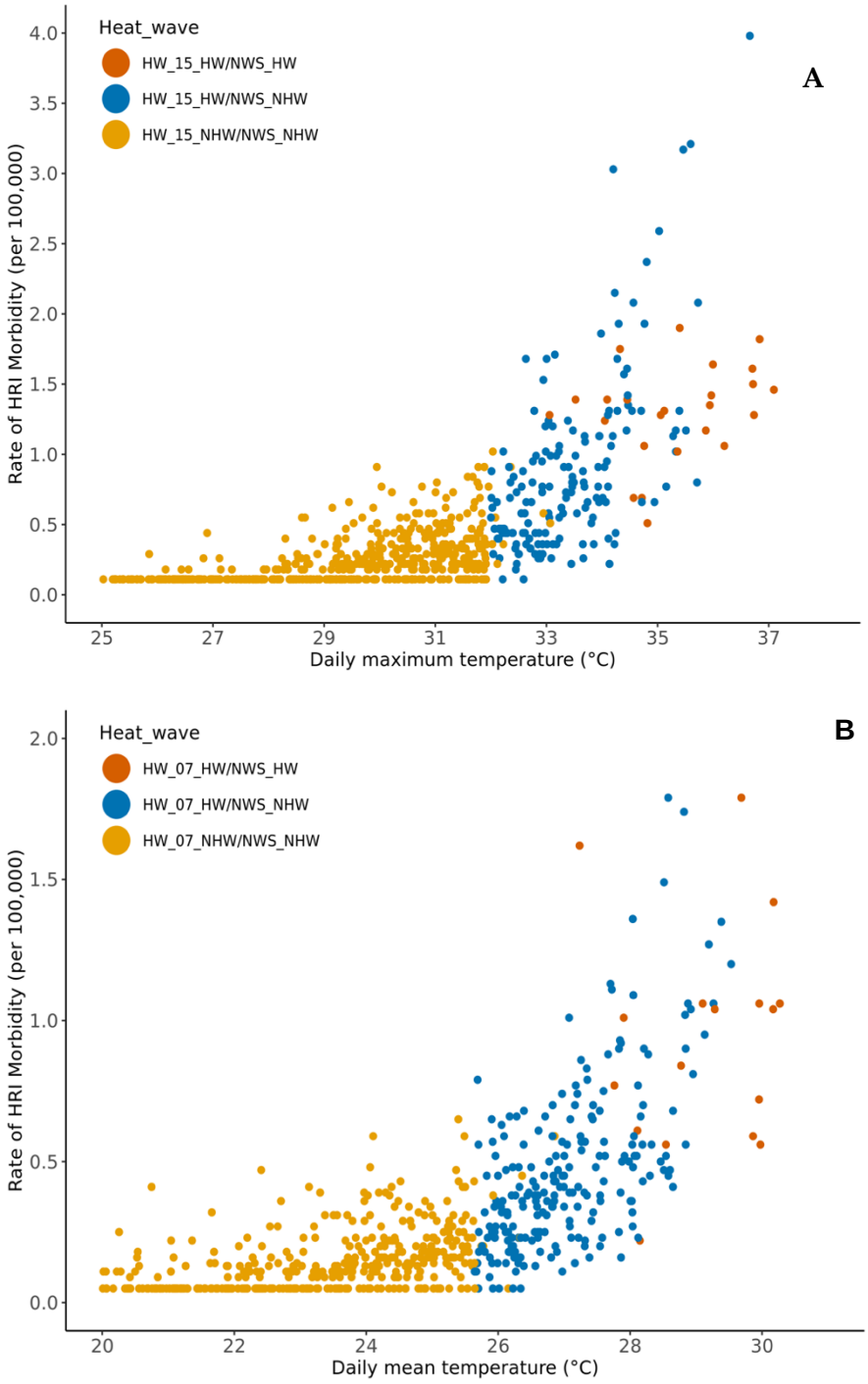

Figure 14. Comparison of the effective heat wave definition with the NWS-Heat alerts.
The X-axis represents daily temperature in degrees Celsius (Coastal: maximum temperature & Piedmont: minimum temperature). The Y-axis represents the daily rate of heat-related illness morbidity per 100,000 population. Panel A – Coastal & B – Piedmont region. Color coding: 1. Red: Categorized as heat wave day from this study (HW_15 or HW_07) and the NWS; 2. Blue: Categorized as heat wave day only based on our result; 3. Beige: Not flagged as a heat wave day from our results nor the NWS.

DISCUSSION

This study compared the optimal model fit using AIC values across the 28 heat wave definitions. Additionally, it compared the heat wave days flagged using the optimal definition identified from this study to the NWS heat products. We observed that the heat wave definition based on the maximum temperature (HW_15) had an optimal performance for the Coastal region and the mean temperature-based heat wave definition (HW_07) for the Piedmont region. The heat wave definitions mentioned above were associated with 2.75 (95% CI 2.40-3.08) times higher rate of HRI morbidity in the Coastal region and 2.72 (95% CI 2.46-3.01) times higher HRI morbidity rate in the Piedmont than the non-heat wave days. During the study period, our results suggest an average of 39 excess heat wave days per year (Coastal-33 days; Piedmont-45 days) based on the heat wave definitions (Coastal: HW_15 and Piedmont: HW_07). During the summer season, most of the days in July were flagged as vulnerable to heat-related emergencies while using the heat wave definitions from this study.

Heterogeneity while evaluating the heat wave definitions across the US climate regions or sub-regions was well established in the literature (McElroy et al., 2020; Vaidyanathan et al., 2016; Vaidyanathan et al., 2019). To address the meteorological heterogeneity within North Carolina, we evaluated the heat waves stratified by physiographic delineations with clustering the administrative boundaries into physiographic regions. In North Carolina, there are two WFOs covering the Coastal region and a WFO covering the Piedmont region. The WFO covering the Piedmont region collaborated with the regional health partners to revise the heat thresholds. The WFO that overlaps the Piedmont region considered revising its heat threshold based on the local conditions for optimization (Ferrell et al., 2017). Independent WFOs setting heat product thresholds at a sub-regional scale would be beneficial for the climate related heterogeneity across the administrative boundaries.

However, a study discussing the heat products across the US reported that the three WFOs across the Coastal and Piedmont regions follow the same threshold value and criteria to release heat products (Ferrell et al., 2017). In contrast to the homogenous heat product thresholds across the physiographic regions, our results suggest heterogeneity of the heat wave definitions between the Coastal and Piedmont regions.

The results from our study overlapped with the observations from a previous study that compared the sensitivity of heat wave definitions across San Diego climate zones, using heat-related hospitalizations as an outcome (McElroy et al., 2020). McElroy et al. (2020) reported using daily maximum temperature above 90th percentile (29.11°C) in a day as a criterion for heat wave definitions in the Coastal region to be most efficient, using heat-related hospitalizations as an outcome. In this study, we observed that the heat wave definition based on daily maximum temperature above 90th percentile (31.97°C) for two or more days had an optimal fit with HRI morbidity in the Coastal region. Additionally, we observed that the heat wave definition based on daily mean temperature was optimal for the Piedmont region, whereas McElroy et al. (2020), reported that heat wave definitions based on daily maximum and minimum temperature had the most impact in the Inland and Desert regions of San Diego. The major difference between our findings and McElroy et al. (2020) is focused on the duration criterion for defining heat waves. We observed that the heat wave definitions using two or more days as a duration criterion had an optimal fit, compared to McElroy et al. (2020) reporting that absolute thresholds were most efficient.

Early heat health warning systems play a crucial role in systematically minimizing the risks associated with outdoor temperature exposure (Ebi et al., 2004). Multiple studies attempted to characterize a gold standard heat wave definition, where most of these studies compared the sensitivity of the heat wave definitions in the context of mortality (Anderson & Bell, 2011; Vaidyanathan et al., 2016; Xu et al.,

2016). Vaidyanathan et al. (2016) evaluated the sensitivity of several heat wave definitions and their association with heat-related deaths by comparing the effect estimates (extreme heat effect). Similarly, Anderson and Bell. (2009) evaluated the sensitivity of heat wave definitions based on the percent increase in relative risk associated with heat-related mortality. McElroy et al. (2020) evaluated heat waves by climate zones, using the attributable risk associated with heat-related hospitalizations. These studies assessed the optimal heat wave definition by comparing the effect estimates/relative or attributable risks associated with health outcomes, whereas we compared and identified an optimal heat wave definition per North Carolina physiographic regions using a model fit metric – lowest AIC value (model fit) instead of the effect estimates (strength of association).

Using AIC as a metric we compared 28 heat wave definitions and identified a heat wave definition with an optimal model fit. The heat wave definition (HW_15) using daily maximum temperature with a percentile value > 90^{th} percentile for two or more consecutive days had an optimal fit for the Coastal region. Similarly, using daily mean temperature with a threshold value > 90^{th} percentile for two or more consecutive days was optimal for the Piedmont region compared to the heat wave definitions included in this study. During the study period, 27% of the summer days in the Coastal and 34% in the Piedmont region were flagged as vulnerable to HRI emergencies by our definition. In contrast, the NWS released heat products during ~2.5% of the summer days. During the study period, there were an average of 783 (6 per day) HRI emergency visits per summer season during the days flagged as vulnerable based on the HW_15 definition in the Coastal region and 1,152 (8 per day) HRI emergencies per summer season in the Piedmont region during the days flagged as vulnerable to heat-related emergencies using the HW_07 definition. Abasilim and Friedman. (2021) reported about 16 heat-related hospitalizations per day during the summer days without NWS excess heat warnings in Illinois.

Our results could be influenced by the interaction between vulnerability factors and risk perception. Additionally, our results are subjective to a variety of unmeasured biases driven by human vulnerabilities such as co-existing medical conditions, occupational vulnerabilities, demographics (age, gender, race, education, urbanicity), and socioeconomic factors (wealth, employment, housing) that were identified to exacerbate the risk of heat-related illnesses (Danzl, 2018; Gronlund, 2014; Guirguis et al., 2018; Fard et al., 2021; Jung et al., 2021; Niu et al., 2021; Sorensen et al., 2021). Additionally, our results could be influenced by effect modifiers such as human behavioral factors that include knowledge on heat risk sensitivity, external locus of control, and emotional and cognitive factors heavily alter the risk perception of heat warnings (Beckmann & Hiete, 2020; Kalkstein & Sheridan, 2007; Toloo et al., 2013). Further studies evaluating heat wave definitions using mixed methods by considering quantitative information from human vulnerability characteristics and qualitative information from heat risk perception, could strengthen the heat health risk ascertainment.

CONCLUSION

Our results showed heterogeneity of the optimal heat wave definitions among the Coastal and Piedmont regions in North Carolina. Additionally, the threshold values associated with the optimal heat wave definitions were smaller compared to the NWS thresholds for the North Carolina physiographic regions. Our results suggest recalibration of the heat wave definitions being used by the NWS WFOs in North Carolina.

CHAPTER 4: JOINT ASSOCIATION BETWEEN OUTDOOR AIR POLLUTANT MIXTURE AND PEDIATRIC ASTHMA EXACERBATIONS

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ABSTRACT

Exposure to air pollutants is known to exacerbate asthma, with prior studies focused on associations between single pollutant exposure and asthma exacerbations. As air pollutants often exist as a complex mixture, there is a gap in understanding the association between complex air pollutant mixtures and asthma exacerbations. We evaluated the association between the joint effect of an air pollutant mixture (52-pollutants) and pediatric asthma exacerbations. This study focused on children (age ≤ 19-years) who lived in Douglas County, Nebraska, during 2016-2019. The seasonal scale association between the joint effect of the outdoor air pollutant mixture, adjusting for potential confounders (temperature, precipitation, wind speed, and wind direction), in relation to pediatric asthma exacerbation-related emergency department (ED) visits, was evaluated using the generalized weighted quantile sum (qWQS) regression with repeated holdout validation. We observed associations between the air pollutant mixture and pediatric asthma exacerbations during the spring (lagged by five days), summer (lag 0-5 days), and fall (lag 1-3 days) seasons. The estimate of the joint outdoor air pollutant mixture effect was higher during the summer season (adjusted-β_{WQS}=1.11, 95% confidence interval [CI]: 0.66-1.55), followed by spring (adjusted-β_{WQS}=0.40, 95% CI: 0.16-0.62) and fall (adjusted-β_{WQS}=0.20, 95% CI: 0.06-0.33) seasons. Among the air pollutants, $PM_{2.5}$, pollen and mold contributed more heavily to the air pollutant mixture. There were associations between the outdoor air pollutant mixture and pediatric asthma exacerbations during the spring, summer, and fall seasons. Among the 52 outdoor air pollutant metrics investigated, $PM_{2.5}$, pollen (sycamore, grass, cedar), and mold (*Helminthosporium*, *Peronospora*, and *Erysiphe*) contributed most heavily to the air pollutant mixture.

INTRODUCTION

Asthma is a chronic airway inflammatory disease characterized by repeated episodes of wheezing, breathlessness, cough, and reversible airway obstruction that is often exacerbated by environmental exposures (Barnes, 2018; Rich et al., 2015).

In the U.S., 46% of the population experience at least one exacerbation of disease per year, and the prevalence among children is 10% higher than in adults (Pate et al., 2021). During 2010-2018, approximately 88 per 10,000 children/year sought emergency care in the U.S. due to an exacerbation of asthma (CDC, 2020). Pediatric asthma incurs a severe economic burden on the U.S. healthcare system, with a total direct cost of $5.9 billion per year (Perry et al., 2019).

Asthma exacerbations are typically associated with environmental factors such as criteria pollutants (sulfur dioxide, nitrogen dioxide, carbon monoxide, ozone, particulate matter), aeroallergens (pollen, mold), and weather conditions (thunderstorms) (Bell et al., 2018; Erfanian & Collins, 2020; Lee et al., 2019; Poole et al., 2019; Saha et al., 2021; Zhang et al., 2020). Exposure to particulate matter with a diameter of less than 2.5 μm ($PM_{2.5}$), sulfur dioxide, nitric oxides, and ozone have each been identified to play an important role in pediatric asthma exacerbations (Bettiol et al., 2021; Liu et al., 2021; Orellano et al., 2017). Unlike the other criteria pollutants, particulate matter is a complex mixture containing several viable and non-viable components including pollen fragments, bacterial products, metal, acids, and organic chemicals (Lippmann & Chen, 2007).

Extensive efforts are emerging on characterizing non-viable particulate matter such as metals, carbon (elemental, organic, black) (Galvao et al., 2018) and its associations with pediatric respiratory outcomes (Ho et al., 2021; Khatri et al., 2021; Kim et al., 2021). Despite ample evidence on the associations between aeroallergens and pediatric asthma (Caillaud et al., 2018; Gent et al., 2012; Li et al., 2019; Marques Mejias et al., 2019), there is limited information available that could be generalized at a community scale. Air pollutants often occur as a complex mixture and evaluating associations between the numerous outdoor air pollutants and human health outcomes requires a multi-pollutant mixture analytic approach (Dockery, 1993). Environmental mixture analysis techniques are ideal for toxin identification, mixture effect, and individual contribution (Gibson, Goldsmith, et al., 2019; Gibson,

Nunez, et al., 2019). To the best of our knowledge, there has been one prior study focused on the combined effect of air pollutants (ozone, nitric oxide, and $PM_{2.5}$) and pediatric asthma using a categorical joint effect model (Gass et al., 2015). However, the compound effect of pollen and mold along with criteria pollutants in the context of the compound effect modeling framework has not been explored. Mixture effect models play a crucial role in understanding the overall synergistic effect of air pollutants and identifying candidate pollutants among the air pollutants that contribute the most to trigger pediatric asthma exacerbations.

Thus, the aim of this study was to evaluate the association in time (0-5 lag days) between outdoor air quality mixtures of 52 air pollutants, including 8 criteria pollutants, 27 pollen metrics, and 17 mold metrics and pediatric asthma exacerbations.

METHODS

Study area

This study evaluated the association between the compound exposure of an air pollutant mixture (criteria pollutants, pollen, and mold) and pediatric asthma exacerbations in Douglas County, Nebraska (NE), from 2016 to 2019. The associations were assessed by meteorological seasons [Winter: December-February (325 days); Spring: March-May (364 days); Summer: June-August (364 days); Fall: September-November (360 days)]. Douglas County is the most populated county in the state of Nebraska, with 29% of the state population concentrated in the county (USCB, 2019). Approximately 28% of the Douglas County population is under 19 years of age (USCB, 2019).

Pediatric asthma exacerbations

Data from emergency department (ED) visits was obtained from the Nebraska Hospital Information System (NHIS), maintained by the Nebraska Hospital Association. The NHIS database contains non-proprietary health care claims data

(837I obtained directly from hospitals (Center for Medicare and Medicaid Services (CMS), 2021; NHA-NHIS, 2021). This study includes ED visit data from January 01, 2016, to December 31, 2019, of children (age ≤ 19 years and living in Douglas County, NE) who visited an emergency department with a primary diagnosis of asthma exacerbation with an ICD-10 code of J45.x (4,195 ED visits). We excluded subjects diagnosed with exercise-induced bronchospasm (J45.990; 44 children). In total, 4,151 children were included. The study protocol was reviewed by the University of Nebraska Medical Center, Institutional Review Board, Protocol #0629-21-EP.

The pediatric population estimates for Douglas County, NE, were obtained from the 2019 American Community Survey (5-Year) data (USCB, 2019).

Air pollutant exposure

This study includes criteria pollutants (8), pollen (27), and mold (17) obtained from multiple sources. Daily observations of the air pollutants and weather data were obtained at the county scale.

Criteria pollutants

We obtained the criteria pollutant measurements from the US Environmental Protection Agency (USEPA) ground monitoring station located at the Douglas County Health Center (AQS Site ID: 31-055-0019) (USEPA, 2020). The daily maximum observations of carbon monoxide (CO), nitric oxide (NO), nitrogen dioxide (NO_y), reactive oxides of nitrogen (NO_y- NO), sulfur dioxide (SO_2), ozone (O_3), and particulate matter ($PM_{2.5}$ and PM_{10}) were obtained from the samples obtained at an hourly scale. The metrics CO and O_3 were measured as parts per million (PPM), NO, NO_y, NO_y-NO, and SO_2 were measured as parts per billion (PPB), and particulate matter ($PM_{2.5}$ and PM_{10}) was measured as micrograms per cubic meter.

Aeroallergens (Pollen and Mold)

The aeroallergen data were obtained from the Asthma and Allergy Center, located in Bellevue, Nebraska (a suburb adjacent to Omaha). The aeroallergen monitoring station located in Bellevue, NE is the only station in Nebraska accredited by the National Allergy Bureau (American Academy of Allergy, Asthma and Immunology (AAAAI), 2021). The aeroallergen monitoring station is located within a 15-mile radius of the Douglas County region. The pollen and mold samples were obtained from a sampling station located on the 3rd story rooftop of the UNMC Bellevue Medical Center. The samples were collected using a Rotorod Sampler Model 40 (1.52*1.52*32 mm). The sampling strategy involves the application of silicone grease to the rod and rotation of the retracting rod at a speed of 2,400 rpm for 1 minute in every 10-minute interval for 24 hours. The samples were then collected daily at 7 AM by placing the retractable rod on the stage adapter. The samples were stained using Calberla's stain and counted at 40X under the microscope. The pollen and mold counts were estimated as particles per 3.12 m^3 of air.

Among the 44 aeroallergens measured at the Asthma and Allergy Center, 27 variables correspond to pollen and 17 to mold. The pollen metrics could be further clustered into 17 tree pollen, 7 weed pollen, 1 grass pollen, and 1 unknown pollen measurement.

Weather indicators

Daily observations of maximum temperature, precipitation, average wind speed, and wind direction (fastest 5-second wind direction) data were obtained from the Global Historical Climatology Network (GHCNd) (NOAA, 2021). These observations were retrieved from the monitoring station located at the Omaha Eppley Airfield (Station ID: USW00014942). The daily temperature was measured in Celsius, precipitation in millimeters, wind speed in miles/hour, and wind direction in degrees.

Missing data imputation

The missing air pollutant observations (~6%) were imputed using Probabilistic Principal Component Analysis (PPCA) (Hegde et al., 2019; Stacklies et al., 2007). Air quality and weather metrics were included as loading variables in the PPCA. We estimated the root mean square percentage error (RMSPE) by performing cross-validation to estimate the prediction error introduced during the imputation and observed that the RMSPE values ranged between 4-12% per metric. The analytic dataset (1,413 days) contains pediatric asthma exacerbation count, air pollutants (52 variables), and weather metrics (6 variables), measured at a daily scale.

Statistical analysis

To assess the correlation across the 52-air pollutants included in this study, we estimated the Spearman correlation coefficients stratified by four seasons. Statistically significant correlations were considered for the correlation coefficients with a p-value less than 0.05. The association between the compound exposure of air pollutant mixture and pediatric asthma exacerbation emergencies was evaluated using generalized Weighted Quantile Sum (gWQS) regression with a repeated holdout (Carrico et al., 2015; Tanner et al., 2019). The regression model was implemented using a mixture of 52 air pollutants constructed on a quantile scale as an exposure variable. The associations were evaluated using uncontrolled interrupted time-series (UITS) design to preserve the temporal trend that allowed us to assess the lagged exposure-response associations by season. The primary outcome was the daily count of pediatric asthma related ED visits. We included daily temperature, precipitation, wind speed and wind direction in the statistical model to adjust for the potential confounding effect of weather metrics on pediatric asthma. The association between air pollutant mixture and pediatric asthma exacerbation-related ED visits was evaluated. The gWQS regression model was implemented assuming that the air pollutants would have a positive association towards pediatric asthma exacerbations due to its conditional homogeneity. These associations were

presented as a same-day exposure-response relationship (lag_0) and delayed associations where the air pollutant mixture exposure was evaluated for potential associations with pediatric asthma exacerbations that could be delayed by 1-5 days.

The analytic dataset was split into training (40%) and validation (60%) data. We considered 100 bootstrap samples per iteration and repeated for 100 iterations using repeated holdout to stabilize the effect estimates. The model output provided a mean effect estimate of the outdoor air pollutant mixture and a 95% confidence interval. Additionally, the contribution of each air pollutant included in the WQS mixture was reported as a median percentage and its 95% confidence interval. All the analysis were conducted using statistical software R version 3.5.1.

RESULTS

In Douglas County, NE, there were 15.8 (age-adjusted) asthma-related ED visits per 10,000 children/year. Over the four years, the age-adjusted rate of ED visits was higher in 2016, with an estimate of 17.96 ED visits per 10,000 children/year (Table 6). During the study period, the rate of pediatric asthma exacerbations was consistently higher during the spring and fall seasons. The annual median crude rate of ED visits was higher among male children of age under five years (102 per 10,000 children/year) and children of age between 5 and 9 years (103.8 per 10,000), compared to children of age 10-14 years (63 per 10,000) and 15-19 years (29 per 10,000). A similar trend was not observed with the female population (Figure 15).

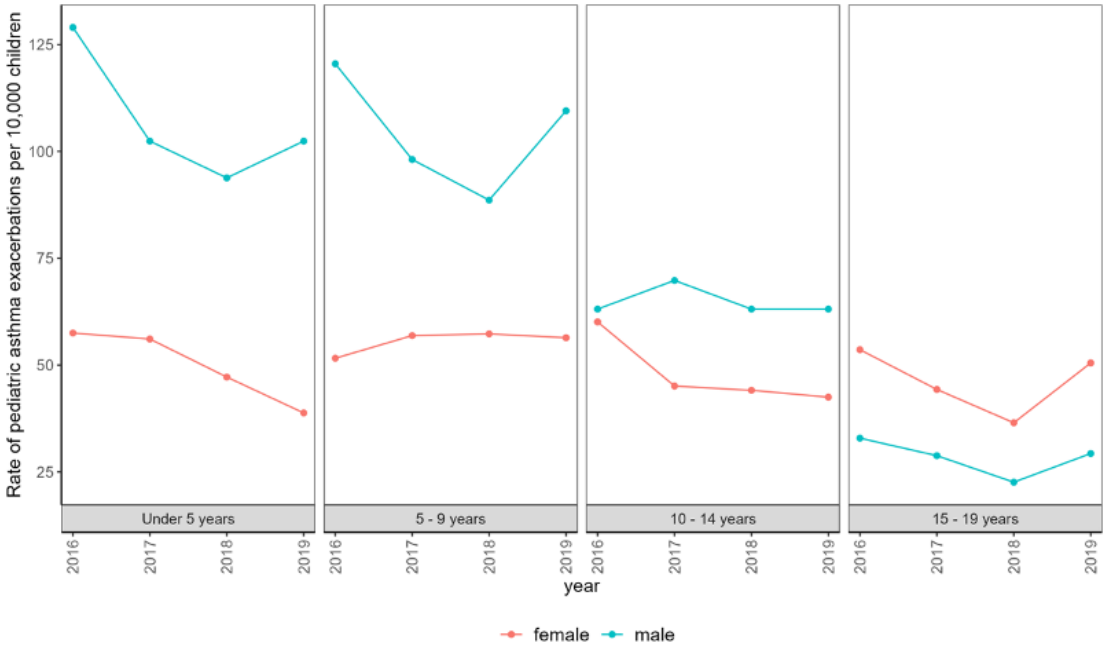


Figure 15. Rate of pediatric asthma exacerbations per 10,000 children stratified by age groups and gender (2016-2019).

Table 6. Rate of pediatric asthma ED visits per season and year per 10,000 children

Year	Season[a]								Overall[b]	
	Winter		Spring		Summer		Fall			
	AAR	CR	AAR	CR	AAR	CR	AAR	CR	AAR	CR
2016	3.23	13.64	5.06	20.80	3.18	10.02	6.38	26.10	17.96	73.56
2017	3.22	13.27	4.50	18.44	3.27	13.32	4.83	19.75	15.83	64.78
2018	1.86	7.60	4.36	17.82	3.57	14.64	4.13	17.01	13.93	57.05
2019	3.03	12.27	4.98	20.50	2.66	10.90	4.80	19.50	15.47	63.16

a-per season (3 months); b-per year; AAR: Age-adjusted rate; CR: crude rate

There were 2-4 ED visits per day in all four seasons during the study period. There were 172 days (12.17%) during the study period (total of 1,413 days) without any ED visits for pediatric asthma exacerbation. The summer season had the highest

number of days (71 days, 19.50%) without any ED visits, followed by winter (53 days, 16.30%), fall (25 days, 6.94%), and spring (23 days, 6.31%). The highest number of ED visits for asthma exacerbations was during the spring and fall season.

We identified statistically significant positive correlations between ozone and mold counts during the winter (r= 3-12%; p-value<0.05); between the 17 mold species (r= 12-83%; p-value<0.05). In spring, we found significant positive correlations between ozone and mold (r= 0.8-26%; p-value<0.05); tree pollen (hickory, walnut, pine) and mold (r=0.2-56%; p-value<0.05). In the summer, there were statistically significant negative correlations between ozone and mold (r=0.3-21%; p-value<0.05), and significant positive correlations between pollen counts from tree and grass (r= 12-47%; p-value<0.05). In the fall season, there were significant negative correlations between mold, pollen (weed and grass) and criteria pollutants (Nitrogen oxides) (r=15-36%; p-value<0.05). In addition, there were significant positive correlations between pollen (weed, grass) and mold count (r=3-69%; p-value<0.05) during fall season.

The association between outdoor air pollutant mixture and pediatric asthma exacerbations was evaluated at a seasonal scale. We observed associations between the outdoor air pollutant mixture and pediatric asthma exacerbations during the spring, summer, and fall seasons. During the winter season, we observed statistically non-significant associations between the air pollutant mixture and pediatric asthma exacerbations. Hence, we emphasized the statistically significant associations observed during the spring, summer and fall seasons.

We found delayed ($lag_{5\text{-days}}$) associations between air pollutant mixture and asthma exacerbations during the spring season. Namely, in the spring season, three deciles increase in the air pollutant mixture was associated with about 1 asthmatic ED visit per day that lagged by 5-days post-exposure (adjusted β_{WQS} 0.40, 95% CI:

0.17-0.63) (Figure 16). Among the air pollutants included in this study, tree pollen (sycamore), grass pollen, and mold (*Helminthosporium, Polythrincium*) contributed the highest weights to the pollutant mixture effect during the spring season (Figure 17). Sycamore and grass pollen are typically seen during April and May, with a peak pollen count in late April, whereas the *Helminthosporium* and *Polythrincium*, were observed during most of the days in the Spring season (Table 7, Figure 17).

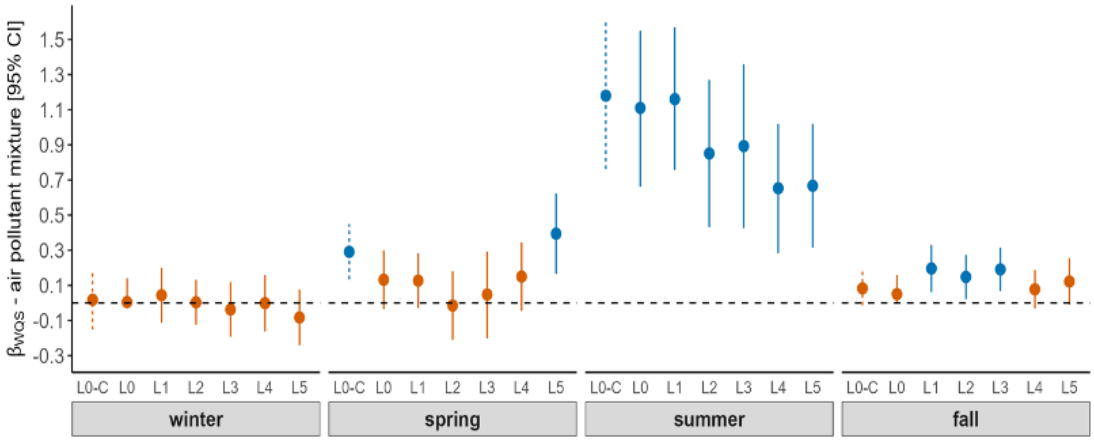


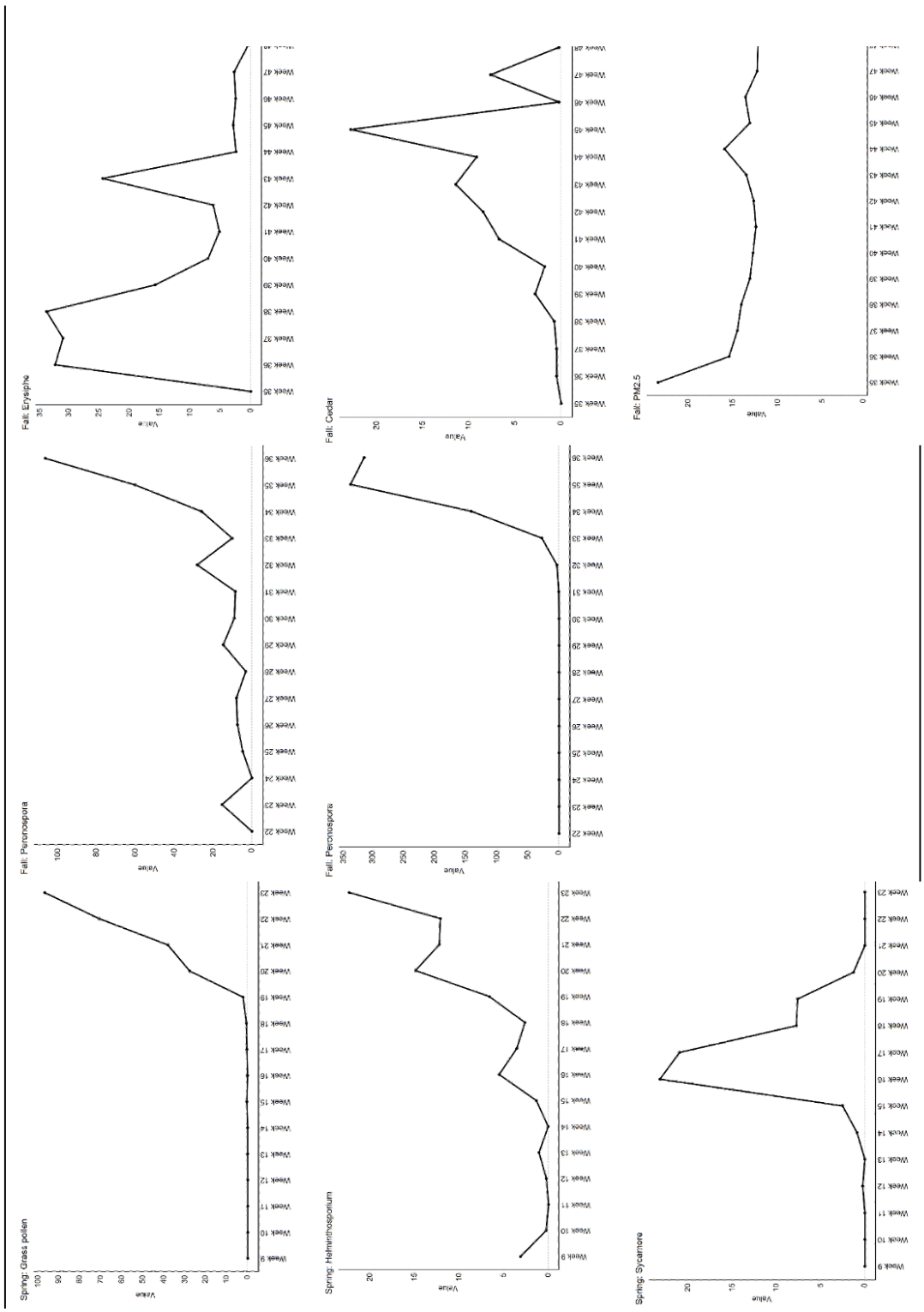
Figure 16. Association between outdoor air pollutant mixture and pediatric asthma exacerbations.
Y-axis represents the beta coefficient (effect estimate) of outdoor air pollutant mixture. X-axis represents seasons of a year. The confidence intervals of the crude model are represented using dotted line and the adjusted model using solid line. Adjusted model includes temperature, precipitation, wind speed and direction as covariates. Effect estimates with statistically significant association were represented using blue and statistically non-significant associations were represented using orange. The effect estimates and 95% confidence intervals were generated using qWQS regression with 100 repeated holdouts. L0-C represent the crude effect estimate with same day exposure-response association. L0-L5 are the adjusted effect estimates, where “0” represent same day association and 1-5 represent the exposure-delayed response associations ranging from 1-5 days.

Table 7. Descriptive statistics of pollutants with a higher contribution to the mixture effect

Season	Pollutant	Mean weight	% Days non-zero values	Air pollutant concentration	
				Median (IQR)	Mean (SD)
Spring	Grass pollen[a]	0.073	24.73	0 (0)	10.30 (37)
	Helminthosporium[a]	0.056	11.26	0 (0)	4.65 (20.1)
	Sycamore[a]	0.052	26.10	0 (0-1)	4.91 (23.4)
	Erysiphe[a]	0.045-0.138*	13.61	0 (0)	12.50 (42.6)
Fall	Cedar[a]	0.044-0.064*	30.83	0 (0-1)	5.60 (25.2)
	PM2.5[b]	0.056-0.057*	100	13 (10-17)	13.60 (5.49)
Summer	Peronospora[a]	0.046-0.157*	16.48	0 (0)	15.40 (49.3)
	Ragweed[a]	0.107-0.145*	28.85	0 (0-2)	39.40 (133)

*-Range of mean percent weights contributed across the lag period (1-3 days for fall season and 0-5 for summer season); a: measured as particles per 3.12 cubic meter of air; b: measured as micrometer per cubic meter; IQR: Interquartile range; SD: Standard deviation.

Figure 17. Aeroallergen trend by week



We observed that associations between air pollutant mixture and pediatric asthma exacerbations lagged by 1-3 days in the fall season. In the fall season, five deciles increase in the air pollutant mixture was associated with approximately 1 ED visit/day (adjusted β_{WQS} range 0.15-0.20), lagged by 1-3 days (Figure 15, Figure 16). Among the air pollutants, mold (*Erysiphe*), tree pollen (cedar), and $PM_{2.5}$ were higher and commonly contributed to the air pollutant mixture effect over lag 1-3 days during the fall season (Figure 18). During the study period, we observed peak spore count of *Erysiphe* during September, followed by a declining trend until November. Although cedar pollen is recognized to commonly peak between February and April, we observed cedar pollen starting from September until May (Figure 17).

During the summer season, we observed associations between air pollutants and pediatric asthma exacerbations (lag 0-5 days). There is a declining trend of effect estimates starting from same day associations to the effect lagging by 5-days. Focusing on the same-day exposure-outcome associations, each decile increase in the outdoor pollutant mixture was associated with about a 1 ED visit per day (adjusted β_{WQS} 1.11, 95% CI: 0.66-1.55) increase in pediatric asthma exacerbations. Mold (*Peronospora*) and weed pollen (ragweed) had higher contributions and commonly contributed to the mixture effect over lag 0-5 days. The effect estimate decreased up to 20% from the same day exposure-response compared to the associations lagging by 2-3 days. Additionally, the effect estimate declined up to 40% from the same day exposure compared to the association lagging by 4-5 days. During the study period, we observed ragweed pollen starting from July, with the annual peak counts during August. In contrast, *Peronospora spore* counts were observed throughout the year with an annual peak spore counts between July and September.

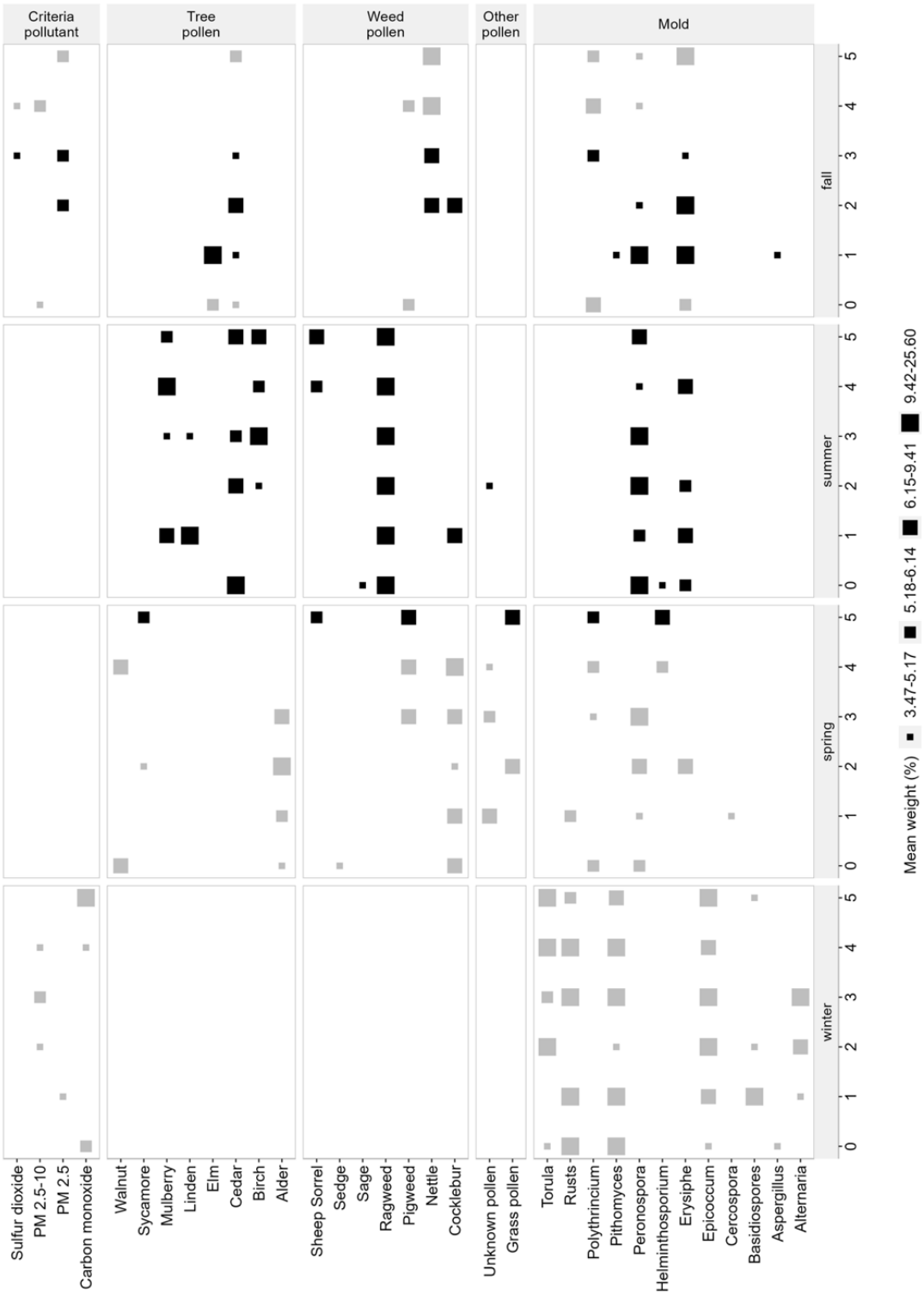


Figure 18. Contribution of individual pollutant to the air pollutant mixture weights. X-axis represent the lag period (0-5 days) by season. Y-axis represent individual air pollutants contributed to the mixture effect. The size of the squares represents the percent mean weight of the pollutant contributed to the pollutant mixture. Larger the size of the square represents higher weight. The color of each square represents if the pollutant weight obtained from a model with statistically significant associations (Grey – Non-significant; Black – Significant associations). Pollutant weights were obtained from the gWQS regression with 100 repeated holdouts.

DISCUSSION

This study evaluated the association between outdoor air pollutant mixture and pediatric asthma exacerbation-related emergency visits in Douglas County, NE. The seasonal scale associations were analyzed using daily scale data over four years (2016-2019). This study focused on evaluating the same day (lag_0) exposure-response and delayed associations that lagged up to 5 days. This study included 52 air pollutants that were categorized as criteria pollutants, pollens, and molds, as a mixture and were included in the gWQS regression model using a quantile scale. Additionally, the joint association of air pollutant mixture was estimated upon adjusting for temperature, precipitation, wind speed, and wind direction.

The rate of pediatric asthma exacerbation-related ED visits peaked during the spring and fall season. The seasonal trend of the pediatric asthma exacerbations that required an ED visit aligned with the results from a national scale study that reported higher asthma rates during the March-May and September-November time periods (Gerhardsson de Verdier et al., 2017). Additionally, Rodrigues et al. (2021) reported similar seasonal pattern of asthma-related hospitalizations among children in Lisbon, Portugal, suggesting the seasonal relevance corresponding to the beginning of the school year. The overlap between increased pediatric asthma exacerbations and the beginning of the school year could be due to an extended outdoor exposure window among children aged 4-19 years (Gao et al., 2022).

In this study, we observed a positive association between outdoor air pollutant mixture and pediatric asthma exacerbations during the spring, summer, and fall seasons. The exposure-outcome associations during the summer season were consistent with a lag of 0-5 days, whereas during the spring season the associations of pollutant mixture levels to pediatric asthma exacerbations lagged by five days, in the fall season there was a lag of 1-3 days. These associations during the summer season could be explained by total outdoor time spent, which is heavily influenced by

weather conditions. Meng et al. (2021) reported that children are more vulnerable to total air pollutant exposure during non-winter days than winter.[43] In this study, there were lower criteria pollutant concentrations and null values for aeroallergen counts for majority of the winter days. This could be also due to logistical issues in measuring aeroallergens during the winter days with snow and ice. In addition, we suspect that harsh winter weather conditions preclude outdoor activities by children and thus minimize exposure.

Pollen from grass and plants (sycamore), as well as mold (*Helminthosporium*) contributed higher weights to the outdoor pollutant mixture in the spring season. In the fall season, mold (*Erysiphe*), trees pollen (cedar), and $PM_{2.5}$ consistently contributed over lag 1-3 days to the outdoor air pollutant mixture. In the summer season, mold (*Peronospora*) and weed pollen (ragweed) consistently contributed to the outdoor air pollutant mixture associated with pediatric asthma exacerbations with a lag period ranging from 0-5 days.

A few case-crossover studies reported that exposure to outdoor air pollutants such as pollen [tree (birch), weed, and grass], mold (*Alternaria, Cladosporium, Aspergillus, Helminthosporium, and Penicillium*), and criteria pollutants [particulate matter ($PM_{2.5}$) and ozone] are associated with an increase in pediatric asthma exacerbations (Batra et al., 2021; De Roos et al., 2020; Denning et al., 2006; Fisk et al., 2007; Gleason et al., 2014; Heguy et al., 2008; Mendell et al., 2011; Niedoszytko et al., 2007; Shrestha et al., 2021). Additionally, Cox et al. (2020) reported that indoor mold exposures have also been associated with wheezing among children. Our results shared some common attributes with the existing literature (Batra et al., 2021; De Roos et al., 2020; Denning et al., 2006; Fisk et al., 2007; Gleason et al., 2014; Mendell et al., 2011; Niedoszytko et al., 2007; Shrestha et al., 2021), by demonstrating the association between outdoor air pollutants (mold and criteria pollutants) and pediatric asthma exacerbations.

Weed pollen exposure as a mixture was associated with increased pediatric asthma exacerbations, whereas a stratified analysis focused on the ragweed exposure was reported to be associated with a decline in pediatric asthma exacerbations (De Roos et al., 2020; Gleason et al., 2014; Heguy et al., 2008). In contrast, a few studies reported that ragweed exposure is associated with increased respiratory symptoms (wheezing, shortness of breath, and cough) and asthma exacerbations among children (Jones et al., 2019; Zhong et al., 2006). These findings suggest conflicting associations between ragweed exposure and pediatric asthma exacerbations reported in the literature. Our results showed that ragweed consistently contributed to the outdoor air pollutant mixture effect that is associated with an increase in pediatric asthma exacerbations during the summer season.

Additionally, tree pollen contributed to the air pollutant mixture during the spring and fall seasons. Even though trees typically pollinate during the spring season, we observed about 31% of days during the fall season with cedar pollen. A similar pattern was observed for cedar pollen measurements among different cities in the Great Plains region (Texas, Missouri, Oklahoma). Lo et al. (2019) reported cedar pollen counts that could be clustered into two seasons (January-March & September-December) that were observed in Missouri (Springfield), Oklahoma (Tulsa, Oklahoma City) and Texas (Waco, Austin, Houston, College Station, San Antonio). Our results suggest that cedar pollen contributed to air pollutant mixture during the fall season (mean pollen concentration:5.6; SD:25.2), which reflects pollen counts 56 times less than the pollen counts during the spring season (mean:311; SD:1,493).

Asthma, one of the most common causes of morbidity and hospitalizations in childhood, is a complex disease influenced by many genetic factors and environmental factors including aeroallergens, pet dander, dust mite, molds, viral infections, indoor and outdoor air pollution (Crain et al., 2002; Rubner et al., 2017; Pavrod et al., 2018; Tiotiu et al., 2020). Several of these environmental agents mediate disease consequences through disrupting the integrity of the airway

epithelium and release of alarmins including thymic stromal lymphopoietin (TSLP), interleukin (IL)-33 and IL-25 (Steinke et al., 2020). These events trigger activation of mast cells, type-2 innate lymphoid cells (ILC2), T helper type 2 (Th2) cells and eosinophilic recruitment and further release of Th2 cytokine (i.e., IL-4, IL-5, IL-9, IL-13) (Steinke et al., 2020). Specific immunoglobulin-E (IgE) to outdoor aeroallergens typically develops after the age of 3 years (Durrani et al., 2020), the aeroallergens demonstrated in our study of grass pollen, tree pollen (sycamore, cedar), weed pollen (ragweed) and mold (*Helminthosporium*) are associated with allergic and asthmatic disease (Bridgewater et al., 2020). Future studies evaluating allergenicity of the molds *Erysiphe* and *Peronospora* are warranted to understand their potential role in influencing allergic and asthma diseases.

This study has several strengths such as utilizing robust outdoor pollutant (criteria pollutants, pollen, and mold) data at a daily scale and evaluating exposure-response associations using mixture effect framework. In the context of air quality and human health outcomes research, most studies have considered criteria pollutants as exposure. The substantial focus on criteria pollutants could be due to the USEPA Clean Air Act (USEPA, 2021) that require monitoring and reporting of criteria pollutants. As a result of the US EPA Clean Air Act, there are more than 4,000 air quality monitoring stations that measure hourly or daily levels of criteria pollutant measurements that are made publicly accessible at the US EPA Air Quality System database (USEPA, 2021). The continuous monitoring and accessibility of criteria pollutant data could be one of the reasons that motivated researchers to evaluate health outcomes associated with criteria pollutants. As of 2021, there are about 85 aeroallergen measuring stations in the United States that collect pollen data at least four days per week (AAAAI, 2021). The availability of criteria pollutant and aeroallergen (pollen and mold) measurements at a daily scale allowed us to conduct a comprehensive study evaluating association between air pollutants as a mixture and pediatric asthma exacerbations in Douglas County, NE. Similar study could be

conducted using time-stratified case-crossover design to adjust for confounders such as age and gender. However, in this study we followed UITS design to preserve temporal trend to assess the lagged associations.

Our study also has limitations, as the exposure data was based on outdoor monitoring stations, and the effect estimates are subject to non-differential misclassification of the exposure. The few studies that compared the air pollutant exposure measured at a monitoring station to personal exposures, found strong correlations for $PM_{2.5}$ and sulfate concentrations that included the elderly population and PM_{10} exposure that included children (Ebelt et al., 2000; Janssen et al., 2005; Sarnat et al., 2000; Williams et al., 2000). As the comparison between outdoor air pollutants and personal exposures is limited to particulate matter, there is a gap in understanding the dynamics of aeroallergens (pollen/mold) with particulate matter (Janssen et al., 1999). We did not consider an effect of single pollutant as our main contribution of this article to assess the joint association between air pollutant mixture (criteria pollutants, pollen, and mold) and pediatric asthma exacerbation related ED visits. However, pollutants with higher weights from our results using air pollutants as a mixture overlapped with the findings from single pollutant model conducted by Gonzales-Ramirez et al. (2019).

Our results were also not standardized for population vulnerabilities such as poverty, race/ethnicity, and education, which could play a key role in differential exposure misclassification. We did not account for indoor exposure to house dust mites, cockroaches, pet dander (dog/cat), and smoking (primary/secondary), resulting in an unmeasured potentially confounding effect. Due to convergence issues in the statistical model, we did not conduct stratified analysis to evaluate the role of confounding, interaction, or effect modification due to age, gender, body mass index, and co-morbidities associated with asthma exacerbations. Our study results are influenced by exposure misclassification, effect modification, and unmeasured confounding, violating exchangeability; therefore, our results do not infer causal

relationships. Further cohort-based studies exploring the controlled direct effect, reference/mediated interaction, and pure indirect effect are necessary to establish a causal relationship between outdoor pollutants and pediatric asthma. A strength of this study was understanding the joint association between 52-air pollutants as a mixture and pediatric asthma exacerbations, future studies may also be warranted to explore interaction terms between air pollutants that contributed to higher weights. Additionally, climate change was identified to alter the aeroallergen season length and timing (Manangan et al., 2021; Schramm et al., 2021). As we observed that aeroallergens played a key role in pediatric asthma exacerbations, future studies evaluating asthma exacerbations in the context of climate change could minimize unmeasured biases.

CONCLUSION

To our knowledge, this is the first study to evaluate the association between air pollutant mixture and pediatric asthma exacerbations. Our findings shared attributes with the existing literature based on single pollutant exposures. As criteria pollutants (influenced by the number of industries and motor vehicles) and aeroallergen levels (due to dominance of tree species and weather conditions) vary by geographic area, our findings have substantial public health implications in the Great Plains region. Identifying air pollutants at the household level and mitigating potential sources associated with indoor pollutants, could substantially improve respiratory health among children.

CHAPTER 5: DISCUSSION

SUMMARY OF FINDINGS

The three studies in this dissertation quantified the environmental health risks associated with human health using public health surveillance systems. The first and second studies were based on the health data obtained from NC-DETECT, a syndromic surveillance database maintained by the NC-DHHS. These studies quantified the HRI morbidity associated with ambient temperature stratified by physiographic regions in North Carolina. The first study quantified the rate of HRI emergency department visits attributable to current and future climate change. In the second study, we compared heat wave definitions with the best model fit associated with HRI morbidity. Additionally, we compared the heat wave definition with the National Weather Service warnings.

The third study assessed the joint association between 52 ambient air pollutants and pediatric asthma exacerbations. Additionally, we estimated the percentage weight of each air pollutant contributing to the joint effect. These associations were evaluated by stratifying them into four meteorological seasons.

Through these studies, we provided a comprehensive outlook on the temporal trend of the acute health outcomes associated with environmental exposures. We quantified the acute exposure-response associations using public health surveillance systems. The primary goal of this dissertation is to provide a framework to assess environmental health risks using public health surveillance databases. Our framework is specific to the use cases where randomized control trials are not feasible to estimate the environmental health risks.

This dissertation has contributed to the literature in the planetary and environmental health domain by assessing environmental health risks that relied on principles that intersected across epidemiology, environmental health, and data science. Additionally, our findings in this dissertation may help community leaders, public health departments, and policymakers to mitigate risks or to develop resilience

plans. Moreover, we described the morbidity trends and preventable fraction of health emergencies associated with environmental exposures.

The first study estimated the HRI morbidity rate attributable to current and future climate change. We assessed the non-linear association using GAM and DLNM framework to rule out the possible distributive association between ambient temperature and HRI morbidity. Using the statistical model assessing the association between temperature exposure and HRI morbidity, we estimated the HRI morbidity attributable to current and future climate change. Findings from our study could help public health departments and actuaries to develop heat risk mitigation strategies to strengthen the resilience of communities against ambient temperature exposure.

Previous studies attributed human health risks to climate change, focusing on extreme events or using mortality as an outcome. Using mortality as an outcome could be appropriate in the studies emphasizing extreme heat events. Exposure to extreme heat events such as the 1995 Chicago heat wave could aggravate HRI mortality. Relying on mortality as an outcome in climate attribution studies focusing on ambient temperature could underestimate the human health risks associated with climate change. Many individuals with HRI could seek medical attention and may not manifest into HRI-related death. We focused on the acute health outcome associated with exposure to heat to minimize possible biases in quantifying human health risks associated with climate change.

The second study compared the sensitivity of heat wave definitions associated with HRI morbidity. We included 28 heat wave definitions from the literature for comparison. We compared the AIC values obtained by fitting a generalized linear model between heat wave definition (binary exposure) and HRI morbidity (count outcome) to identify the sensitive heat wave definition. As the median HRI count is greater than the average, we assumed negative binomial distribution of the outcome. We observed heterogeneity between the sensitivity of heat wave definitions across the Coastal and Piedmont regions of North Carolina.

Additionally, we compared these heat wave definitions with the NWS heat products. We observed a significantly higher number of heat waves using the definitions from this study compared to the NWS warnings. During the summer days flagged as heat waves using the definitions from this study, we observed an average of 7 HRI emergency department visits per day.

Several studies compared heat wave definitions to identify a gold standard but used mortality as an outcome and larger geographic areas (climate regions or political boundaries). As mentioned earlier, we relied on HRI morbidity to minimize possible outcome estimation bias associated with ambient temperature exposure. This is the first study that compared epidemiology-based heat wave definitions with NWS heat products. We hypothesize that the NWS heat products could efficiently minimize HRI mortality and supplementing epidemiologic-based definitions with the NWS heat products could minimize HRI morbidity.

Transitioning to the findings from the third study, we assessed the joint association between ambient air pollutants and pediatric asthma exacerbations. We observed a higher rate of pediatric asthma exacerbations during the fall and spring seasons during the study period. However, we observed a statistically significant association between ambient air pollutant mixture and pediatric asthma exacerbations during the summer, fall (lagged by 1-3 days), and spring (lagged by 5 days) seasons. Among the 52 air pollutants included in this study, pollen and mold contributed a higher weight among the ambient air pollutant exposures.

We observed a heterogeneous pattern among the contribution of ambient air pollutants to the pediatric asthma exacerbations that varied by season. Our findings from this study, identifying the joint association of the air pollutant mixture and estimating the contribution of each pollutant from the air pollutant mixture, could support public health departments and healthcare providers to improve environmental health literacy in communities.

CONTRIBUTION TO THE LITERATURE

The studies included in this dissertation contributed to the literature by targeting specific dimensions in quantifying environmental health risks using public health surveillance systems. In the first study, we contributed to the field by estimating the fraction of HRI-related emergency department visits attributable to the current and future climate change. A few studies attributed all-cause or HRI-related mortality to climate change, using administrative boundaries. This study used physiographic delineations to estimate the acute outcome (HRI morbidity) associated with ambient temperature exposure. Moreover, this is the first study that reported both the acute and distributive exposure-response associations between outdoor heat metrics and HRI morbidity.

The second study made a unique contribution by comparing the sensitivity of 28 heat wave definitions to HRI morbidity. A few studies compared numerous heat wave definitions using mortality as an outcome and emphasized extreme heat events. But there is limited information on moderate and frequent heat wave events that could worsen HRI-related emergencies and hospitalizations. To address the gap, we focused on identifying a heat wave definition with the best model fit (lowest AIC value) associated with HRI morbidity. This is the first study to compare the results from an epidemiologic-based heat wave definition to the NWS heat products.

In the third study, we contributed by assessing the joint association of 52 ambient air pollutants as a mixture and pediatric asthma exacerbation-related emergency department visits. We quantified the joint associations and individual contributions of the pollutants associated with pediatric asthma exacerbations.

Overall, this dissertation contributed by addressing several gaps in the environmental health discipline using public health surveillance systems. Similar, studies could be conducted using a cross-sectional design by decomposing the temporal information (Wu et al., 2020), which is more likely to introduce systematic biases such as exposure measurement bias (Lash et al., 2021). There are pros and

cons associated with ITS and cross-section study designs. The ITS design minimizes potential systematic bias but limits the usage of covariates measured at an individual scale (age, gender, comorbidities). The cross-sectional study design would allow the researchers to expand analysis using covariates but introduce systematic bias that would distort the effect estimates.

However, this dissertation highlighted the scope of environmental epidemiologic research using ITS study design and relying on the public health surveillance systems to minimize the systematic bias and confounding effects. Unlike the existing literature (Hategeka et al., 2020), the three studies included in this dissertation were implemented using the ITS design, which allowed us to account for temporal autocorrelation, using a control (time-period for two studies), and lagged exposure-response associations. Additionally, we considered acute exposure-outcome associations (emergency department visits) and assessed associations on a daily scale to minimize potential systematic bias. Findings from this dissertation could be helpful to public health departments, healthcare providers, and communities to strengthen the awareness related to environmental health risks.

POLICY IMPLICATIONS AND RECOMMENDATIONS

Based on our results, we suggest developing region-specific pilot-scale environmental risk mitigation planning and supporting rigorous public health education based on the epidemiologic studies could substantially minimize environmental health risks. For example, researchers from Barcelona Spain quantified human health risks associated with urban environmental pollutants and intervened by introducing Superblocks (preventing motor-vehicle access to certain blocks) to minimize air and noise pollution (Mueller et al., 2020).

Similarly, the findings from this dissertation could be used as supporting material by the public health departments to promote behavioral changes. Additionally, it could be used as a resource by the public health departments and healthcare providers to expand environmental health risk education. We assume that

our results could be relatable to the targeted communities due to the outcome data source obtained by public health surveillance.

Additionally, an active collaboration between the policymakers, public health departments, and researchers could improve the quantification, mitigation of environmental health risks, and evaluation of public health intervention effectiveness using evidence-based insights generated from the public health surveillance systems. The uncertainty in quantifying environmental health risks could be improved by gaining access to suppressed data and incorporating socio-demographic information. This could decompose the total exposure-outcome associations to interaction, mediation, and indirect association pathways. The decomposition of the overall associations could substantially minimize the uncertainty between exposure-response associations. In collaboration with public health departments and policymakers, these environmental risks could be mitigated by deploying pilot-scale interventions in communities, and the effectiveness of the interventions could be validated for further expansion.

LIMITATIONS

Regardless of the notable strengths of the studies included in this dissertation using public health surveillance systems, these findings are subject to several limitations due to the ITS study design. As public health surveillance systems are primarily designed for tracking community health outcomes (non-research purpose), the data collection strategies may not support secondary use cases such as environmental risk assessments (Huybrechts & Schneeweiss, 2021). Additionally, ITS studies by design may violate the causality assumptions (exchangeability) due to their non-randomized nature (Hernán & Robins, 2020b).

Data accessibility constraints could introduce unmeasured confounder bias (social, lifestyle, occupational, and genetic factors). Additionally, the use of public health surveillance data for environmental health risk quantification could introduce selection bias (inclusion of individuals with adverse health conditions who visited a

medical facility) and exposure measurement bias (ambient exposures measured at a community scale) (Hernán & Robins, 2020a; Huybrechts & Schneeweiss, 2021; Lash et al., 2021). The unmeasured confounding driven by the aforementioned factors restricted the studies included in this dissertation to the total exposure-outcome associations. Accessibility to the comprehensive socio-demographic information from the public health surveillance systems could increase the flexibility to decompose the exposure-association pathways behind the total effects observed in this dissertation. Transitioning to the impact of selection bias in this study, health beliefs (susceptibility, severity, and barriers) could play a role in human health behavior in seeking medical attention for managing adverse health outcomes (Jack et al., 2010). Inter-individual variability in health behavior could introduce bias while estimating the health outcome. Additionally, non-differential exposure misclassification bias due to ambient exposure measurements than using personal exposures could result in exposure-outcome associations towards null.

FUTURE DIRECTION

Limitations associated with measured effect modifiers could be addressed by considering stratification. ITS studies that include areas with higher population density or an extensive (multi-state or multi-country) hierarchical geographic structure specified within the design will allow flexibility to conduct stratified analysis. Stratum-specific effect estimates would enable us to understand the environmental health risks associated with vulnerable populations such as pregnant women, occupational hazards, and age-related vulnerabilities (children and elderly).

Further studies comparing the personal exposure measurements to the ambient exposure estimates will strengthen the exposure assessments and allow quantifying the degree of non-differential exposure misclassification bias in studies using ambient measurements as exposure. A few studies compared ambient and personal exposure measurements. Pilot-scale expansion of exposure measurement

validations for environmental risk factors could further strengthen the validity of population health studies using public health surveillance systems.

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