Extreme weather and mortality among a nationwide cohort of Veterans with COPD

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Dedication

To my family.

Abstract

Climate change is increasing the frequency, severity and duration of extreme weather events. Individuals with climate sensitive diseases such as chronic respiratory diseases are at an enhanced risk of health challenges due to climate change. However, there is a lack of individual level studies examining how extreme weather events such as heat and cold waves may increase the risk of mortality among individuals with chronic obstructive pulmonary disease (COPD), a climate sensitive respiratory disease. Using nationwide individual level health data from the Veterans Health Administration, three studies were designed to estimate heat and cold wave associated mortality risk among this susceptible population.

The first study evaluated heat and cold wave mortality risk among the entire population of patients with COPD and examined health disparities by individual characteristics including gender, age, race and ethnicity. Results indicated cisgender females had an increased heatwave associated mortality risk. While some racial disparities in mortality risk were detected, the evidence was weak. The second study further examined disparities in heat and cold wave associated mortality via less commonly studied effect measure modifiers including comorbidities, smoking status and urbanicity. Patients with concurrent COPD and asthma had a greater risk of heatwave related mortality whereas patients with COPD alone had the greatest cold wave associated mortality risk. Smokers and patients living in urban settings had enhanced risk of both heat and cold wave related mortality. The third study assessed the added mortality risk incurred during compound climate hazards (droughts and heatwaves) among this susceptible population. Results indicated heatwaves that occurred during droughts had larger mortality risks compared to heatwaves during non-drought conditions.

These three studies provide evidence that individuals with COPD are at risk of adverse health events from heat and cold waves and identified heterogeneities in risk based on characteristics including social, biological and geographical constructs. There is an apparent need in climate and health epidemiology for more large-scale individual level assessments of people with climate sensitive diseases. As contemporary impacts of climate change are realized, it is imperative to devote resources and energy into

elucidating health risks associated with extreme weather events to identify and protect at-risk segments of the population.

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List of abbreviations

AAPI: Asian American and Pacific Islanders

ACOS: Asthma-COPD overlap syndrome

AIAN: American Indian and Alaska natives

AR: Attributable risk

CAD: Coronary artery disease

CDW: Corporate data warehouse

CHF: Congestive heart failure

CKD: Chronic kidney disease

COPD: Chronic obstructive pulmonary disease

DLM: Distributed lag model

EPA: Environmental Protection Agency

ICD: International classification of diseases

IRR: Incidence rate ratio

NLDAS-2: North American Land Data Assimilation System

$PM_{2.5}$: Fine particulate matter

PRISM: Parameter elevation Regressions on Independent Slopes

RUCA: Rural-urban commuting area

SPI: Standardized precipitation index

SPEI: Standardized precipitation-evapotranspiration index

UHI: Urban heat island

USDM: United states drought monitor

VA: Department of Veterans affairs

VHA: Veterans health administration

VTE: Venous thromboembolism

Chapter 1: Introduction

Climate change & health

Anthropogenic climate change, driven by large volumes of greenhouse gas emissions in the atmosphere, is hastening the rate at which Earth's temperature is increasing. The last four decades have been warmer than any decade that came before it since 1850[1]. This increase in temperature corresponds with warmer ocean temperatures, bleaching of coral reefs, melting polar ice caps, and rising sea levels. Climate change is also anticipated to cause shifts in global climate zones, changes in storm tracks and precipitation patterns[1].

Extreme weather events such as droughts, wildfires, hurricanes and floods are expected to increase in frequency, severity and geographic distribution as a result of climate change[2]. These extreme weather events can lead to infrastructure damage, economic losses, displacement of people, and loss of life. Public health challenges emerge as a growing body of evidence suggests extreme weather events may be associated with a variety of infectious[3,4] and non-infectious diseases[4]. Thus, it is imperative for researchers to elucidate the magnitude by which climate change impacts human health to improve public health surveillance, policy interventions and clinical treatments.

One class of climate sensitive diseases is respiratory diseases, a growing segment of the population in terms of absolute numbers[5]. In 2017, 545 million people worldwide had a chronic respiratory disease, an increase of 39.8% compared to 1990[5]. Respiratory diseases are challenged by climate change due to a variety of mechanisms including aeroallergens, air pollution, extreme temperatures, floods and natural disasters which can worsen existing disease symptoms and lead to adverse health outcomes[6].

Chronic obstructive pulmonary disease (COPD)

COPD epidemiology

Chronic obstructive pulmonary disease (COPD) is one example of a chronic respiratory disease affected by climate change. COPD is a heterogeneous, degenerative pulmonary disease characterized by airflow obstruction. The Global Initiative for Chronic

Obstructive Lung Disease guidelines define COPD as a ratio of post-bronchodilator forced expiratory volume at 1 second to forced vital capacity less than 0.70[7]. Symptoms of COPD include dyspnea, persistent cough, wheezing, excess production of mucus, sputum and phlegm, difficulty breathing and chest tightness[8,9]. In 2019, the Global Burden of Disease Study estimated the global prevalence of COPD at 212 million cases and ranked it as the 3rd leading cause of mortality among the 174 level 3 causes of death with approximately 3.2 million deaths annually[10]. COPD is the most prevalent chronic respiratory disease accounting for over half of the global population diagnosed with a chronic respiratory disease[5]. Globally, the prevalence of COPD increased 20.8% from 2010 to 2019[5]. Among the general population, COPD prevalence is estimated to be 1% and as high as 8-10% among people aged 40 years and older[11]. The overall lifetime risk for developing COPD is relatively high. One study estimated the overall lifetime risk of physician diagnosed COPD by age 80 was 27.6%[12]. Overall lifetime risk was higher in men compared to women, in people with lower socioeconomic status and in people from rural areas[12].

COPD imposes a large burden on existing healthcare infrastructure. In 2011, there were 10.3 million physician visits, 1.5 million emergency department visits and 699,000 hospital discharges for COPD in the United States[13]. Nearly 16 million Americans had a COPD diagnosis in 2013 and those most likely to have a diagnosis included: women, the elderly, people who were unemployed or unable to work, had less than high school education, current or former smokers, and people with a history of asthma[14]. While the overall age adjusted mortality rate of COPD in the United States decreased in recent decades, improvements in mortality were not equally distributed among the population. While age adjusted mortality rates in males decreased, age adjusted mortality rates in females remained relatively unchanged[15,16]. African American women were the only race-sex combination that had an increase in age adjusted mortality rates from 2004 – 2018[15].

The primary risk factor for developing COPD is smoking[8,17] although outdoor and indoor air pollution are suspected environmental causes[17]. Indoor air pollution exposure via burning of biomass for heat and fuel is associated with increased risk of COPD particularly in the developing world and among women who have higher levels of

exposure due to domestic activities[18,19]. Abnormal inflammatory responses in the lungs due to the inhalation of toxic particulate and gaseous substances is thought to be a key driver in the physiological development of COPD[20]. Other risk factors include occupational exposure to dust, fumes and chemicals[19,21], history of respiratory tract infections in childhood[22], history of pulmonary tuberculosis[19], family history of asthma[22] and poor airway function during infancy or childhood[23]. A rare genetic disorder, alpha-1 antitrypsin deficiency, can also lead to COPD development[9].

Given the diverse array of exposures through which an individual can develop COPD, there may be a need in the future to differentiate between COPD caused by smoking versus environmental pollution versus genetics due to differences in pathophysiology and life course of disease[18]. Indeed, there is growing research describing risk factors for COPD development specifically in people who never smoked tobacco to further isolate and describe COPD pathophysiology in this historically underestimated population. Prior research estimated 25% to >30% of COPD cases were in individuals who were never-smokers[19].

People living with COPD also tend to be afflicted with one or more comorbidities such as heart disease, hypertension, diabetes, lung cancer, and chronic kidney disease among several others which contributes to further debilitation and overall poorer health[18,24]. While exact biological mechanisms are not yet known, it is suspected COPD might act as a systemic disorder via low-grade chronic inflammation which may accelerate the natural life course of other comorbidities[20,24].

COPD pathophysiology

One of the primary functions of the lungs is gas exchange, specifically the delivery of oxygen to the blood for use in bodily functions and removal of CO_2[25]. Gas exchange occurs through a vast network of airways starting with the bronchial tree that further branches out into many thousands of smaller, thinner tubes called bronchioles[25]. At the terminal ends of the bronchioles are clusters of tiny round air sacs (alveoli) where gas exchange occurs. Alveoli are surrounded by small blood vessels (capillaries) and along their walls is where oxygen passes and gets carried away by red blood cells and

hemoglobin. Meanwhile, CO_2 simultaneously moves through the capillaries into the alveoli as a waste produce to be expelled[25]. The alveoli and airways are elastic allowing them to expand with air and then passively deflate with exhalation[25]. In people with COPD, less air flows in and out of the airways due to 2 primary reasons 1) loss of lung elasticity and alveoli and 2) increased airway resistance due to inflammation and blockage due to mucus production. These mechanisms describe the physiology of emphysema and chronic bronchitis which are two major phenotypes of COPD[9,26].

In emphysema, the walls of the alveoli become damaged and lose their elasticity that leads to alveolar rupture and the formation of large air spaces in the lungs[9,27]. The loss of elasticity increases the effort needed to breathe and the loss of alveoli results in decreased oxygen delivery[9,27]. In chronic bronchitis, the walls of the bronchial tubes are inflamed which causes them to thicken. The airways may also become clogged due to increased mucus production leading to persistent coughing with mucus colloquially known as a smoker's cough[9,28]. COPD can be due to other causes that damage the airways including irritants such as air pollution as well as other risk factors previously enumerated above.

COPD misclassification

While COPD is a common disease affecting millions of people around the world, misdiagnosis of COPD is relatively high due to relying on self-reported COPD diagnosis or lacking diagnostic spirometry information. Misdiagnosis of COPD can include overdiagnosis (false positive) and underdiagnosis (false negative) and the strongest predictor of a COPD misdiagnosis is the lack of spirometry information used in the diagnosis[29]. A recent review reported 10-12% of adults over 40 years of age globally had evidence of persistent airflow obstruction measured by spirometry but only 20-30% had a COPD diagnosis suggesting up to 70% of COPD cases worldwide may be underdiagnosed[30]. Conversely, 30-60% of patients with physician diagnosed COPD may be overdiagnosed[30]. Another review found a large variation in global COPD misdiagnosis prevalence with 10-95% prevalence of underdiagnosed COPD and 5-60% prevalence of overdiagnosed COPD reported in previous research[29].

The variability in misdiagnosis rates may be attributable to differences in diagnostic approaches and the lack of spirometry availability in rural areas of developing countries where COPD prevalence is likely to be higher[29]. One study in Canada estimated the prevalence of COPD could be four times greater if people who were underdiagnosed had been counted as having COPD. Likewise, they also estimated that for every case of COPD, four of these cases with self-reported COPD are overdiagnosed[31]. Another study found COPD misdiagnoses were five times more common than correctly diagnosed COPD in a Canadian cohort[32]. Compared to people without COPD, those overdiagnosed with COPD had higher rates of hospitalizations, emergency department visits and ambulatory care visits[32]. People with underdiagnosed COPD had higher rates of hospitalizations[32].

Risk factors associated with overdiagnosis include sex, smoking status, morbid obesity, age, high comorbidity burden and older age of primary care physician[31,33]. Risk factors associated with underdiagnosis include age, smoking status, sex, respiratory symptoms, co-diagnosis of asthma, low comorbidity burden and lower socioeconomic status[31,33]. Age, sex and smoking status, while associated with misdiagnosis of COPD overall, have unclear directions of associations with over and underdiagnosis specifically[31,33]. COPD as a cause of death has also been historically underreported on death certificates with past research estimating 21 – 43% of COPD deaths are misclassified[34–36].

Misdiagnoses of COPD and death due to COPD are critical to consider from an epidemiological perspective as studies investigating associations between environmental exposures and adverse health outcomes among those with COPD are likely not capturing all COPD cases and deaths. Undercounts of cases and deaths may underestimate the true magnitude of effect environmental exposures have on COPD related health outcomes. Furthermore, since misdiagnoses may not be completely random, there is a risk of bias in effect estimates which can hamper the utility of epidemiological studies to inform public health and clinical interventions.

Extreme temperatures & health

The physiology of exposure to extreme heat and cold

Exposure to extreme heat and cold engenders physiologic responses in the human body that may contribute to negative health outcomes including injury, morbidity and mortality. The human body responds to extreme heat exposure via two mechanisms, 1) vasodilation (i.e. the redistribution of blood toward the skin to facilitate the transfer of heat from muscles) and 2) sweating (the evaporation of sweat acts to remove heat and cool the body)[37]. As a physiologic response, vasodilation increases demand on the heart to pump blood faster which can affect individuals with underlying cardiovascular impairments[37]. Vasodilation can cause a mismatch between the high oxygen demand of the heart (by pumping faster), and an individual's damaged heart that cannot keep up with the demand[37]. This increased cardiovascular strain can cascade to cardiac ischemia, myocardial infarction and finally cardiovascular collapse[37]. The increase in cardiovascular strain caused by vasodilation explains why cardiovascular diseases are the primary cause of death during heatwave events and partially accounts for why heat stress is especially challenging for the elderly[37]. Extreme heat may also lead to dehydration which decreases blood volume and adds additional strain to the heart and can lead to acute kidney injury and subsequent kidney failure[37]. Additionally, high internal body temperatures (39 - 40°C) can lead to heat stroke with tissue and organ damage that can impact the brain, kidneys, heart, gastrointestinal tract, liver and lungs[37]. Survivors of heat stroke may have permanent damage to organ systems and possible long-term bodily impairment[38].

With regard to extreme cold exposure, the most recognizable physiological effects in humans include conditions such as hypothermia and frostbite. Hypothermia occurs when the body's core temperature falls below 35°C and has symptoms including shivering, slurred speech, confusion and loss of consciousness[39]. Similar to heat stroke, people with difficulties thermoregulating (i.e. balancing overall heat load from the external environment and heat produced via metabolism) are at greater risk for developing hypothermia and include subpopulations such as the elderly, infants and people with certain comorbidities[40]. Drugs and alcohol are other important risk factors for

hypothermia. Specifically, alcohol impairs judgement, inhibits shivering and causes vasodilation which is counteractive to the body's typical thermoregulatory response to cold[40]. Cold can also affect both the respiratory and cardiovascular systems. Individuals with bronchial hypersensitivity (e.g. asthma) may be more sensitive to temperature changes and the sudden inhalation of cold air may cause bronchospasms and/or bronchoconstriction[41]. Cold exposure is also known to impact biomarkers of cardiovascular disease and is associated with increases in systolic and diastolic blood pressure, serum low density lipoprotein cholesterol and decreases in serum high density lipoprotein cholesterol[42]. Among survivors of myocardial infarction, cold temperatures are associated with increases in C-reactive protein and other inflammatory markers[43].

The physiology of extreme temperatures and COPD

People with COPD are vulnerable to environmental perturbations including extreme heat and cold exposure due to compromised breathing and high rates of comorbidities. Extreme heat may affect individuals with COPD via: fluid loss, impaired pulmonary perfusion and inflammation of the bronchial mucosa[44]. Research in Baltimore found when COPD patients were outside, maximum daily outdoor temperature was associated with worsening breathlessness, cough and sputum scale scores after adjusting for outdoor ambient air pollution exposure[45]. The exact biological mechanisms associated with cold weather exposure and COPD are currently unknown. Proposed biological pathways include: rhinorrhea, nasal congestion and damage to the nasal epithelium[44]. Increases in respiratory viral infections, bronchoconstriction and decreased muco-ciliary clearance are other plausible pathways[46]. A study in Massachusetts found cold outdoor ambient temperature was associated with increased respiratory symptoms, rescue inhaler use, and decreased lung function despite COPD patients having limited outdoor exposure[47]. This suggests transient outdoor exposure to cold temperatures may have deleterious health effects[47].

Research gaps & future directions

COPD is generally understudied with regard to extreme weather exposure. Previous research investigated the effects of ambient temperature on several COPD related health outcomes including lung function and COPD related symptoms[45,47–49],

emergency department visits[50,51], hospitalizations[50,52,53,53–60] and mortality[61–63] (Table 1-1). Relatively few studies investigated the relationship between COPD and discrete meteorological events such as heat and cold waves[56,61]. Previous work is also limited by geographic scope, sample size, and exposure data quality.

The overwhelming majority of research studies examining the associations of extreme weather with COPD health outcomes studied relatively small populations and geographic areas. Most studies were completed only using data on singular cities or regions with a smaller number of studies examining larger geographic areas. While some studies had sample sizes in the hundreds of thousands, these studied were limited by being ecological studies evaluating aggregate counts of COPD related health outcomes which precludes understanding of individual level risk to extreme weather exposure (Table 1-1). When considering studies of individuals in well-defined COPD cohorts, sample sizes ranged from the tens to hundreds of individuals (Table 1-1). There is a need for more individual level studies using well-defined cohorts of individuals with COPD to facilitate a better understanding of disease etiology with regard to extreme weather exposure.

Secondly, the data used to measure weather conditions in prior research typically came from weather stations which is prone to missing data problems and incomplete spatial coverage. It is unclear how representative a single station's measurements are for the surrounding climate especially in areas of complex terrain and land use[64,65]. For instance, there is sparse station density in mountainous regions which represent areas of diverse and complex climates[66]. This lack of spatial coverage leads to issues in exposure misclassification. Indeed, point based exposure assessments using data from airports have been shown to underestimate the magnitude of association between ambient temperature and adverse health outcomes[67,68]. The use of gridded climatological data is preferred in exposure assessments of extreme weather because it allows for complete spatial and temporal coverage of weather conditions[67,68].

Table 1-1:Summary of populations used to study ambient temperature and extreme weather events with COPD related health outcomes

Population[A]	Study Units[B]	Sample Size	Primary exposure(s)[C]	Outcome(s)	Study
General population	Counts	18,548	Temperature	Hospitalizations	Almagro et al., 2015[52]
		507,703	Temperature, precipitation, humidity	Hospitalizations	Chong et al., 2022[53]
		7,863	Diurnal temperature range	Mortality	Gu et al., 2022[63]
		197,143	Cold waves	Mortality	Hu et al., 2022[61]
		239,152	Temperature	Hospitalizations	Lam et al., 2018[69]
		397,026	Temperature	Hospitalizations	Li et al., 2021[55]
		3,263	Diurnal temperature range	Emergency department visits	Liang et al., 2009[51]
		84,571	Cold waves	Hospitalizations	Y. Liu et al., 2021[56]
		413,023	Temperature	Mortality	Luan et al., 2019[62]
		320,411	Temperature (heat)	Hospitalizations	Konstantinoudis et al., 2022[54]
		39,384	Temperature	Outpatient visits	Wang & Lin 2015[70]
		143,318	Temperature	Hospitalizations	Y. Zhang et al., 2020[57]
		523,307	Temperature (heat)	Hospitalizations	Y. Zhao et al., 2019[58]
	Individuals	162,338	Temperature	Hospitalizations	de Miguel Diez et al., 2019[59]
		229,133	Temperature	Emergency department visits and hospitalizations	Jo et al., 2021[50]
		16,254	Temperature (cold)	COPD exacerbations	Tseng et al., 2013[71]
COPD cohort		594	Temperature	COPD exacerbations	J. Lee et al., 2019[72]
		1,103	Temperature, humidity	Lung function	Lepeule et al., 2018[48]
		277	Temperature, humidity, atmospheric pressure	Hospitalizations	Lin et al., 2018[60]
		69	Temperature (heat)	COPD symptoms	McCormack et al., 2016[45]

		84	Temperature (cold)	COPD symptoms, lung function	McCormack et al., 2017[47]
		82	Temperature, humidity	COPD symptoms	Mu et al., 2017[49]

[A]General population studies gathered data from the population at-large in their study area. COPD cohort studies used a pre-defined group of individuals with COPD for their analysis.
[B]Counts refers to studies that used aggregate sums of COPD related health events in their analysis. Individual refers to studies that examined individual level health data.
[C]Exposures listed included only the primary meteorological exposure studied. Non-weather-related exposures are not listed.

Motivation for the dissertation

The limitations and gaps left by previous research motivated the studies developed for this dissertation which seeks to estimate individual level mortality risks associated with heat and cold waves among a population of individuals with COPD. Specifically, the population of study used in this dissertation is Veterans diagnosed with COPD in the United States from the Veterans Health Administration (VHA).

A primer on Veterans

A Veteran is an individual who served in the active armed forces and was discharged from duty under circumstances other than dishonorable[73]. Veterans are generally eligible for VHA care if they served at least 24 consecutive months or the full term of active duty which they were called upon, with some exceptions[74]. The VHA is the largest integrated healthcare system in the United States serving 9 million Veterans annually at over 1,000 medical facilities[75]. The VHA has a unified electronic health record system from 1999 to present day[75]. In 2018, 7% of the adult American population (18 million individuals) identified as Veterans with a median age of 65 years[76]. Approximately 2.9% of Veterans in 2018 did not have health insurance and 36.8% received VHA care at some point in time[76]. In 2021, nearly 20,000 Veterans experienced sheltered homelessness accounting for 8% of all adults experiencing sheltered homelessness[77]. Veterans experiencing sheltered homelessness accounted for 11 out of every 1,000 Veterans[77].

Veterans face several health challenges and are more likely to have greater levels of comorbidities than the general population. A recent national assessment found even after adjusting for age and smoking, Veterans were more likely to have multiple chronic conditions (2+ conditions) than non-Veterans[78]. Use of tobacco products is also high in this population. Findings from survey data reported Veterans had greater self-reported usage of tobacco products across all age and sex groups except males over 50 years of age compared to non-Veterans[79]. Overall, 29.2% of Veterans self-reported current tobacco use[79].

There are relatively high rates of COPD among the Veteran population. Previous studies estimated the prevalence of COPD ranged from 8% to 43%[80,81] much higher than the prevalence in the general population in the United States estimated at around 6%[14]. Veterans with COPD tend to be smokers, male and older[81]. Among Veterans with COPD, 54% are active smokers[81]. Akin to the global population, misdiagnosis of COPD is also prevalent in the Veteran population with one study reporting 38% of Veterans with COPD were overdiagnosed[82]. Veterans with COPD also suffer additional health challenges compared to Veterans without COPD. Veterans with COPD have higher all-cause and respiratory related inpatient and outpatient healthcare utilization (e.g. physician encounters, emergency department visits, total bed days of care), higher overall healthcare related costs, and one more comorbid condition on average[83]. One study of COPD related healthcare costs at a single VHA hospital found the total cost of COPD related healthcare encounters totaled $21.4 million in 2008 ($2.4 million in clinic visits, $0.21 million in emergency department visits, $18.7 million in hospitalizations and $0.89 million in prescriptions)[84]. The top 20% of COPD patients ranked by cost accounted for 86% of the total cost of COPD related healthcare[84].

While Veterans have access to the VHA as a healthcare provider, private insurance, Medicare and Medicaid serve as alternative options and some Veterans are dually enrolled using a combination of these coverage options. In previous work, reliance on VHA care was found to be dependent on age of the Veteran and access to VHA care[85]. VHA reliance was higher in Veterans over 65 and for those with shorter travel distances to a VHA healthcare facility[85]. Among Veterans dually enrolled in VHA and Medicaid,

VHA utilization was similar before and after Medicaid enrollment[86]. Factors associated with increased VHA reliance included shorter Medicaid enrollment periods, older age and having a service-related disability[86]. Factors associated with decreased VHA reliance included: months enrolled in Medicaid, managed care enrollment, Medicaid eligibility type, greater drive time to a VHA facility and Medicaid generosity and quality[86]. Another study of Veterans under age 65 who were dually enrolled in VHA and Medicaid found differences in utilization of VHA and Medicaid were dependent on the type of care received[87]. Dually enrolled Veterans went to the VHA for the majority of their outpatient care other than emergency department, obstetrics/gynecology and dental care visits and received most of their inpatient care from Medicaid except for mental health, respiratory and cancer care[87].

Foreword to the dissertation

In the subsequent chapters, a big data approach is applied to evaluate the associations between heat and cold waves and all-cause mortality among a population of Veterans all of whom have a COPD diagnosis.

Chapter 2, a methodological chapter, provides a treatment on the theory and practice of case-crossover studies. The case-crossover study design is implemented in each of the primary chapters of the dissertation and is integral to this work. Thus, a full description of its history and properties is critical for a full understanding of this dissertation.

Chapter 3, the first of three studies presented in this dissertation, establishes the relative and absolute magnitude of risk heat and cold waves confer on mortality in the overall population of Veterans with COPD using a time stratified case-crossover study design and conditional logistic regression models. Furthermore, health disparities by race, ethnicity, age and gender are evaluated and described.

Chapter 4 seeks to distinguish nuances in heat and cold wave mortality risk via novel effect measure modifiers including additional underlying comorbidities, smoking status and urbanicity of Veterans. This was completed using the same dataset used in Chapter 3. A time stratified case-crossover study was designed and conditional logistic

regression models with a distributed lag model (DLM) framework were used to estimate single day and cumulative lag day heat and cold wave associated mortality risks.

Chapter 5 evaluates a novel dual climate exposure by estimating the added risk heatwaves confer on mortality when they co-occur during a drought event. This lays the groundwork for future studies to measure compound climate related hazards and their impacts on climate sensitive diseases. The study design and statistical models used were the same as those presented in Chapter 4.

Chapter 2: A history & properties of the case-crossover study design

Properties of the case-crossover study design

A case-crossover study[88] is a case only study design containing elements of both a matched case control study and a crossover study where each person serves as his or her own control to evaluate the effects of an intermittent exposure on an acute outcome with an abrupt onset[89]. Therefore, inferences in case-crossover studies are based on a comparison of the exposure distribution rather than the risk of disease in populations[90]. The case-crossover study is uniquely positioned to measure the health effects of ephemeral exposures such as ambient temperature, heatwaves, cold waves, and ambient air pollution.

Case-crossover study designs are most optimal when three conditions are fulfilled, 1) the exposure is intermittent 2) the effect of the exposure on disease risk is instantaneous and transitory and 3) the disease has an sudden onset[89]. The goal of a case-crossover study is to answer the question of whether the case-defining event was triggered by something unusual that happened before by comparing exposure levels immediately prior to the case-defining event with the same individual's exposure levels at several referent times that are meant to represent typical values of exposure that an individual experienced[89,91]. Thus, a major challenge in case-crossover studies is determining how unusual the exposure was that preceded the case-defining event which varies depending on the exposure and disease under study[89]. Studies that include the following attributes are most suitable for case-crossover study designs.

1) *Acute cases*: The disease under study should have an abrupt onset and a short latency period for detection[89,90]. Additionally, the time between initial exposure and onset of disease should be short[90].
2) *Crossover*: At least some of the individuals in the study must have crossed over from low to high exposure or vice versa[89].
3) *Ephemerality of effect*: The exposure must be ephemeral and should vary within short time intervals[89].

In facilitating further discussion of the case-crossover design, several key terms must first be defined.

- *Induction period*: the time from the beginning of the exposure to onset of the disease. The maximum induction period is analogous to washout periods

developed for crossover studies after which carryover effects are hypothesized not to occur[89].

- *Trigger*: the suspected cause of a case-defining event that is proximal in time to that event[89].
- *Effect period*: the time between the minimum and maximum induction periods in the population[89].
- *Hazard period*: the time window after a trigger occurs and when the population experiences an increased risk of the outcome caused by the trigger[89]. The hazard period is equal to the effect period plus the duration of the exposure[89].
- *Referent period (time)*: the times at which the case-defining event did not occur. The exposure distribution during the referent period is compared against the exposure distribution during the hazard period to determine if the exposure (trigger) is associated with an increased risk of disease[92].

The estimated effect and hazard periods used in research are typically imprecise since they must incorporate variation among the individual induction times and the uncertainty in the timing of the trigger and the health outcome[89].

Another way of thinking about case-crossover studies is that they are used to evaluate triggers of a health outcome. This can be expressed in a counterfactual statement as "*some of the exposed cases would not have occurred at the time that they did had they not been exposed immediately prior to the case-defining event*"[89]. This distinction differentiates case-crossover studies from other study designs including case control and cohort studies since case-crossover studies ask the question of "*why now?"* whereas case control and cohort studies ask the question of "*why them?"*[89]. Therefore, the impetus of case-crossover studies is to determine why individuals experience a disease outcome at one moment in time instead of some other time in the recent past. In constructing a causal hypothesis, it could be stated that among individuals who had the case-defining event, it is expected that exposure levels during the hazard period were higher on average than exposure levels during the referent period[90].

Beyond the three previously listed conditions that maximize the utility of a case-crossover study (acute cases, crossover and ephemeral effects), several other assumptions must be met to ensure validity of the study design. Case-crossover studies assume the disease is rare in the population and that the baseline risk of the outcome is stable within the referent period[88]. However, a recent simulation study found little evidence for bias

and good coverage of confidence intervals when applying the case-crossover study design to pre-term births, a health outcome known for unstable risk over the course of a pregnancy[93]. After properly selecting referent times to adjust for long term and seasonal trends in the exposure, the exposure distribution should be stationary (i.e. all temporal trends in the exposure should be removed)[94,95]. Finally, when the relevant hazard period of exposure is specified, there should be no carryover effects of the exposure beyond the hazard period (i.e. the exposure can only cause an increased risk of the case-defining event during the hazard period and cannot confer increased risk beyond the specified hazard period). Otherwise, exposure in the distant past could be the cause of the case-defining event rather than the hypothesized exposure during the hazard period[91].

In being a self-matched study design, case-crossover studies adjust for time invariant confounding, both measured and unmeasured, by design[92]. However, this does not mean case-crossover studies are immune to other biases including selection bias, time varying confounding and other systematic biases which threaten the validity of effect estimates. A major decision in the design of case-crossover studies is the selection of referent periods in which exposure is assessed to compare against exposure during the hazard period. This is important for two reasons, 1) environmental exposures such as air pollution and weather are shared in the population and have seasonal and long-term trends. Therefore, it is important to select referent periods in such a way that temporal confounding such as season, long term trends and day of week effects are adjusted to satisfy the stationarity assumption and 2) the conditional logistic regression model (the most commonly used statistical model in case-crossover studies) becomes biased when the referent times are not chosen a priori and are functions of the observed event times (case-defining events), known as overlap bias[96]. Overlap bias is a purely mathematical bias that is caused by selecting non-disjoint strata to partition the population in a matched case control study[96].

Referent selection strategies for case-crossover studies

Several selection strategies have been proposed to select referent periods. In the selection of referent periods, case-crossover studies make the implicit assumption of stationarity for the exposure[97]. Five distinct referent selection strategies have been

proposed, each with their own advantages and disadvantages. Designs can be classified as localizable or non-localizable[96]. Localizable designs provide unbiased estimates from the conditional logistic regression model and non-localizable designs are those where no unbiased conditional logistic regression estimates are available[96]. The localizable designs can be further broken down into ignorable and non-ignorable categories. In ignorable designs, the referent sampling scheme can be ignored in completing the analysis (i.e. the selection of referent times does not depend on the timing of the case-defining event). For non-ignorable designs, the referent sampling scheme cannot be ignored, and the referent times being used are dependent on the timing of the case-defining event (i.e. overlap bias). Overlap bias is usually small, but the direction and magnitude of the bias is unpredictable and it can be completely avoided using localizable, ignorable designs[96]. In the following section is a list of the five case-crossover referent selection strategies, their properties, advantages and disadvantages.

1) **Unidirectional sampling**[88]: One or more referent times (e.g. days) are selected prior to the case-defining event[98].
    a. Advantages: Confounding by season and day of week can be adjusted for by choosing referent times that are temporally proximal to the case-defining event[97].
    b. Disadvantages: Non-localizable. Selecting referent times that only occur before the case-defining event can lead to time trend bias in exposures such as air pollution[97].
2) **Full stratum bi-directional sampling**[99]: For each case-defining event, all the days in the time series other than the day of the case-defining event are chosen as controls[98].
    a. Advantages: Localizable and ignorable. Time trend in exposure is controlled for by design[97].
    b. Disadvantages: Time dependent confounding must be adjusted for since the referent period is large[97].
3) **Symmetric bi-directional sampling**[94]: Two or more referent times are chosen at equal distances in time from the day of the case-defining event[98]. (e.g. $\pm$7 and $\pm$ 14 days)
    a. Advantages: If the referent times are within the same season and on the same day of week as the case-defining event, bias from time trends and confounding by season and day of week are adjusted for by design[97].
    b. Disadvantages: Non-localizable[97].
4) **Semi-symmetric bi-directional sampling**[100]: Two candidate referent times are identified at equal distances in time from the day of the case-defining event (e.g.

±7 days) and one is randomly chosen to use as the control[98]. If only one of these days is available (i.e. as a result of the event day being at either end of the exposure time series), then it serves as the referent day by default[97].
    a. Advantages: Localizable. Confounding by season and day of week can be adjusted for by design if the candidate referent times are selected using a small lag that is a multiple of 7[97].
    b. Disadvantages: Non-ignorable[97].
5) **Time stratified sampling**[101]: Referent times are selected from pre-specified strata of time that are fixed and disjointed (e.g. year, month and day of week)[98]. This typically results in 3-4 referent days per case-defining event day.
    a. Advantages: Localizable and ignorable[97]. There is no bias from time trends since there is no pattern in the selection of referent times relative to the day of the case-defining event (i.e. the selection of referent times is random and does not depend on the case-defining event). Confounding by season and day of week can be adjusted for by design by choosing referent times that are in the same year, month and day of week as the case-defining event[97].
    b. Disadvantages: Even when selecting referent times within a single month, there may still be residual seasonal trends in the exposure time series for exposures that have highly seasonal patterns such as air pollution and ambient temperature[102]. Including decomposed weekly time series trends of the exposure has been proposed as a method for adjustment[103].

While some bias may occur in selecting referent times that occur after an individual is no longer at risk of experiencing the disease, under the rare disease assumption, this bias is typically small and negligible[101]. In fact, the exclusion of referent times that occur after the case-defining event would typically induce greater problems in selection bias[101]. More referent times may improve the efficiency of case-crossover studies but as more are added, confounding bias becomes a bigger threat[97].

Bias & confounding in case-crossover studies

Biases in case-crossover studies can result from violating assumptions integral to the study design, selection bias or confounding. The first category of biases arises from violating key assumptions of the case-crossover study design including stationarity, autocorrelation and overlap bias. Violating the stationarity assumption results from lack of proper control for seasonal and long term trends in the exposure, disease and in confounders that need to be adjusted for via the selection of referent times[92]. Autocorrelation of the exposure between the hazard period and control periods (referent

times) violates the assumption of independence between exposure in the hazard and control periods (i.e. carryover effect)[92]. This is similar to the importance of a washout period in crossover studies and can be adjusted for by choosing referent times that are sufficiently spaced in time from the case-defining event[97]. Finally, overlap bias results from choosing referent times that are dependent upon the timing of the case-defining event[96] which can be overcome by using a time stratified referent sampling scheme[97].

The second category of biases arise from selection and confounding bias. Selection bias in case-crossover studies can occur when the referent periods are not representative of the exposure distribution in the hazard period which can happen even when the exposure distribution is stationary[95]. This type of selection bias can be reduced by choosing shorter referent spacing lengths from the case-defining event[95]. The selection of referent times may also be subject to selection bias if selection is not independent of the exposure[92].

Confounding bias can occur via residual temporal confounding by improperly adjusting for seasonal and long-term trends in the exposure through the selection of referent times[95]. Confounding may also occur via transient co-exposures that are not controlled for in the primary analysis[92]. Since each case serves as their own control in a case-crossover study, confounding by stable and slow moving characteristics both measured and unmeasured are adjusted for by design[92]. Over short periods of time, the person-time in the hazard period is assumed to be exchangeable with that individual's person-time in the referent period since the baseline risk of the disease is expected to be constant within the referent period[92]. Conditional exchangeability can be obtained in a case-crossover study by properly stratifying on time through the referent selection strategy and by choosing referent times that are close enough in time to the case-defining event such that exchangeability is satisfied but separate enough from the hazard period so that exposure is independent from the case-defining event to prevent short-term autocorrelation and carryover effects[92].

While using all person-time available via approaches such as a cohort study may provide greater statistical accuracy, in the absence of confounding and selection bias both approaches of using the entirety of the person-time and a sample of the person-time (e.g. case-crossover studies) should yield equivalent results in expectation. This is because all

case control studies can be viewed as an efficient sampling from the underlying pool of available person-time in the population[104], and recall that case-crossover studies are similar to matched case control studies. This notion of sampling person-time explains why the odds ratio estimated from a case-crossover study is equivalent to an incidence rate ratio in a cohort study[92].

Chapter 3: Heat and cold wave related mortality risk among united states veterans with pre-existing chronic obstructive pulmonary disease (COPD): a case-crossover study

Background: Chronic obstructive pulmonary disease (COPD) is a heterogeneous pulmonary disease affecting 16 million Americans. Individuals with COPD are susceptible to environmental disturbances including heat and cold waves that can exacerbate disease symptoms.

Methods: We collected individual level data with geocoded residential addresses from the Veterans Health Administration on 377,545 deceased patients with COPD (2016 – 2021). A time stratified case-crossover study was designed to estimate the incidence rate ratios (IRR) of heat and cold wave mortality risks using conditional logistic regression models examining lagged effects up to 7 days. Attributable risks (AR) were calculated for the lag day with the strongest association for heat and cold waves respectively. Effect measure modification by age, gender, race and ethnicity was also explored.

Results: Heatwaves had the strongest effect on all-cause mortality at lag day 0, IRR: 1.04 (95% CI: 1.02, 1.06) with attenuated effects by lag day 1. The AR at lag day 0 was 651 (95% CI: 326, 975) per 100,000 Veterans. The effect of cold waves steadily increased from lag day 2 and plateaued at lag day 4, IRR: 1.04 (95% CI: 1.02, 1.07) with declining but still elevated effects over the remaining 7-day lag period. The AR at lag day 4 was 687 (95% CI: 344, 1,200) per 100,000 Veterans. Differences in risk were also detected upon stratification by gender and race.

Discussion: Our study demonstrated harmful associations between heat and cold waves among a high-risk population of Veterans with pre-existing COPD using individual level health data. Future research should emphasize using individual level data to better estimate the associations between extreme weather events and health outcomes for high-risk populations with pre-existing chronic medical conditions.

Introduction

Anthropogenic climate change is causing harmful planetary effects with increased frequency, intensity, duration and geographic extent of extreme weather events including heatwaves, droughts, wildfires and floods[1,2]. Furthermore, climate change disproportionately affects children, the elderly, racial minorities, impoverished communities, and those living with underlying comorbidities such as chronic obstructive pulmonary disease (COPD)[2,105].

COPD is a heterogeneous, degenerative pulmonary disease characterized by airflow obstruction[7]. In the United States, approximately 6.2% of adults had a diagnosis of COPD in 2017[106]. While the overall age adjusted mortality rates of COPD in the United States decreased in recent decades, improvements in COPD mortality were not equally distributed among the population. Age adjusted mortality rates in males have decreased over time, but age adjusted mortality rates in females remained relatively unchanged[15,16]. African American women were the only race-sex combination that had an increase in age adjusted mortality rates from 2004 – 2018[15]. Individuals with COPD are more susceptible to environmental perturbations due to compromised respiratory health and high rates of comorbidities which lead to further debilitation and poorer health[18,24].

While extremes in ambient temperature (heat and cold) are known to increase the risk of general mortality[107–109], there is a dearth of evidence on heat and cold wave impacts at the individual level for populations with underlying chronic disease. Many studies evaluate the health risks from heat and cold waves using ecological time series analyses, however, these studies are limited in the ability to make inferences at the individual level, typically relying on aggregated counts of morbidity or mortality using hospital discharge or non-specific government data. This complicates the development of public health interventions and impedes understanding of disease etiology by failing to assess individual level characteristics that may cause an individual to be more or less susceptible to extreme heat and cold. In addition, research findings based on the general population may not accurately represent the health risks experienced by those living with underlying chronic diseases who may be more susceptible to climate related hazards.

To facilitate the development of improved public health interventions and climate change adaptation plans, we designed a time stratified[101] case-crossover study[88] to examine the associations between heat and cold waves with all-cause mortality among a population of individuals diagnosed with pre-existing COPD using data from the Veterans Health Administration (VHA) in the United States (2016 to 2021). We evaluated health disparities in heat and cold wave mortality risk for several effect modifiers: age, gender, race and ethnicity.

Methods

Study population

We extracted electronic health record data from the Veterans Health Administration (VHA) Corporate Data Warehouse (CDW). The study population was derived from a source cohort of Veterans[73] who had a diagnosis of COPD between 2016 to 2019 from the VHA (N = 1,124,705). We identified patients with COPD using at least two clinical encounters with an International Classification of Diseases Ninth Revision or Tenth Revision codes (ICD-9: 490, 491.XX, 492.XX, 496 or ICD-10: J40, J41.X, J42, J43.X, J44.X) for COPD (Table S3-1)[110]. This included both Veterans who were newly diagnosed or who had prevalent COPD between 2016 to 2019. We included patients aged $\geq$35 and <100 years of age at the initial date of COPD diagnosis.

Our study included exposure information for only those Veterans diagnosed with COPD who were deceased. Mortality data is updated quarterly by the VHA using data from the Social Security Master Death File, the Medicare Vital Status File and the Veterans Benefits Administration's Beneficiary Identification and Records Locator System. Mortality events are only recognized if death certificates were made at a VHA facility or under their auspices or presented to the VHA by the National Cemetery Administration. This is done to protect Veterans who are alive from being misclassified as deceased[111].

Veterans living outside of the contiguous United States or who lived outside of the range of our weather data raster surface were excluded. Our outcome of interest was the association between heat and cold waves with all-cause mortality among this targeted

Veterans population with pre-existing COPD. We obtained patients' age at death, and self-reported: gender (man, woman, transgender), race (American Indian / Alaska Native, Asian American / Pacific Islander, Black, and White), ethnicity (Hispanic and non-Hispanic) and a geocoded residential address from the VHA Patient Enrollee files in the CDW[111]. Race is a social construct to consider when evaluating the impacts systemic discrimination may have on exposure to climate related hazards and subsequent health outcomes. Unlike private healthcare systems, the VHA is an equal access healthcare system with presumably fewer barriers to care, which may attenuate disparities in mortality from heat and cold wave exposure between race groups.

Environmental data

We assigned daily meteorologic conditions (mean ambient temperature, total precipitation, mean specific humidity, and mean wind speed) to the residential addresses of the study cohort using data from GridMet.[112] GridMet is a blended dataset of Parameter elevation Regressions on Independent Slopes (PRISM) and the North American Land Data Assimilation System (NLDAS-2), obtained at a spatiotemporal resolution of daily 4 x 4km grid cells[112].

A 30-year distribution of weather data (1992 to 2021) was used to calculate percentile thresholds to determine heat and cold wave status. Using 30 years of meteorological data ensured we captured heat and cold waves that were anomalous for each Veterans' geocoded residence in comparison to an historical record of usual weather conditions. We defined heatwaves as 2 or more consecutive days whose mean ambient daily temperature was above the 90th percentile of warm season (April to September) mean ambient daily temperature values from 1992 to 2021 and cold waves as 2 or more consecutive days whose mean ambient daily temperature was below the 10th percentile of cold season (October to March) mean ambient daily temperature values from 1992 to 2021. The use of less extreme percentiles to define heat and cold waves is a newer concept in the climate and health literature[56,113–116], but important for a COPD study population that may be more susceptible to climate change and have a lower tolerance than the general population.

Daily mean fine particulate matter ($PM_{2.5}$) concentrations were obtained from the United States Environmental Protection Agency (EPA)[117] air monitor networks from December 1, 2015 to the most recent available data at the time of our analysis, November 11, 2021. We removed outlying days exceeding the 99.5^{th} and 0.5^{th} $PM_{2.5}$ percentiles as these may have been anomalies in the data recording process and set any days with negative values for $PM_{2.5}$ to 0. Daily concentrations were assigned by averaging all active $PM_{2.5}$ monitor values on a given day within a 10km buffer of each Veteran's geocoded address.

Study design

We examined the associations between heat and cold waves with all-cause mortality using a time stratified[101] case-crossover[88] study design. Each Veteran's date of death was matched with referent days in the same year, month and day of week as the date of mortality (event day), adjusting for confounding by season and day of week[97]. Under this matching strategy, each Veteran was guaranteed at least 3 referent days. Since the case-crossover study design is a self-matched study, both observed and unobserved time-invariant confounding are controlled for by design, including unmeasured risk factors such as comorbidities, smoking history, genetics or lifestyle[92]. We adjusted for daily time varying weather confounders including precipitation, specific humidity, and wind speed. Specific humidity is a mass-based measurement of atmospheric moisture and is a better representation of suspended water vapor than relative humidity[118]. We also adjusted for holiday status which included all federally recognized United States' holidays[119] and several other major holidays including Christmas Eve, New Year's Eve, Easter and Halloween.

Statistical analyses

Conditional logistic regression models were used to estimate incidence rate ratios (IRR)[92,120] describing associations between heat and cold wave exposure with all-cause mortality. Heat and cold wave assessments were restricted to warm (April to September) and cold (October to March) seasons respectively. We examined delayed effects from lag day 0 to 7 (i.e. day of death to 7 days prior) where each lag was evaluated in a separate model.

Our statistical models assumed the following form:

$$logit(\pi_{ik}) = \alpha_i + \beta_1 x_{ik1} + \beta_2 x_{ik2} + \beta_3 x_{ik3} + \beta_4 x_{ik4} + \beta_5 x_{ik5}$$

Where β_1 is an indicator variable to denote heat or cold wave status for the i^{th} person on the k^{th} day of the matched set respectively, β_2 and β_3 are linear terms for precipitation and wind speed, β_4 is a linear term for specific humidity in the cold season model but is a natural cubic spline with 5 degrees of freedom for the warm season model, and β_5 is an indicator variable to denote holiday status. An assessment of non-linearity among exposure variables identified heatwave status and specific humidity to have a non-linear relationship. We used AIC to determine an optimal parameterization to account for this non-linear relationship and a natural cubic spline with 5 degrees of freedom was chosen as the best smoother for specific humidity. No other non-linear relationships were detected, and linear terms were deemed appropriate.

To test for effect modification, we used stratified data subsets based on the effect modifiers of age, gender, race and ethnicity. For age, we created a binary stratification for Veterans <70 and >=70 years of age. Models of heat and cold waves estimated IRRs for each subgroup. To determine the presence of effect modification, we employed a Z-test[121] to compare the IRRs of each strata at lag 0 to 7 days (Equation S1). Missing data were treated as a separate stratum in our subgroup analyses. Attributable risks (AR) for the overall population were calculated for the strongest lag day (Equation S2).

All statistical analyses were completed in R statistical software (version 4.1)[122] within the secure VA Informatics and Computing Infrastructure environment.

Sensitivity analyses

We completed sensitivity analyses to examine model robustness against 1) definitions of heat and cold waves (intensity, duration and reference distribution), 2) potential confounding from ambient air pollution, and 3) the COVID-19 pandemic.

Multiple heat and cold wave definitions were evaluated. First, we reassigned heat and cold waves using alternative 95th, 97.5th and 99th percentiles (heatwaves) and 5th, 2.5th and 1st percentiles (cold waves) of the 30-year mean temperature reference distribution

during the warm and cold seasons to test model robustness to more severe heat and cold wave events. Second, we applied a shorter reference distribution of 20 years (2002 to 2021) to assess model sensitivity to recent patterns of climate exposure. Third, we excluded Veterans who were exposed to heat or cold waves that lasted longer than 10 days and compared model results against our primary analysis. This was performed because under our primary definitions, some heat and cold wave events were anomalously long in duration. Fourth, we excluded Veterans residing in areas with relatively mild 30-year percentile thresholds for heatwaves (<25°C) and cold waves (>5°C) and compared model results against our primary analysis. The purpose of this evaluation was to test the degree of influence Veterans living in areas with mild climates had on the overall associations between heat and cold waves with all-cause mortality.

We assessed the potential role of air pollution, which could not be considered in our main models due to spatially incomplete air monitor data, in a sub-evaluation. We restricted our dataset to Veterans living within a 10km buffer of EPA $PM_{2.5}$ air monitors and ran separate models with and without adjustment for daily $PM_{2.5}$ as a confounder for both heat and cold wave events. Estimates for models with and without air pollution were compared for the amount of confounding bias that may be present. Finally, since increased mortality likely occurred during the COVID-19 pandemic, we ran a stratified analysis comparing Veterans who died pre and post January 31, 2020, the day the United States Department of Health and Human Services declared COVID-19 a public health emergency[123]. State level COVID-19 deaths at the weekly time interval were acquired from the National Center for Health Statistics[124] to include as a time varying confounder if stratified analyses suggested differences in the heat and cold wave effect estimates pre and post the COVID-19 public health emergency declaration.

Ethics Statement

This study was approved by the institutional review boards at the Minneapolis VA and the University of Minnesota.

Results

Descriptive statistics

The source cohort of Veterans with COPD included 1,124,705 individuals. For our case-crossover study, we identified 377,545 deceased Veterans with COPD. These deceased Veterans lived in 3,058 out of 3,109 counties in the United States (98.4%). All 48 states and the District of Columbia were represented in the study sample (Figure 1). The study population was predominately male and older with the largest racial / ethnic group being non-Hispanic White (Table 1-1). All Veterans identified died by December of 2021.

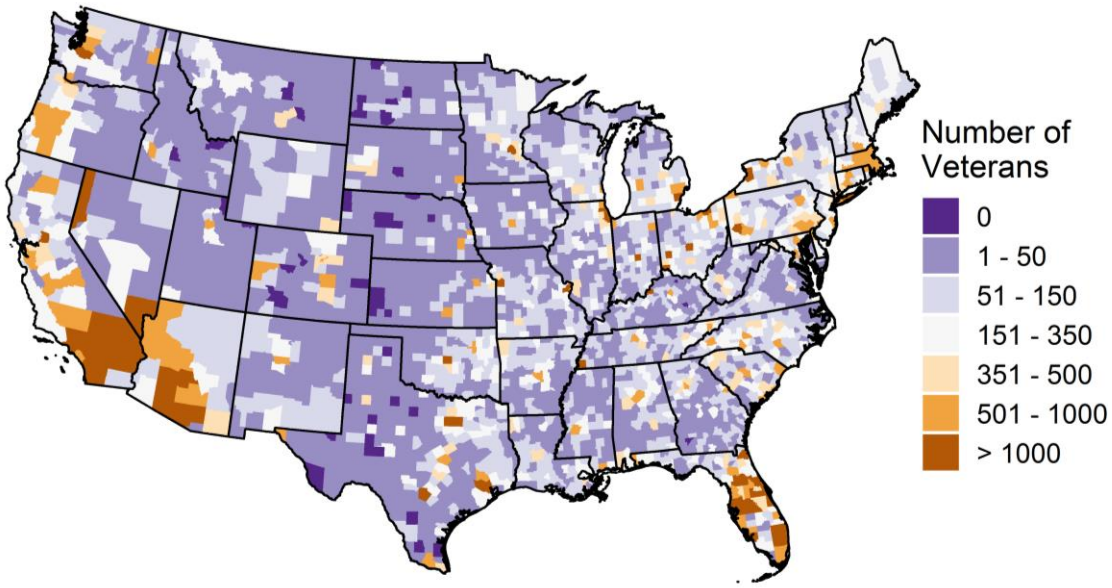

Figure 3-1: County level totals of deceased Veterans with COPD (2016 to 2021) in the VHA healthcare system

Table 3-1:Baseline characteristics of deceased Veterans with COPD (2016 to 2021) in the VHA healthcare system

Age (years)	
<70 years, frequency (%)	96,437 (25.6%)
Gender, frequency (%)	
Cisgender male	369,535 (97.9%)
Cisgender female	8,004 (2.1%)
Transgender	6 (<1%)
Race, frequency (%)	
White	298,978 (79.2%)
Black	42,754 (11.3%)
American Indian / Alaska Native (AIAN)	3,329 (<1%)
Asian American / Pacific Islander (AAPI)	3,600 (<1%)
Missing	28,884 (7.7%)
Ethnicity, frequency (%)	
Non-Hispanic	353,983 (93.8%)
Hispanic	7,889 (2.1%)
Missing	15,673 (4.1%)

Exposure to heat and cold waves in our study population occurred with 28.4% and 24.7% of patients having either an event or referent day exposed to heatwaves and cold waves respectively (Table 3-2). A total of 183,725 patients died during the warm season resulting in a warm season mortality rate of 16,335 per 100,000 patients in this cohort of Veterans with COPD. Of those who died during the warm season, 17,621 patients died during a heatwave event (9.6% of warm season mortality events). A total of 193,820 patients died during the cold season resulting in a cold season mortality rate of 17,233 per 100,000 patients in the entire Veteran population with COPD. Of those who died during the cold season, 13,961 patients died during a cold wave event (7.2% of cold season mortality events) (Table 3-2). The total number of study days (event and referent days) in the case-crossover study classified as heat and cold waves were 9.4% and 7.1% of the total study period days within the warm and cold seasons respectively (Table 3-2).

Table 3-2: Frequencies of heat and cold wave exposure for individual Veterans and by event and referent day status

	Warm Season		Total
	Heatwave	Non-heatwave	
Exposed Veterans[A]	52,258 (28.4%)	131,467 (71.6%)	183,725
Exposure during event day[B]	17,621 (9.6%)	166,104 (90.4%)	183,725
Exposure during referent day[C]	58,246 (9.3%)	568,087 (90.7%)	626,333
Total study days[D]	75,867 (9.4%)	734,191 (90.6%)	810,058
	Cold Season		
	Cold wave	Non-Cold wave	
Exposed Veterans	47,802 (24.7%)	146,018 (75.3%)	193,820
Exposure during event day	13,961 (7.2%)	179,859 (92.8%)	193,820
Exposure during referent day	46,355 (7.1%)	610,286 (92.9%)	656,641
Total study days	60,316 (7.1%)	790,145 (92.9%)	850,461

[A]Where Veterans who were exposed on either an event or referent day were considered as exposed. This row represents counts of unique deceased Veterans.
[B]Counts only include exposure during the event day for each deceased Veteran.
[C]The unit of measurement for this row is days as Veterans have multiple matched referent days.
[D]Where the total number of event and referent days used for the study were included in the totals for this row.

Table 3-3 demonstrates higher mean ambient temperatures during heatwave days on which patients died compared to non-heatwave days and lower mean ambient temperature during cold wave days on which patients died compared to non-cold wave days. Non-heatwave / non – cold wave days tended to have greater precipitation compared to heatwave days and cold wave days. Heatwave days tended to have greater atmospheric moisture than non-heatwave days, the reverse was seen for cold waves (Table 3-3).

Table 3-3: Meteorological data summaries on days of mortality for Veterans with COPD (2016 to 2021) in the VHA healthcare system stratified by heat and cold wave status

Exposure	Heatwave	Non-Heatwave	Cold wave	Non-cold wave
Mean temperature (°C) Mean (SD)	27.91 (3.07)	20.49 (6.41)	-4.55 (8.64)	9.01 (8.18)
Total precipitation (mm) Mean (SD)	2.27 (6.90)	3.66 (10.19)	1.25 (4.45)	2.86 (8.21)
Mean specific humidity (g/kg) Mean (SD)	14.1 (3.97)	10.5 (4.41)	2.27 (1.72)	5.33 (3.24)
Mean wind speed (m/s) Mean (SD)	3.39 (1.34)	3.75 (1.54)	4.69 (2.09)	4.27 (1.86)

Overall associations

Associations between heatwaves and all-cause mortality showed the strongest effect on lag day 0 with an IRR of 1.04 (95% CI: 1.02, 1.06). Effects lasted until lag day 1 (IRR: 1.02, 95% CI: 1.00, 1.04) after which heatwave effects became attenuated (Figure 3-2). There was minimal effect of measured confounders on the heatwave effect estimate comparing crude and adjusted models (Table S3-2). Among patients exposed to heatwaves on lag day 0, 651 (95% CI: 326, 975) deaths per 100,000 were attributable to heatwaves. Cold waves increased the risk of all-cause mortality from lag days 2 to 7 with the strongest effect on lag day 4 with an IRR of 1.04 (95% CI: 1.02, 1.07). Effects of cold waves gradually increased from lag day 2, plateaued at lag day 4, and decreased through lag day 7 (Figure 3-2). A comparison of crude and adjusted cold wave models indicated potential confounding by measured confounders primarily on lag days 0 to 2, but minimal confounding of effect estimates from lag days 3 to 7 (Table S3-2). Among patients exposed to cold waves on lag day 4, 687 (95% CI: 344, 1,200) per 100,000 deaths were attributable to cold waves.

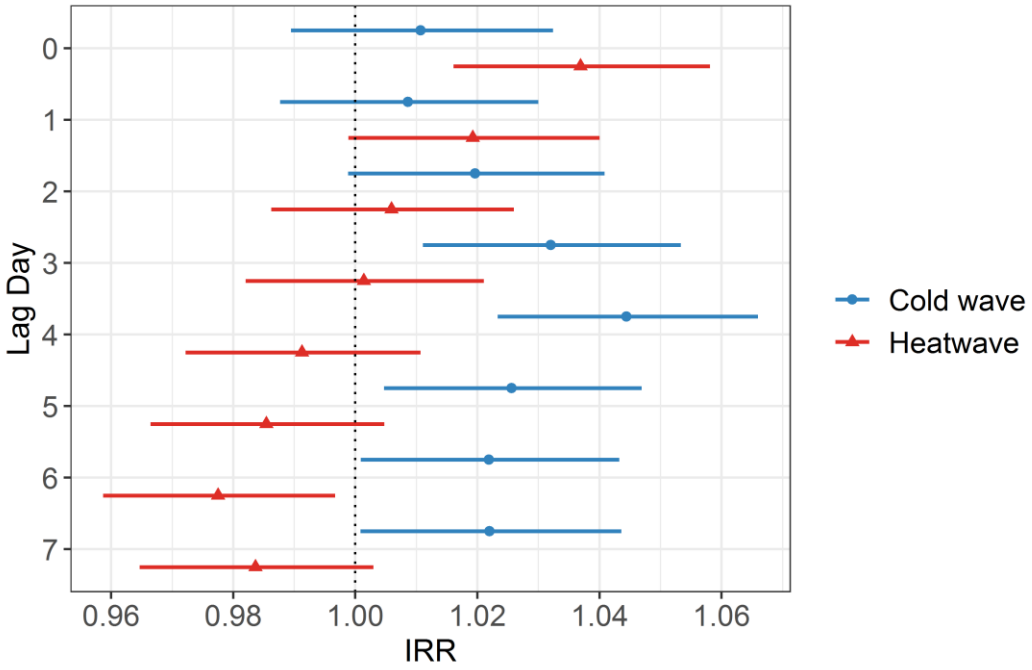

Figure 3-2: Adjusted incidence rate ratios (IRRs) for heat and cold waves effects on all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 to 7

Age

Heatwaves increased the risk of all-cause mortality within the younger (age <70 years) group from lag days 0 to 2 with the strongest effect detected on lag day 0 (IRR: 1.05, 95% CI: 1.01, 1.10) whereas in the older (age 70+) group, heatwave effects were only seen on lag day 0 (IRR: 1.03, 95% CI: 1.01, 1.06) (Figure 3-3). Cold wave associated mortality risks were observed in the younger age group from lag day 2 to 6 with the highest risk at lag days 3 and 4 (IRR lag day 3: 1.05, 95% CI: 1.00, 1.09). In the older age group cold wave related effects persisted from lag day 3 to 5 and lag day 7 with the highest risk at lag day 4 (IRR: 1.04, 95% CI: 1.02, 1.07) (Figure 3-3). Age group estimates for heat and cold waves were not statistically different from each other (Table S3-3).

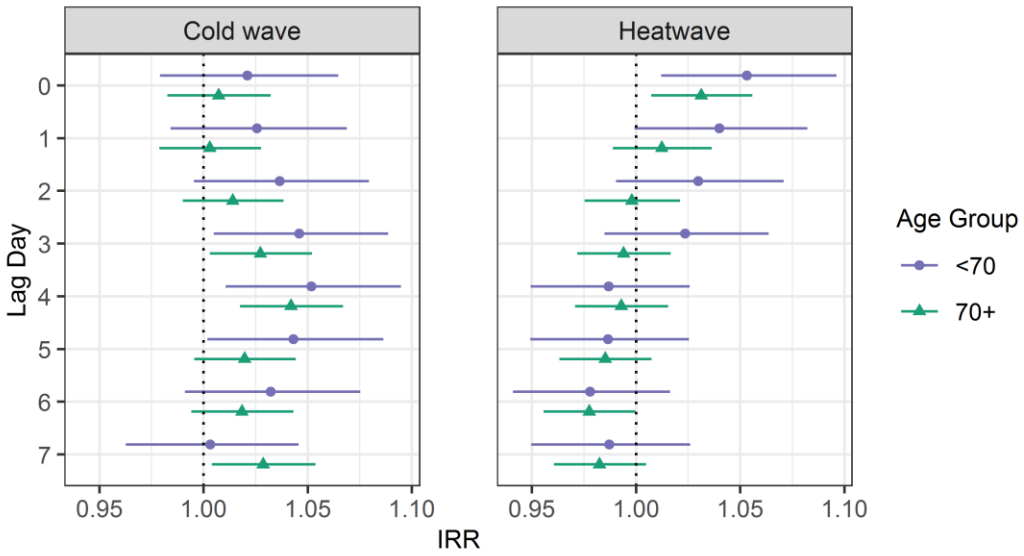

Figure 3-3: Age stratified heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 to 7

Gender

Cisgender men had heatwave related mortality risk at lag day 0 (IRR: 1.03, 95% CI: 1.01, 1.06), whereas cisgender women had heatwave associated mortality risk from lag days 0 to 2 with the greatest estimated risk on lag day 1 (IRR: 1.26, 95% CI: 1.10, 1.44), a 25% significant difference in risk compared to cisgender men on that same day (Figure 3-4, Table S3-4). For cold waves, cisgender men had an elevated risk of mortality at all lag days 2 to 7 with the greatest risk seen on lag day 4 (IRR: 1.04, 95% CI: 1.02, 1.07). The point estimates for cold wave related mortality among cisgender women were similar to cisgender men, however the estimates were less statistically precise (Figure 3-4). A small number of individuals identified as transgender (n = 6) and were excluded.

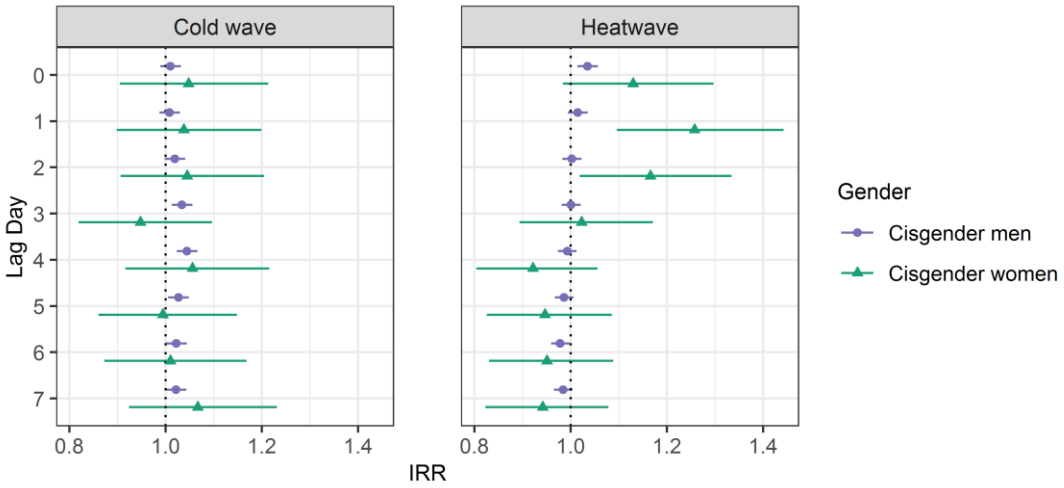

Figure 3-4: Gender stratified heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 – 7

Race

Black patients had the largest overall risk of heatwave associated mortality among all race groups with the greatest risk on lag day 0 (IRR: 1.09, 95% CI: 1.02, 1.15). White patients also showed heightened, but smaller heatwave mortality associations on lag day 0 (Figure 3-5) while all other race groups showed no associations with heatwaves (Table S3-5). AIAN patients had relatively large cold wave related mortality risks on lag days 3 to 5 with the greatest effect seen on lag day 4 (IRR: 1.32, 95% CI: 1.08, 1.62). Among White patients, cold wave associations with mortality were not detected until lag day 3 with gradually increasing risk that plateaued at lag day 4 (IRR: 1.04, 95% CI: 1.02, 1.07) with lower but heightened risks through lag day 6 (Figure 3-5). AAPI and Black patients' point estimates for cold wave related mortality risk followed a similar trend to White patients, however the estimates were less statistically precise driven in part by a smaller sample size compared to White patients (Table S3-5).

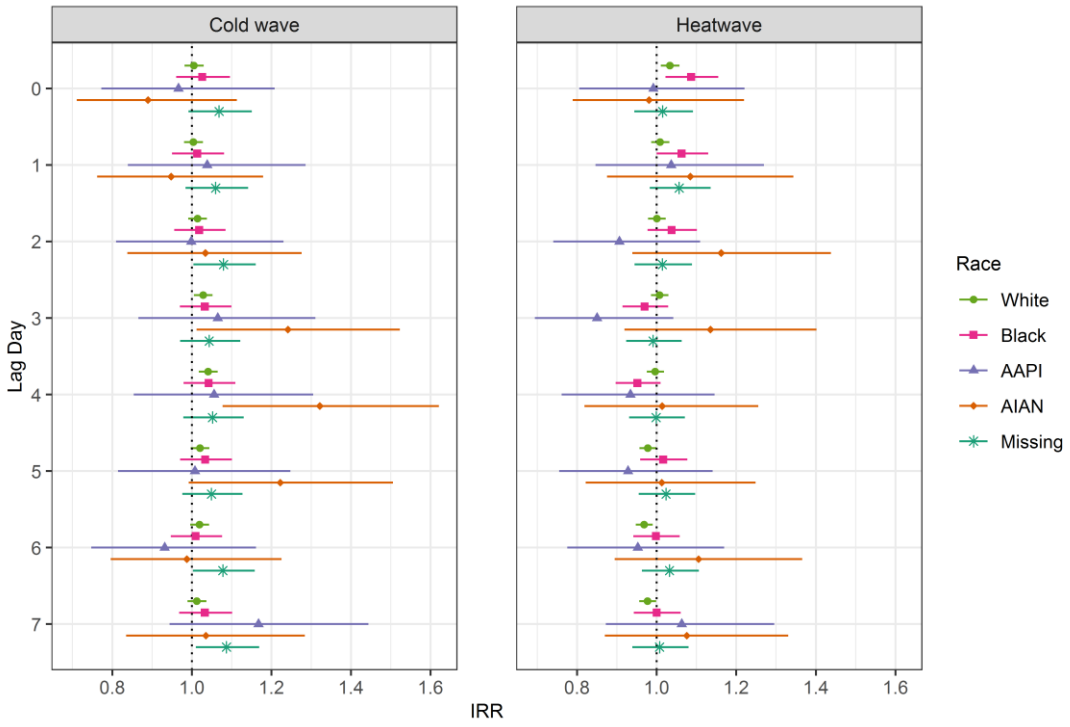

Figure 3-5: Race stratified heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 – 7 (AAPI – Asian American and Pacific Islander, AIAN – American Indian and Alaska Native)

Ethnicity

Heatwave effects among Non-Hispanic patients lasted from lag days 0 to 1 with the strongest effect on lag day 0 (IRR: 1.04, 95% CI: 1.02, 1.06). Hispanic patients did not have any associations with heatwaves (Table S3-6). For cold waves, Non-Hispanic patients had associations from lag days 2 to 6 with lag day 4 having the greatest risk of all-cause mortality (IRR: 1.04, 95% CI: 1.02, 1.07). Hispanic patients showed much larger cold wave associated risk from lag days 4 to 5 with the greatest risk seen on lag day 4 (IRR: 1.15, 95% CI: 1.00, 1.32) but we did not observe significant differences in heat and cold wave effects by ethnicity (Table S3-6). Individuals with missing ethnicity data comprised 4.1% of Veterans and were not evaluated as a separate stratum.

Sensitivity analyses

Our sensitivity analysis for more stringent percentile thresholds of heat and cold waves illustrated a trend of robustness in our interpretation, although higher percentiles of heatwaves did elicit an elevated risk of mortality on lag day 0 (Table S3-7). Cold wave

results were generally unchanged, except for the 1st percentile of exposure which showed an increased risk of mortality on lag day 6 (Table S3-7). More stringent percentile thresholds for both heat and cold waves resulted in a substantial decrease in exposed mortality days which limits our ability to evaluate broader trends and distinctions within at-risk subpopulations.

Changing the reference period from a 30-year to a 20-year period for heat and cold waves did not impact our results (Table S3-8). Our model results were also robust to the exclusion of patients who were exposed to long duration heat and cold wave events, and to the exclusion of patients who resided in locales with mild 30-year percentile threshold values (Tables S3-9 to S3-10).

In our assessment evaluating confounding bias by air pollution ($PM_{2.5}$) we found minimal changes to the effect estimate for heatwaves (Table S3-11). When adjusting for daily mean $PM_{2.5}$ among patients who lived within 10km of an EPA air monitor, the IRR at lag day 0 was IRR: 1.12 (95% CI: 1.05, 1.18) compared to IRR: 1.11 (95% CI: 1.05, 1.18) in a model without daily mean $PM_{2.5}$. For cold waves, estimates were unchanged in models with and without daily mean $PM_{2.5}$ adjustment (Table S3-11).

In the sensitivity assessment evaluating potential COVID-19 pandemic influences, we identified significant differences in heat and cold wave mortality associations for patients who died pre vs post the COVID-19 emergency declaration (Table S3-12). To assess whether this difference is attributable to COVID-19 incidence, we ran new models including state level, weekly COVID-19 case rates per 100,000 as a fixed effect into statistical models. No changes were observed in the heat and cold wave effect estimates suggesting that any lag specific differences in heat and cold wave associations were not attributable to underlying incidence of COVID-19 cases (Table S3-13).

Discussion

Our findings demonstrate an increased risk of mortality associated with heat and cold waves among a population of Veterans diagnosed with COPD. Heatwaves had an immediate impact on all-cause mortality showing the greatest mortality risk on lag day 0

for all populations except cisgender women. The finding of acute, intense heatwave effects is a common observation in other studies[125,126]. Conversely, cold wave effects demonstrated a delayed response starting on lag day 2 with the greatest effect detected at lag day 4 for most populations although elevated risk persisted throughout the remainder of the 7-day exposure period. Within specific sub-populations, the effect of heatwaves was larger in women compared to men, and in Black Veterans compared to White Veterans. Of note, the effect of cold waves was notably greater in AIAN and Hispanic Veterans compared to White and Non-Hispanic Veterans respectively.

A potential explanation for the disparate responses in heat and cold wave effects may be attributed to the underlying cause of death. Heatwaves are predominately associated with more acute causes of death such as cardiovascular dysfunction or heat stress[127,128]. Cardiovascular related mortality events are the primary cause of death attributable to extreme heat[37]. As the body attempts to thermoregulate via vasodilation, there can be a mismatch between increased cardiac demand and the ability of the heart to pump blood faster to meet this demand especially among individuals with underlying cardiac impairments[37]. This mismatch can cascade into severe cardiovascular health events including cardiovascular collapse[37]. There may also be a direct impact of extreme heat on the respiratory system although it has yet to be known how extreme heat impacts COPD[129]. Among individuals with asthma, research suggested inhalation of hot and humid air may induce bronchoconstriction mediated via the cholinergic reflex[130].

The biological mechanisms underlying delayed effects of cold waves on health risks are less understood, and may be most associated with more subacute causes of death such as COPD exacerbations[71]. In a population of individuals with COPD, delayed impacts of cold wave associated mortality may be attributed to viral respiratory infections and bacterial pneumonia, both more common in the cold season of the year[44,46,131]. Higher rates of adverse COPD related outcomes including exacerbations and hospitalizations in the cold season is another well-documented phenomenon that may explain our results[132–134]. Inflammation and bronchoconstriction are two postulated mechanisms by which cold exposure negatively affects individuals with COPD[46,129].

Both heatwaves and cold waves conferred a similar absolute risk of mortality on their strongest lag days in the Veteran population with 651 deaths per 100,000 attributable to heatwave lag day 0 exposure and 687 deaths per 100,000 attributable to cold wave lag day 4 exposure respectively. Cold waves had a higher AR due to the elevated mortality rates in the cold season compared to the warm season. These attributable risk measures are effective in illustrating the public health impact of extreme weather exposure among this vulnerable population and may be useful to both physicians and patients in assessing the potential benefits of engaging in protective behaviors during periods of extremely hot or cold weather and improving the housing conditions of individuals living with COPD.

Our results for heat and cold wave mortality risks on the multiplicative scale were similar to those reported in other studies of the general population. The increase in heatwave associated risk for mortality in the general population ranged from 3% - 24.6% compared to our highest estimated mortality risk of 4%[113,114,128,135–139]. Cold wave associated risk for mortality in the general population ranged from a relative risk (RR) of 1.01 to 1.57[140–144]. A recent meta-analysis reported an RR of 1.10 (95% CI: 1.04 to 1.07) for cold wave effects on all-cause mortality compared with our highest estimated IRR of 1.04[145]. While our estimated multiplicative associations for heat and cold waves were relatively lower than most estimates reported in the literature, they fall within the range of previously reported effect estimates. The cause of this attenuation is unknown but may be attributed to our population being composed entirely of individuals diagnosed with a pre-existing chronic respiratory disease. Such individuals, while more susceptible, may also be more conscious of their fragile health state and take precautionary measures to avoid extreme weather exposure compared to a healthy population that may be outdoors in suboptimal temperatures. One study detected a 4.9% decrease in asthma hospitalizations during cold wave days which the authors suggested could be related to individuals with asthma taking extra medical precautions during extremely cold weather events[146].

Prior research provides evidence for sex-based disparities with higher heatwave related mortality risk in women compared to men, attributed to differences in physiology,

behavioral patterns or occuptation[105,136]. Our results were congruent with the prior literature in that cisgender women had a significantly greater heatwave associated mortality risk compared to cisgender men. Heatwave effects on mortality for men ranged from RR 1.02 to 1.06[113,114,139] and for women RR 1.06 to 1.12[113,114,139] compared to our maximum effect estimates of IRR 1.03 in cisgender men and IRR:1.26 in cisgender women. Our results may suggest cisgender women Veterans with pre-existing COPD have greater heatwave related mortality risk compared to previous studies in the general population. While our point estimates for cold wave related mortality among cisgender women followed a similar trend as cisgender men, the estimates were imprecise and did not indicate an association unlike prior research[141,144].

Age stratified estimates failed to detect differences between older and younger Veterans in our population contrary to other research that found age related disparities in heat[113,114,126,135,139] and cold wave associated mortality[56,140,142,143,145]. Indeed, a recent review concluded strong evidence for higher mortality risk in elderly populations due to extreme heat and cold exposure attributed to physiology, behavioral practices, prevalence of comorbidities, living alone and access to indoor heat and air conditioning[105]. Furthermore, it would be expected that as a Veteran aged and transitioned into a retirement phase, living conditions, behaviors and physical health would change that could enhance susceptibility to extreme weather events. The lack of disparate mortality risk between the age groups in our study could, however, be reflective of the quality and access of care received at the VHA.

Our results mostly failed to show differences in the effects of heat and cold waves when comparing racial and ethnic minorities to White and Non-Hispanic individuals. This may be due to the relatively small number of Veterans in our cohort who identified as racial and ethnic minorities combined with a scarcity of mortality events occurring on heat and cold wave exposure days. Some of our effect estimates indicated heightened heatwave related mortality risk particularly for Black Veterans and cold wave related mortality risk for AIAN and Hispanic Veterans, although caution should be used in interpreting AIAN mortality risks as sample sizes in this group were relatively small. Another plausible explanation for the lack of race and ethnicity-based differences is that

the VHA healthcare system has fewer access barriers compared to private healthcare for Veterans. Indeed, the VHA provides a high level of care often matching or outperforming care at peer non-VHA healthcare facilities[147,148]. In treatment of COPD specifically, the VHA outperforms 94% of healthcare market regions compared to non-VHA hospitals[148]. As an equal access healthcare system with facilities that are widespread, including many clinics in rural areas, this may minimize racial inequities in care within the VHA. One study estimated the 30-day mortality rate in patients sent by ambulance to a VHA hospital was 20.1% lower compared to non-VHA hospitals with even better outcomes for Black and Hispanic patients with a 25.8% and 22.7% lower mortality rate respectively[147]. This is not to say there are no racial disparities in health outcomes within the VHA, only that these disparities may be smaller than in the non-Veteran population. One study comparing mortality in White vs Black Veterans compared to non-Veterans found the disparity in mortality rates to be smaller in the Veteran population than the non-Veteran population which may be due to the relatively elevated socioeconomic status of Black Veterans compared to Black non-Veterans[149].

Our work has several limitations. The composition of the study cohort was overwhelmingly male and older, the latter reflecting that COPD is predominantly a disease of older adults. There was missingness in the race data that could have hampered our ability to detect potential differences in heat and cold wave mortality risk. In addition, the specific causes of mortality could not be distinguished. We did not have data on the severity of COPD among our cohort which prohibited an evaluation of heat and cold wave associated mortality risks with respect to severity of disease. This is important to consider for future research as individuals with severe disease may have a larger risk of mortality associated with extreme weather exposure compared to those with mild disease. Exposure misclassification is possible as we assigned heat and cold wave exposure to a geocoded residence which is a proxy for outdoor exposure and cannot account for routine or seasonal travel. It is also possible some Veterans with pre-existing COPD were missed in our study population due to misdiagnoses or if a Veteran switched to private medical insurance. We were limited in using ICD codes alone to identify patients with COPD. Diagnostic spirometry information is considered a gold standard measure in identifying

individuals with COPD, but we did not have spirometry information for our cohort and these data are not uniformly collected in the VHA Health Care System. One prior nationwide study of Veterans found less than 52% had spirometry information within 2 years of the initial date of COPD diagnosis[150]. However, prior research in VA populations found ICD codes perform modestly well with fairly high specificity and moderate sensitivity[151–153]. Lastly, our study was a relatively short 5-year time period that evaluated a rare exposure which limits our ability to detect associations within subpopulations.

The primary strength of our study was the Implementation of an Individual level national assessment focused entirely on individuals with a pre-existing chronic respiratory disease, a growing population with high vulnerability to extreme weather events. The results of this study will inform clinical, policy and public health practice on the effects of climate change and extreme weather events among individuals with chronic respiratory illnesses. Our study may also facilitate the development of targeted early warning systems for heat and cold waves among high-risk populations as current warning systems are built primarily for the general population which may have a higher tolerance for perturbations in ambient temperature compared to high-risk groups.

Conclusion

In the United States Veteran population with pre-existing COPD, heat and cold waves increased the risk of all-cause mortality with cold waves conferring a greater number of excess deaths compared to heatwaves. Cisgender women were estimated to have greater risks of mortality due to heatwave exposure with suggestive evidence of elevated heatwave risk in Black Veterans. AIAN and Hispanic Veterans may have elevated risk due to cold wave exposure. This study elucidated the impacts of heat and cold waves among a population of Veterans with a pre-existing chronic respiratory disease and these results can inform future clinical treatment and public health policy to lessen the burden of climate related hazards in high-risk populations.

Supplement

Table 3-S1: ICD-10 diagnosis codes used for inclusion of Veterans into the study population from the VHA healthcare system

ICD-10 Code	Description
J40	Bronchitis, not specified as acute or chronic
J41	Simple and mucopurulent chronic bronchitis
J41.0	Simple chronic bronchitis
J41.1	Mucopurulent chronic bronchitis
J41.8	Mixed simple and mucopurulent chronic bronchitis
J42	Unspecified chronic bronchitis
J43	Emphysema
J43.0	Unilateral pulmonary emphysema
J43.1	Pan lobular emphysema
J43.2	Centrilobular emphysema
J43.8	Other emphysema
J43.9	Emphysema, unspecified
J44	Other chronic obstructive pulmonary disease
J44.0	Chronic obstructive pulmonary disease with (acute) lower respiratory tract infection
J44.1	Chronic obstructive pulmonary disease with (acute) exacerbation
J44.9	Chronic obstructive pulmonary disease (unspecified)

$$Z = (\beta_1 - \beta_2) / \text{sqrt}((SE_1)^2 + (SE_1)^2)$$

Equation S3-1: Z-test formula to determine statistical significance of the difference between effect modifier estimates

Where β_1 and β_2 are the un-exponentiated coefficients from the conditional logistic regression models for the two strata of effect modifiers being compared and SE_1 and SE_2 are their standard errors.

$$AR = \frac{I_e}{p_{e+}\frac{1}{IRR - 1}}$$

Equation S3-2: Attributable risk formula

Where I_e is the season specific mortality rate in the entire population of Veterans with COPD, p_e is the proportion of control days that were exposed to heat or cold waves and

IRR is the effect estimate of heat and cold wave effects on mortality estimated via conditional logistic regression models.

Table 3-S2: Crude and adjusted models of heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag 0 – 7

Exposure	**Lag**	**Crude IRR (95% CI)**	**Adjusted IRR (95% CI)**
Heatwaves	0	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)
	1	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
	2	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
	3	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
	4	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
	5	0.99 (0.97, 1.00)	0.99 (0.97, 1.00)
	6	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
	7	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
Cold waves	0	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)
	1	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)
	2	1.01 (0.99, 1.03)	1.02 (1.00, 1.04)
	3	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)
	4	1.04 (1.02, 1.06)	1.04 (1.02, 1.07)
	5	1.03 (1.00, 1.05)	1.03 (1.00, 1.05)
	6	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
	7	1.02 (1.00, 1.05)	1.02 (1.00, 1.04)

Table 3-S3: Age stratified models of heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag 0 – 7

Exposure	**Lag**	**<70 years (N = 47,608)[A] IRR (95% CI)**	**70+ years (N = 136,117) IRR (95% CI)**	**P value[B]**
Heatwaves	0	1.05 (1.01, 1.10)	1.03 (1.01, 1.06)	0.37
	1	1.04 (1.00, 1.08)	1.01 (0.99, 1.04)	0.25
	2	1.03 (0.99, 1.07)	1.00 (0.98, 1.02)	0.17
	3	1.02 (0.98, 1.06)	0.99 (0.97, 1.02)	0.20
	4	0.99 (0.95, 1.03)	0.99 (0.97, 1.02)	0.79
	5	0.99 (0.95, 1.03)	0.99 (0.96, 1.01)	0.95
	6	0.98 (0.94, 1.02)	0.98 (0.96, 1.00)	0.98
	7	0.99 (0.95, 1.03)	0.98 (0.96, 1.00)	0.84
		<70 years (N = 48,829) IRR (95% CI)	**70+ years (N = 144,991) IRR (95% CI)**	**P value**
Cold waves	0	1.02 (0.98, 1.06)	1.01 (0.98, 1.03)	0.58
	1	1.03 (0.98, 1.07)	1.00 (0.98, 1.03)	0.36
	2	1.04 (1.00, 1.08)	1.01 (0.99, 1.04)	0.36
	3	1.05 (1.00, 1.09)	1.03 (1.00, 1.05)	0.45
	4	1.05 (1.01, 1.09)	1.04 (1.02, 1.07)	0.69
	5	1.04 (1.00, 1.09)	1.02 (1.00, 1.04)	0.34
	6	1.03 (0.99, 1.08)	1.02 (0.99, 1.04)	0.57
	7	1.00 (0.96, 1.05)	1.03 (1.00, 1.05)	0.31

[A]N is the stratum specific sample size.
[B]The <70 group was set as the referent group.

Table 3-S4: Gender stratified models of heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag 0 – 7

Exposure	**Lag**	**Cisgender Men (N = 179,850)[A] IRR (95% CI)**	**Cisgender Women (N = 3,872) IRR (95% CI)**	**P value[B]**
Heatwaves	0	1.03 (1.01, 1.06)	1.13 (0.98, 1.30)	0.22
	1	1.01 (0.99, 1.04)	1.26 (1.10, 1.44)	<0.01
	2	1.00 (0.98, 1.02)	1.17 (1.02, 1.33)	0.03
	3	1.00 (0.98, 1.02)	1.02 (0.89, 1.17)	0.75
	4	0.99 (0.97, 1.01)	0.92 (0.80, 1.06)	0.29
	5	0.99 (0.97, 1.01)	0.95 (0.83, 1.09)	0.56
	6	0.98 (0.96, 1.00)	0.95 (0.83, 1.09)	0.68
	7	0.98 (0.97, 1.00)	0.94 (0.82, 1.08)	0.53
Cold waves		**Cisgender Men (N = 189,685) IRR (95% CI)**	**Cisgender Women (N = 4,132) IRR (95% CI)**	**P value**
	0	1.01 (0.99, 1.03)	1.05 (0.90, 1.21)	0.63
	1	1.01 (0.99, 1.03)	1.04 (0.90, 1.20)	0.70
	2	1.02 (1.00, 1.04)	1.04 (0.91, 1.20)	0.74
	3	1.03 (1.01, 1.06)	0.95 (0.82, 1.10)	0.25
	4	1.04 (1.02, 1.07)	1.06 (0.92, 1.22)	0.88
	5	1.03 (1.01, 1.05)	0.99 (0.86, 1.15)	0.67
	6	1.02 (1.00, 1.04)	1.01 (0.87, 1.17)	0.87
	7	1.02 (1.00, 1.04)	1.07 (0.92, 1.23)	0.56

[A]N is the stratum specific sample size.
[B]Cisgender men were set as the referent group.

Table 3-S5: Race stratified models of heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag 0 – 7

Exposure	Strata (N)	Lag	IRR (95% CI)	P value
Heatwaves	White (N = 145,575)	0	1.03 (1.01, 1.06)	Referent
		1	1.01 (0.99, 1.03)	Referent
		2	1.00 (0.98, 1.02)	Referent
		3	1.01 (0.99, 1.03)	Referent
		4	1.00 (0.97, 1.02)	Referent
		5	0.98 (0.96, 1.00)	Referent
		6	0.97 (0.95, 0.99)	Referent
		7	0.98 (0.96, 1.00)	Referent
	American Indian / Alaska Native (N = 1,609)	0	0.98 (0.79, 1.22)	0.64
		1	1.08 (0.88, 1.34)	0.51
		2	1.16 (0.94, 1.44)	0.17
		3	1.13 (0.92, 1.40)	0.27
		4	1.01 (0.82, 1.26)	0.87
		5	1.01 (0.82, 1.25)	0.74
		6	1.11 (0.89, 1.37)	0.22
		7	1.08 (0.87, 1.33)	0.38
	Asian American / Pacific Islander (N = 1,720)	0	0.99 (0.81, 1.22)	0.70
		1	1.04 (0.85, 1.27)	0.79
		2	0.91 (0.74, 1.11)	0.34
		3	0.85 (0.69, 1.04)	0.10
		4	0.93 (0.76, 1.15)	0.54
		5	0.93 (0.76, 1.14)	0.62
		6	0.95 (0.78, 1.17)	0.87
		7	1.06 (0.87, 1.30)	0.41
	Black (N = 20,987)	0	1.09 (1.02, 1.15)	0.13
		1	1.06 (1.00, 1.13)	0.12
		2	1.04 (0.98, 1.10)	0.26
		3	0.97 (0.91, 1.03)	0.24
		4	0.95 (0.90, 1.01)	0.15
		5	1.02 (0.96, 1.08)	0.22
		6	1.00 (0.94, 1.06)	0.35
		7	1.00 (0.94, 1.06)	0.47
	Missing (N = 13,834)	0	1.01 (0.94, 1.09)	0.64
		1	1.06 (0.98, 1.14)	0.23
		2	1.01 (0.94, 1.09)	0.72
		3	0.99 (0.92, 1.06)	0.66
		4	1.00 (0.93, 1.07)	0.95
		5	1.02 (0.95, 1.10)	0.22
		6	1.03 (0.96, 1.11)	0.09
		7	1.01 (0.94, 1.08)	0.42
Cold waves	White (N = 153,403)	0	1.01 (0.98, 1.03)	Referent
		1	1.00 (0.98, 1.03)	Referent
		2	1.01 (0.99, 1.04)	Referent
		3	1.03 (1.00, 1.05)	Referent

		4	1.04 (1.02, 1.07)	Referent
		5	1.02 (1.00, 1.04)	Referent
		6	1.02 (1.00, 1.04)	Referent
		7	1.01 (0.99, 1.04)	Referent
	American Indian / Alaska Native (N = 1,720)	0	0.89 (0.71, 1.11)	0.29
		1	0.95 (0.76, 1.18)	0.61
		2	1.03 (0.84, 1.28)	0.86
		3	1.24 (1.01, 1.52)	0.07
		4	1.32 (1.08, 1.62)	0.02
		5	1.22 (0.99, 1.51)	0.09
		6	0.99 (0.80, 1.23)	0.78
		7	1.04 (0.83, 1.28)	0.84
	Asian American / Pacific Islander (N = 1,880)	0	0.97 (0.77, 1.21)	0.73
		1	1.04 (0.84, 1.29)	0.76
		2	1.00 (0.81, 1.23)	0.88
		3	1.06 (0.87, 1.31)	0.74
		4	1.06 (0.85, 1.3)	0.90
		5	1.01 (0.81, 1.25)	0.91
		6	0.93 (0.75, 1.16)	0.42
		7	0.97 (0.77, 1.21)	0.19
	Black (N = 21,767)	0	1.03 (0.96, 1.10)	0.57
		1	1.01 (0.95, 1.08)	0.78
		2	1.02 (0.96, 1.08)	0.91
		3	1.03 (0.97, 1.10)	0.90
		4	1.04 (0.98, 1.11)	0.97
		5	1.03 (0.97, 1.10)	0.71
		6	1.01 (0.95, 1.08)	0.77
		7	1.03 (0.97, 1.10)	0.58
	Missing (N = 15,050)	0	1.07 (0.99, 1.15)	0.13
		1	1.06 (0.98, 1.14)	0.17
		2	1.08 (1.00, 1.16)	0.11
		3	1.04 (0.97, 1.12)	0.71
		4	1.05 (0.98, 1.13)	0.79
		5	1.05 (0.98, 1.13)	0.47
		6	1.08 (1.00, 1.16)	0.15
		7	1.09 (1.01, 1.17)	0.07

Table 3-S6: Ethnicity stratified models of heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag 0 – 7

Exposure	**Lag**	**Non-Hispanic (N = 172,445)[A] IRR (95% CI)**	**Hispanic (N = 3,819) IRR (95% CI)**	**P value[B]**
Heatwaves	0	1.04 (1.02, 1.06)	0.98 (0.86, 1.11)	0.36
	1	1.02 (1.00, 1.04)	1.02 (0.89, 1.16)	0.99
	2	1.00 (0.98, 1.03)	0.98 (0.87, 1.12)	0.73
	3	1.00 (0.98, 1.02)	1.03 (0.91, 1.17)	0.64
	4	0.99 (0.97, 1.01)	1.05 (0.93, 1.2)	0.31
	5	0.98 (0.96, 1.00)	1.00 (0.88, 1.14)	0.75
	6	0.97 (0.95, 0.99)	1.00 (0.89, 1.14)	0.63
	7	0.98 (0.96, 1.00)	1.01 (0.89, 1.15)	0.60
		Non-Hispanic (N = 181,538) IRR (95% CI)	**Hispanic (N = 4,070) IRR (95% CI)**	**P value**
Cold waves	0	1.01 (0.99, 1.03)	0.94 (0.81, 1.08)	0.30
	1	1.01 (0.99, 1.03)	0.95 (0.82, 1.10)	0.43
	2	1.02 (1.00, 1.04)	1.04 (0.91, 1.20)	0.77
	3	1.03 (1.01, 1.05)	1.12 (0.97, 1.29)	0.27
	4	1.04 (1.02, 1.07)	1.15 (1.00, 1.32)	0.19
	5	1.02 (1.00, 1.05)	1.12 (0.98, 1.29)	0.19
	6	1.02 (1.00, 1.04)	1.09 (0.95, 1.25)	0.35
	7	1.01 (0.99, 1.04)	1.13 (0.98, 1.30)	0.14

[A]N is the stratum specific sample size.

[B]The Non-Hispanic group was set as the referent.

Table 3-S7: Adjusted incidence rate ratios (IRR) for heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 to 7, using the 95th, 97.5th and 99th of ambient mean daily temperature to define heatwaves and the 5th, 2.5th and 1st percentile of ambient mean daily temperature to define cold waves

Heatwaves IRR (95% CI)				
Lag	**90th percentile N = 17,621 (9.6%)[A]**	**95th percentile N = 7,579 (4.1%)**	**97.5th percentile N = 3,174 (1.7%)**	**99th percentile N = 986 (0.5%)**
0	1.04 (1.02, 1.06)	1.04 (1.01, 1.07)	1.07 (1.02, 1.11)	1.10 (1.02, 1.18)
1	1.02 (1.00, 1.04)	1.02 (1.00, 1.05)	1.04 (0.99, 1.08)	1.03 (0.96, 1.11)
2	1.01 (0.99, 1.03)	1.00 (0.97, 1.03)	1.03 (0.99, 1.07)	1.02 (0.94, 1.09)
3	1.00 (0.98, 1.02)	0.99 (0.97, 1.02)	1.01 (0.96, 1.05)	1.03 (0.95, 1.10)
4	0.99 (0.97, 1.01)	0.99 (0.96, 1.02)	0.97 (0.93, 1.01)	0.98 (0.91, 1.05)
5	0.99 (0.97, 1.00)	0.96 (0.93, 0.99)	0.97 (0.93, 1.01)	0.95 (0.88, 1.02)
6	0.98 (0.96, 1.00)	0.96 (0.93, 0.98)	0.96 (0.93, 1.01)	0.96 (0.89, 1.03)
7	0.98 (0.96, 1.00)	0.98 (0.95, 1.01)	0.97 (0.93, 1.01)	0.95 (0.88, 1.02)
Cold waves IRR (95% CI)				
	10th percentile N = 13,961 (7.2%)	**5th percentile N = 6,790 (3.5%)**	**2.5th percentile N = 3,583 (1.8%)**	**1st percentile N = 1,596 (0.8%)**
0	1.01 (0.99, 1.03)	1.00 (0.97, 1.03)	1.01 (0.97, 1.05)	1.01 (0.95, 1.07)
1	1.01 (0.99, 1.03)	1.00 (0.97, 1.03)	1.02 (0.98, 1.06)	1.00 (0.95, 1.06)
2	1.02 (1.00, 1.04)	1.02 (0.99, 1.05)	1.03 (0.99, 1.07)	1.03 (0.97, 1.09)
3	1.03 (1.01, 1.05)	1.05 (1.02, 1.08)	1.05 (1.01, 1.09)	1.04 (0.98, 1.10)
4	1.04 (1.02, 1.07)	1.04 (1.01, 1.07)	1.04 (1.00, 1.08)	1.03 (0.97, 1.09)
5	1.03 (1.00, 1.05)	1.03 (1.00, 1.06)	1.04 (1.00, 1.08)	1.04 (0.98, 1.10)
6	1.02 (1.00, 1.04)	1.03 (1.00, 1.06)	1.03 (0.99, 1.07)	1.08 (1.02, 1.14)
7	1.02 (1.00, 1.04)	1.03 (1.00, 1.06)	1.01 (0.97, 1.05)	1.02 (0.96, 1.08)

[A]N is the number (percent) of Veterans who died during heat or cold wave exposure at a given percentile. The 90th and 10th percentiles were used in the primary analysis of this study.

Table 3-S8: Adjusted incidence rate ratios (IRR) for heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 to 7 using a 20-year reference period (2002 to 2021) to calculate the 90th and 10th percentiles used to define heat and cold waves respectively

Exposure	**Lag**	**IRR (95% CI) 20-year reference period (2002 – 2021)**	**IRR (95% CI) 30-year reference period (1992 – 2021)[A]**
Heatwaves	0	1.04 (1.01, 1.06)	1.04 (1.02, 1.06)
	1	1.03 (1.01, 1.05)	1.02 (1.00, 1.04)
	2	1.00 (0.98, 1.03)	1.01 (0.99, 1.03)
	3	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
	4	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
	5	0.97 (0.95, 0.99)	0.99 (0.97, 1.00)
	6	0.97 (0.95, 0.99)	0.98 (0.96, 1.00)
	7	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
Cold waves	0	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
	1	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
	2	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
	3	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)
	4	1.04 (1.02, 1.07)	1.04 (1.02, 1.07)
	5	1.03 (1.00, 1.05)	1.03 (1.00, 1.05)
	6	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
	7	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)

[A]The 30-year reference period was used in the primary analysis.

Table 3-S9: Adjusted incidence rate ratios (IRR) for heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 to 7 excluding Veterans who were exposed to heat or cold waves that lasted longer than 10 days

Exposure	**Lag**	**Veterans exposed to heatwaves <=10 days[A] (N = 180,826)[B] IRR (95% CI)**	**All Veterans (N = 183,725) IRR (95% CI)**
Heatwaves	0	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)
	1	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
	2	1.00 (0.98, 1.02)	1.01 (0.99, 1.03)
	3	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
	4	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
	5	0.98 (0.96, 1.00)	0.99 (0.97, 1.00)
	6	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
	7	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
		Veterans exposed to cold waves <=10 days[1] (N = 192,081) IRR (95% CI)	**All Veterans (N = 193,820) IRR (95% CI)**
Cold waves	0	1.01 (0.99, 1.04)	1.01 (0.99, 1.03)
	1	1.01 (0.99, 1.04)	1.01 (0.99, 1.03)
	2	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
	3	1.03 (1.01, 1.06)	1.03 (1.01, 1.05)
	4	1.05 (1.02, 1.07)	1.04 (1.02, 1.07)
	5	1.03 (1.01, 1.05)	1.03 (1.00, 1.05)
	6	1.03 (1.00, 1.05)	1.02 (1.00, 1.04)
	7	1.02 (1.00, 1.05)	1.02 (1.00, 1.04)

[A]Where Veterans exposed to heat/cold waves lasting longer than 10 days were excluded from the analysis. Comparisons are to be made between the primary analysis results that included all Veterans to the subset analysis that only used Veterans exposed to heat/cold waves $\leq$10 days. Any changes in the effect estimates may indicate the degree of influence Veterans exposed to heat/cold waves longer than 10 days had on the overall results.
[B]N is the stratum specific sample size.

Table 3-S10: Adjusted incidence rate ratios (IRR) for heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 to 7 excluding Veterans whose 30-year (1992-2021) 90th percentile for ambient mean temperature in the warm season was <25°C or whose 10th percentile for ambient mean temperature in the cold season was >5°C

Exposure	**Lag**	**Veterans with 90th percentile >=25°C[A] (N = 130,572)[B] IRR (95% CI)**	**All Veterans (N = 183,725) IRR (95% CI)**
Heatwaves	0	1.04 (1.02, 1.07)	1.04 (1.02, 1.06)
	1	1.02 (0.99, 1.04)	1.02 (1.00, 1.04)
	2	1.02 (0.99, 1.04)	1.01 (0.99, 1.03)
	3	1.01 (0.98, 1.03)	1.00 (0.98, 1.02)
	4	0.99 (0.97, 1.02)	0.99 (0.97, 1.01)
	5	0.99 (0.96, 1.01)	0.99 (0.97, 1.00)
	6	0.97 (0.95, 1.00)	0.98 (0.96, 1.00)
	7	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
		Veterans with 10th percentile <=5°C (N = 150,508) IRR (95% CI)	**All Veterans (N = 193,820) IRR (95% CI)**
Cold waves	0	1.02 (0.99, 1.04)	1.01 (0.99, 1.03)
	1	1.01 (0.99, 1.04)	1.01 (0.99, 1.03)
	2	1.02 (1.00, 1.05)	1.02 (1.00, 1.04)
	3	1.03 (1.01, 1.05)	1.03 (1.01, 1.05)
	4	1.04 (1.02, 1.07)	1.04 (1.02, 1.07)
	5	1.02 (1.00, 1.05)	1.03 (1.00, 1.05)
	6	1.02 (1.00, 1.05)	1.02 (1.00, 1.04)
	7	1.02 (0.99, 1.04)	1.02 (1.00, 1.04)

[A]Where Veterans residing in areas whose 30-year ambient mean temperature values for the 90th and 10th percentiles were <25°C for the warm season or >5°C for the cold season were excluded from the analysis. Comparisons are to be made between the primary analysis results that included all Veterans to the subset analysis that only used Veterans residing in areas whose 30-year ambient mean temperature values for the 90th and 10th percentiles were $\geq$25°C for the warm season or $\leq$5°C for the cold season. Any changes in the effect estimates may indicate the degree of influence Veterans residing in areas with mild 30-year temperature thresholds had on the primary analysis results.

[B]N is the stratum specific sample size.

Table 3-S11: Adjusted incidence rate ratios (IRR) for heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 to 7 who lived within a 10km buffer of an EPA regulatory monitor site

Exposure	**Lag**	**Model not adjusted for daily mean $PM_{2.5}$ (N = 20,735)[A] IRR (95% CI)**	**Model adjusted for daily mean $PM_{2.5}$ (N = 20,735) IRR (95% CI)**
Heatwaves	0	1.11 (1.05, 1.18)	1.12 (1.05, 1.18)
	1	1.12 (1.06, 1.18)	1.12 (1.06, 1.19)
	2	1.03 (0.97, 1.09)	1.03 (0.97, 1.09)
	3	1.00 (0.95, 1.06)	1.00 (0.95, 1.06)
	4	0.96 (0.91, 1.02)	0.96 (0.91, 1.02)
	5	0.98 (0.93, 1.04)	0.98 (0.93, 1.04)
	6	0.94 (0.89, 1.00)	0.94 (0.89, 1.00)
	7	0.93 (0.88, 0.99)	0.93 (0.88, 0.99)
		Model not adjusted for daily mean $PM_{2.5}$ (N = 21,535) IRR (95% CI)	**Model adjusted for daily mean $PM_{2.5}$ (N = 21,535) IRR (95% CI)**
Cold waves	0	0.97 (0.91, 1.04)	0.97 (0.91, 1.04)
	1	1.01 (0.95, 1.08)	1.01 (0.95, 1.07)
	2	1.04 (0.98, 1.1)	1.04 (0.98, 1.1)
	3	1.05 (0.99, 1.12)	1.05 (0.99, 1.12)
	4	1.01 (0.96, 1.08)	1.01 (0.95, 1.08)
	5	1.02 (0.96, 1.08)	1.02 (0.96, 1.08)
	6	0.97 (0.92, 1.03)	0.97 (0.91, 1.03)
	7	1.03 (0.97, 1.1)	1.03 (0.97, 1.09)

[A]N is the stratum specific sample size.

Table 3-S12:Adjusted incidence rate ratios (IRR) for heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 to 7 stratified on mortality events occurring before and after January 31st, 2020, the date that the United States Department of Health and Human Services declared COVID-19 as a public health emergency

Exposure	**Lag**	**Pre-COVID (N = 116,583)[A] IRR (95% CI)**	**Post-COVID (N = 67,142) IRR (95% CI)**	**P value[B]**
Heatwaves	0	1.02 (0.99, 1.04)	1.07 (1.03, 1.11)	0.02
	1	1.00 (0.97, 1.02)	1.06 (1.03, 1.10)	<0.01
	2	0.99 (0.97, 1.02)	1.03 (1.00, 1.07)	0.04
	3	0.99 (0.97, 1.02)	1.02 (0.99, 1.05)	0.18
	4	0.98 (0.96, 1.01)	1.01 (0.98, 1.04)	0.16
	5	0.98 (0.95, 1.00)	1.00 (0.97, 1.03)	0.30
	6	0.97 (0.95, 0.99)	0.99 (0.96, 1.02)	0.34
	7	0.97 (0.95, 1.00)	1.00 (0.97, 1.03)	0.25
		Pre-COVID (N = 132,051) IRR (95% CI)	**Post-COVID (N = 61,769) IRR (95% CI)**	**P value**
Cold waves	0	1.02 (1.00, 1.05)	0.97 (0.93, 1.02)	0.05
	1	1.03 (1.00, 1.05)	0.96 (0.92, 1.00)	0.01
	2	1.03 (1.01, 1.06)	0.98 (0.94, 1.03)	0.06
	3	1.04 (1.02, 1.07)	0.99 (0.95, 1.04)	0.04
	4	1.05 (1.03, 1.08)	1.01 (0.97, 1.06)	0.09
	5	1.03 (1.01, 1.06)	1.01 (0.96, 1.05)	0.33
	6	1.03 (1.00, 1.05)	1.01 (0.97, 1.06)	0.65
	7	1.02 (0.99, 1.04)	1.05 (1.00, 1.09)	0.26

[A]N is the stratum specific sample size.

[B]Pre-COVID is the referent group.

Table 3-S13:Adjusted incidence rate ratios (IRR) for heat and cold wave associations with all-cause mortality among Veterans with COPD (2016 to 2021) from lag day 0 to 7 adjusting for COVID-19 incidence

Exposure	**Lag**	**Model not adjusted for COVID-19[A] IRR (95% CI)**	**Model adjusted for COVID-19 IRR (95% CI)**
Heatwaves	0	1.04 (1.02, 1.06)	1.04 (1.02, 1.06)
	1	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
	2	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
	3	1.00 (0.98, 1.02)	1.00 (0.98, 1.02)
	4	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)
	5	0.99 (0.97, 1.00)	0.99 (0.97, 1.01)
	6	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
	7	0.98 (0.96, 1.00)	0.98 (0.96, 1.00)
		Model not adjusted for COVID-19 IRR (95% CI)	**Model adjusted for COVID-19 IRR (95% CI)**
Cold waves	0	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
	1	1.01 (0.99, 1.03)	1.01 (0.99, 1.03)
	2	1.02 (1.00, 1.04)	1.02 (1.00, 1.04)
	3	1.03 (1.01, 1.05)	1.03 (1.01, 1.06)
	4	1.04 (1.02, 1.07)	1.04 (1.02, 1.07)
	5	1.03 (1.00, 1.05)	1.03 (1.00, 1.05)
	6	1.02 (1.00, 1.04)	1.02 (1.00, 1.05)
	7	1.02 (1.00, 1.04)	1.03 (1.00, 1.05)

[A]Model not adjusted for COVID-19 is the primary analysis.

Chapter 4: Comorbidities, tobacco exposure & geography: added risk factors of heat and cold wave related mortality among United States Veterans with chronic obstructive pulmonary disease

Background: Heat and cold waves are associated with increased mortality risk in the general population, however, disparities in heat and cold wave mortality risks among vulnerable populations living in diverse geographic locations are less understood.

Methods: We investigated heat and cold wave related mortality risks in a cohort of Veterans with chronic obstructive pulmonary disease (N = 377,545) from 2016 – 2021 and explored disparities among strata of comorbidities, smoking status and urbanicity. We developed a time stratified case-crossover study and used distributed lag models with conditional logistic regression to estimate incidence rate ratios (IRR) of heat and cold wave mortality risk from lag days 0 – 3 for heatwaves and 0 – 7 for cold waves. Attributable risks (AR) per 100,000 Veterans were also calculated.

Results: Our results indicated Veterans with concurrent COPD and asthma had the largest heatwave related mortality risk, cumulative lag day 0 – 3 AR: 14,016 (95% CI: -326, 30,706) and Veterans with COPD and no other additional comorbidities had the largest cold wave related mortality burden, cumulative lag day 0 – 7 AR: 1,704 (95% CI: 759, 2,686). Current smokers had the greatest heatwave related mortality risk (cumulative lag day 0 – 1 AR: 906 (95% CI: 261, 1,572) whereas former smokers had the largest cold wave related mortality risk (cumulative lag day 0 – 7 AR: 1,639 (95% CI: 328, 3,004). Veterans residing in urban settings had the greatest heatwave (cumulative lag day 0 – 1 AR: 1,062 (95% CI: (576, 1,559) and cold wave (cumulative lag day 0 – 7 AR: 1,261 (95% CI: 440, 2,105) related mortality risk.

Discussion: Our results may inform clinical practice and public health policy with regard to the treatment of individuals with additional underlying risk factors that may predispose them to enhanced risk of adverse health events from extreme weather conditions.

Introduction

Climate related hazards are a growing public health concern as climate change is altering global climate zones, changing storm tracks, and increasing temperatures[1]. However, climate related health risks are not uniform across the population. Several health, behavioral and socioeconomic mechanisms may predispose an individual to become more sensitive to climate related hazards. To promote public health equity, vulnerable subpopulations should be considered in climate change adaptation strategies.

Chronic obstructive pulmonary disease (COPD) is a climate sensitive respiratory disease afflicting 200 million people globally[10]. COPD is a complex disease often occurring in older individuals and is associated with systemic, chronic low grade inflammation, accelerating the natural life course of other comorbidities[20]. This is relevant in the United States as the prevalence of other chronic diseases is relatively large, 7.2% of people have coronary artery disease, 15% have chronic kidney disease, 41.9% are obese and 11.3% are diabetic[154–157]. However, there is a paucity of research examining how concomitant comorbidities act as added risk factors for adverse health outcomes associated with climate change in a vulnerable population[158–160].

In addition to comorbidities, smoking status and the geographic settings in which people live heighten one's susceptibility to climate related hazards. Smoking increases one's health risk due to increased oxidant exposure that can be accentuated by environmental conditions. Residents of urban and rural settings may experience disparities in extreme weather health risks due to the differences in building environments, and access to indoor heat and cooling[105]. The urban heat island (UHI) effect increases overall temperatures of urban areas and may amplify effects of extreme heat[161]. In the United States, urban areas have daytime temperatures that are 0.5 – 4°C hotter than surrounding non-urban areas[162].

We hypothesize individuals with COPD and multiple comorbidities and/or who smoke are at an increased risk of heat and cold wave related mortality compared to those without these risk factors. Additionally, we hypothesize heat and cold wave mortality risks are unevenly distributed between urban and rural residents. To evaluate our

hypotheses, we designed a time stratified case-crossover study using data from the United States Veterans Health Administration (VHA) from 2016 – 2021 on a cohort of Veterans with a COPD diagnosis. The results of this study will inform the development of targeted public health interventions and climate change mitigation strategies by identifying at-risk segments of the population.

Methods

Study cohort

The study cohort was obtained from the national VA Corporate Data Warehouse and consisted of Veterans between the ages of 35 to 100 with COPD, defined as having 2+ clinical encounters with an International Classification of Diseases 9th or 10th revision codes for COPD between 2016 – 2019 (Table S4-1). A full description of the study population and inclusion criteria is previously described in Chapter 3. Demographic data including age, gender, race, comorbidities, smoking status and geocoded home address were obtained. Comorbidities were diagnosed using ICD-10 codes within one year after the initial COPD clinical encounter and included asthma, coronary artery disease, congestive heart failure, chronic kidney disease, diabetes, lung cancer, and obesity (Table S4-1). Smoking status categories included current, former, never, and unknown smoking status.

Weather and urbanicity data

Daily weather data (mean ambient temperature, total precipitation, mean specific humidity, and mean wind speed) were assigned to the geocoded residential addresses of patients by spatially overlaying the home locations to gridded climatological datasets. GridMet, a highly resolved spatiotemporal meteorological dataset, was obtained at a resolution of 4x4km grid cells and used to assign weather exposure[112]. Heatwaves were defined as 2+ consecutive days whose mean ambient daily temperature was above the 90th percentile of warm season (April – September) mean ambient daily temperature values from 1992 – 2021 and cold waves were defined as 2+ consecutive days whose mean ambient daily temperature was below the 10th percentile of cold season (October – March) mean ambient daily temperature values from 1992 – 2021. These 30-year percentile cutoffs were specific for each patient's home address using the GridMet data.

Urbanicity was determined using the 2010 Rural-Urban Commuting Area (RUCA) codes at the census tract level[163]. A three-level categorization of urban, rural and highly rural was specified. Urban was defined using RUCA codes 1.0 and 1.1, highly rural was defined as RUCA code 10 and all other RUCA codes were classified as rural. This definition of urban is narrow compared to other research, however we chose to use this definition to be consistent with VHA policy and prior research[111].

Study design

We used a time stratified case-crossover study design to estimate heat and cold wave associations with all-cause mortality among strata of comorbidities, smoking status and urbanicity as potential effect measure modifiers. In the case-crossover study design, each patient's date of death is matched with referent days in the same year, month and day of week guaranteeing a minimum of 3 referent days per patient mortality event, and simultaneously adjusting for seasonal, day of week and time invariant confounding by design[97]. We adjusted for daily time varying confounders including precipitation, specific humidity, wind speed, and holiday status which included all federally recognized United States' holidays[119] and other major holidays including Christmas Eve, New Year's Eve, Easter and Halloween.

Statistical analyses

We built distributed lag models (DLM)[164] with conditional logistic regression to estimate incidence rate ratios (IRR) describing single lag and cumulative lag heat and cold wave associations with all-cause mortality within strata of our effect measure modifiers. Delayed effects from lag days 0 – 3 were evaluated for heatwaves and lag days 0 – 7 for cold waves. Cumulative effects were calculated for lag days 0 – 1 and 0 – 3 for heatwaves and lag days 0 – 4 and 0 – 7 for cold waves. Heat and cold wave evaluations were restricted to the warm (April to September) and cold (October to March) seasons. Attributable risks (AR) for the cumulative heat and cold wave effects were also calculated (Equation S4-1). We tested for effect measure modification using stratified data subsets based on comorbidities, smoking status and urbanicity. A Z-test was used to compare the IRRs of each strata at each lag day and for the cumulative lagged effects against a referent category[121].

Most patients had multiple comorbidities. We categorized the comorbidities into i) metabolic syndrome-associated diseases consisting of coronary artery disease (CAD), congestive heart failure (CHF), diabetes or obesity (but no other comorbidities), ii) asthma, iii) chronic kidney disease (CKD) and iv) lung cancer.

All analyses were completed in R statistical software (version 4.1)[122].

Sensitivity analyses

We stratified smoking status into binary datasets of never smokers and ever-smokers (current and former smokers) to test the robustness of our smoking analysis. For our comorbidity assessment, we created stratified datasets based on the number of additional underlying comorbidities a patient had, agnostic to the specific underlying disease. We created categories of 1, 2 – 3, and 4+ additional comorbidities and compared our results against patients who only had COPD (0 additional comorbidities). The scarcity of heat and cold wave events during our study period prohibited sensitivity evaluations concerning duration and intensity of these events.

Ethics Statement

This study was approved by the institutional review boards at the Minneapolis VA Health Care System and the University of Minnesota.

Results

Summary statistics

The source population contained 1,124,705 patients with COPD of which 377,545 were deceased and used for our case-only study. Mortality events occurred between 2016 – 2021 with heterogenous mortality rates across the United States (Figure S4-1). The study cohort was primarily male, older and White race. Most patients currently or previously smoked (55.5%) with another 33.2% having an unknown smoking status (Table 4-1). Most patients lived in urban settings although >40% lived rural settings (Table 4-1).

Multiple comorbidity diagnoses were common with 73.4% of the cohort having 1+ comorbidities whereas 26.6% had no additional comorbidities (Table 4-1).

Cardiovascular related comorbidities (CAD and CHF) were the most common comorbidities while asthma was the least common (Table 4-1).

Table 4-1: Demographic, health and behavioral characteristics of deceased patients with COPD

Baseline Characteristic	Mean (SD) / Frequency (%)
Age (years), mean (SD)	77.0 (10.1)
Gender, frequency (%)	
Male	369,535 (97.9%)
Female	8,004 (2.1%)
Transgender	6 (<1%)
Race, frequency (%)	
White	298,978 (79.2%)
Black	42,754 (11.3%)
American Indian / Alaska Native	3,329 (<1%)
Asian American / Pacific Islander	3,600 (<1%)
Missing	28,884 (7.7%)
Smoking status, frequency (%)	
Current	107,988 (28.6%)
Former	101,366 (26.9%)
Never	42,714 (11.3%)
Unknown	125,477 (33.2%)
Number of additional comorbidities other than COPD (diagnosed within 1-year of the index date)	
0	100,292 (26.6%)
1	105,804 (28.0%)
2	79,868 (21.2%)
3	51,418 (13.6%)
4	29,276 (7.8%)
5	9,957 (2.6%)
6	917 (<1%)
7	13 (<1%)
Additional comorbidities, frequency (%) (within 1-year of the index date)[A]	
Asthma	15,086 (4%)
Coronary artery disease	150,301 (39.8%)
Congestive heart failure	107,428 (28.5%)
Chronic kidney disease	92,130 (24.4%)
Diabetes	147,046 (38.9%)
Lung cancer	33,486 (8.8%)
Obesity	46,799 (12.4%)
Urbanicity, frequency (%)	

Urban	223,942 (59.3%)
Rural	147,317 (39.0%)
Highly rural	6,285 (1.7%)
Missing	1 (<1%)

[A]Comorbidity was diagnosed within 1 year of the initial COPD clinical encounter that occurred between 2016-2019 which was used to enroll patients into the initial study cohort. Patients can have multiple comorbidity diagnoses.

Of the 3,058 counties in which deceased patients lived, 2,300 (75.2%) counties experienced a heatwave, and 2,302 (75.2%) counties experienced a cold wave during patient mortality days (Figure 4-1). Exposure to heat and cold waves on mortality days were consistent across strata of comorbidities, smoking status, and urbanicity with around 9% of mortality events occurring during heatwaves and 7% of mortality events occurring during cold waves (Table S4-2).

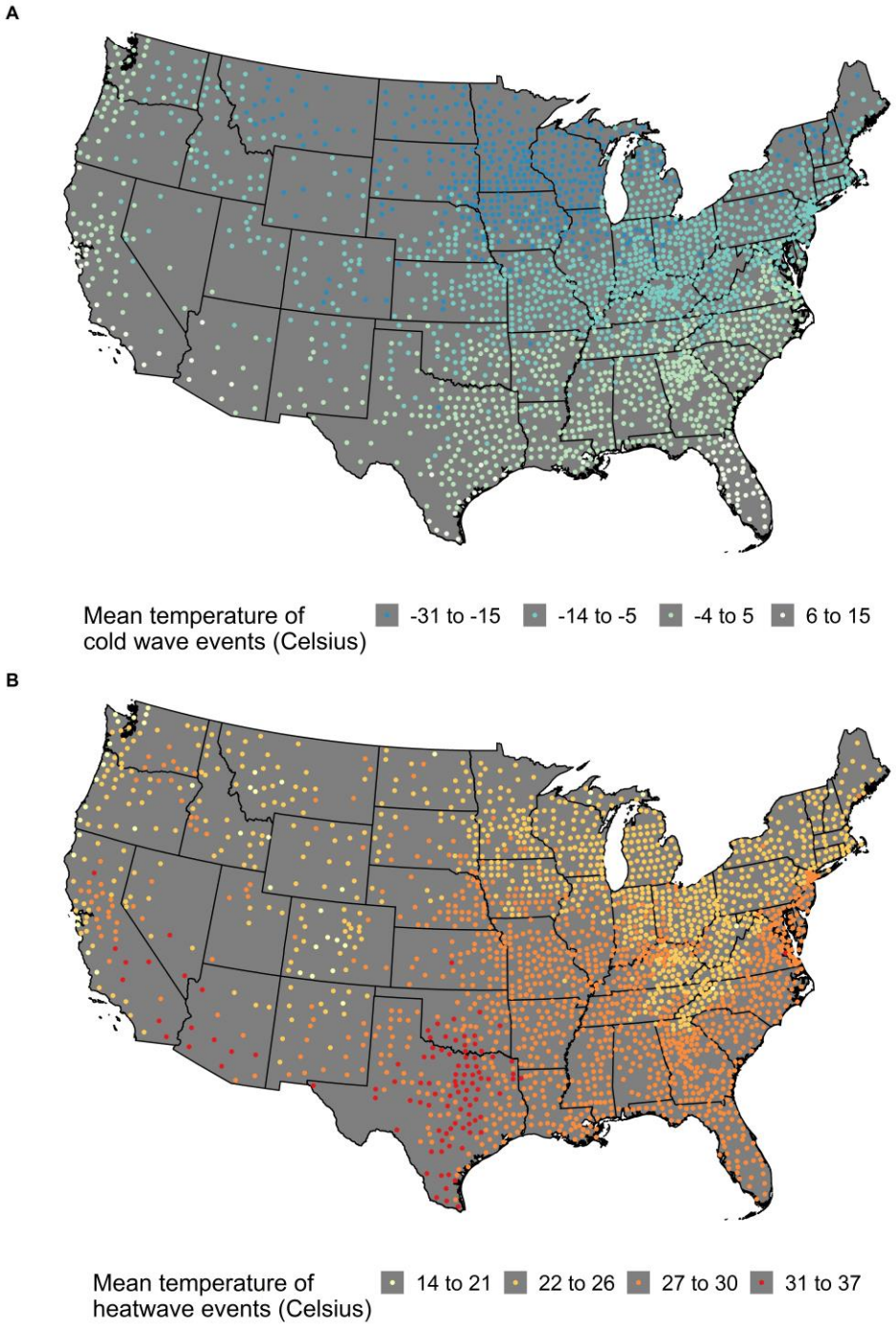

Figure 4-1: Average mean daily ambient temperature (Celsius) of heat and cold wave events (2016 – 2021) during event (mortality) days among counties with deceased patients. Dots represent county centroids.

Comorbidities

Of the 377,545 deceased patients in the cohort, 274,403 (72.7%) were retained for the stratified comorbidity analysis. We excluded 103,142 patients with multiple comorbidities that did not fit into one of our four pre-determined comorbidity categories.

Among patients with concurrent asthma and COPD, 14,016 deaths per 100,000 (95% CI: -326, 30,706) were attributable to cumulative lag day 0 – 3 heatwave exposure. Although this was the largest mortality risk associated with heatwaves it was not statistically significant at the 95% confidence level (Figure 2, Table 2, Table S3). Patients with COPD only followed a different pattern; 836 (95% CI: 272, 1,419) deaths per 100,000 were attributable to cumulative heatwave exposure on lag days 0 – 1 (Table 4-2). No associations were detected between heatwaves and mortality among patients with CKD, lung cancer, or metabolic syndrome-associated diseases (Figure 4-2, Table 4-2, Table S4-3).

Patients with COPD and without reported comorbidities had the greatest cold wave associated mortality risk (Figure 4-3, Table 4-2, Table S4-3). The cumulative effect of cold waves on mortality over the entire 7-day lag period was relatively high, IRR: 1.13 (95% CI: 1.06, 1.21), and this elevated risk translated to an AR of 1,704 (95% CI: 759, 2,686) deaths per 100,000 attributable to cumulative cold wave exposure (Table 4-2). Patients with concurrent asthma and COPD had elevated cold wave mortality risks on lag days 6 – 7 but did not have heightened risks associated with cumulative cold wave exposure (Figure 4-2, Table S4-3). Patients with COPD and metabolic syndrome-associated diseases had an increased risk of cold wave related mortality for the cumulative lag period of lag days 0 – 7 with an IRR: 1.05 (95% CI: 0.99, 1.11). Among patients with COPD and metabolic syndrome-associated disease, 2,464 (95% CI: -480, 5,509) deaths per 100,000 were attributable to cumulative cold wave exposure. However, neither asthma nor metabolic syndrome-associated comorbidities reached statistical significance (Table S4-3). Patients with CKD or lung cancer did not have a greater risk of mortality associated with cold waves (Figure 4-2, Table S4-3).

Table 4-2: Attributable risks per 100,000 patients for cumulative effects of heatwaves (lag day 0 – 1 and lag day 0 – 3) and cold waves (lag day 0 – 4 and lag day 0 – 7) by levels of comorbidities, smoking status and urbanicity

Strata	Heatwaves		Cold waves	
	Cumulative lag day period		Cumulative lag day period	
	Lag days 0 – 1 AR (95% CI)	Lag days 0 – 3 AR (95% CI)	Lag days 0 – 4 AR (95% CI)	Lag days 0 – 7 AR (95% CI)
Additional comorbidities				
None (COPD only)	836 (272, 1,419)	827 (174, 1,501)	544 (-177, 1,293)	1,704 (759, 2,686)
Asthma	10,180 (-1,517, 23,873)	14,016 (-326, 30,706)	-9,959 (-21,792, 4,956)	-1,851 (-18,662, 19,510)
Chronic kidney disease	3,060 (-3,263, 10,026)	5,086 (-2,407, 13,339)	-38 (-8,072, 9,011)	-1,525 (-11,361, 9,699)
Lung cancer	3,627 (-2,708, 10,590)	-2,088 (-8,921, 5,472)	4,388 (-3,539, 13,196)	2,207 (-7,402, 12,993)
Metabolic syndrome	1,027 (-729, 2,832)	977 (-1,058, 3,071)	1,344 (-968, 3,730)	2,464 (-480, 5,509)
Smoking status				
Current smoker	906 (261, 1,572)	858 (113, 1,627)	428 (-387, 1,274)	1,008 (-36, 2,093)
Former smoker	586 (-176, 1,373)	182 (-687, 1,082)	1,285 (252, 2,357)	1,639 (328, 3,004)
Never smoker	389 (-610, 1,441)	71 (-1,070, 1,273)	681 (-669, 2,114)	1,121 (-608, 2,964)
Unknown	444 (-242, 1,151)	448 (-351, 1,270)	192 (-687, 1,102)	991 (-134, 2,156)
Urbanicity				
Urban	1,062 (576, 1,559)	790 (234, 1,358)	689 (47, 1,347)	1,261 (440, 2,105)
Rural	-130 (-724, 481)	-75 (-768, 639)	357 (-405, 1,144)	1,035 (59, 2,044)
Highly rural	439 (-2,409, 3,735)	-336 (-3,601, 3,490)	2,705 (-1,005, 6,943)	819 (-3,359, 5,655)

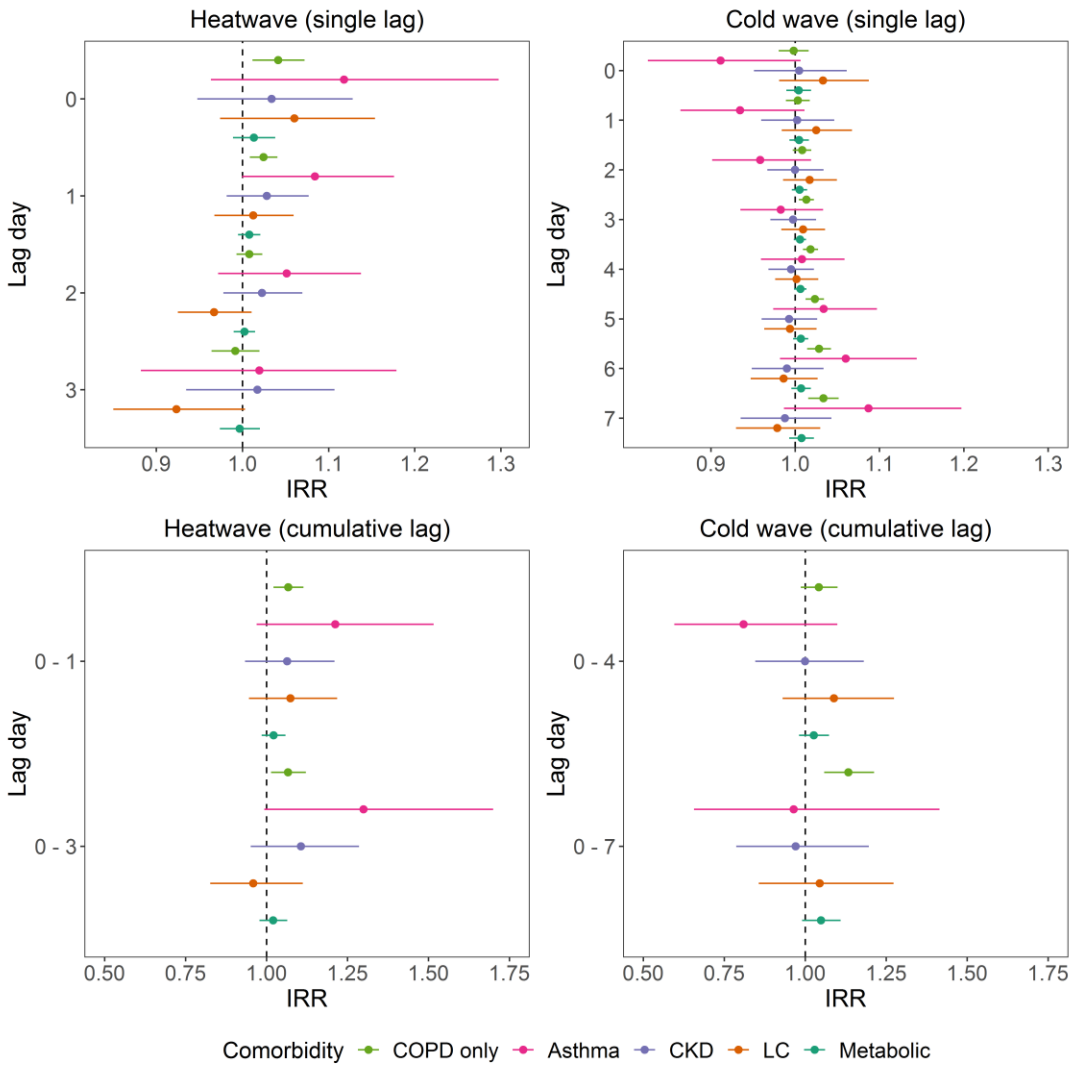

Figure 4-2: Adjusted incidence rate ratios (IRRs) for heat and cold wave associated mortality risk among patients with COPD stratified by additional underlying comorbidities. CKD = chronic kidney disease, LC = lung cancer, Metabolic = metabolic syndrome-associated diseases. Single lag IRRs are presented for lag days 0 – 3 for heatwaves as well as cumulative lagged periods of lag days 0 – 1 and 0 – 3. For cold waves, single lag IRRs are presented for lag days 0 – 7 as well as cumulative lagged periods of lag days 0 – 4 and 0 – 7

Smoking status

Current smokers had the greatest heatwave associated mortality risk (cumulative lag day 0 – 1 period IRR: 1.06 (95% CI: 1.02, 1.11), although differences comparing current and former smokers to never smokers did not exclude the null at the 95% confidence level (Table S4-4). Among current smokers exposed to heatwaves, 906 (95%

CI: 261, 1,572) deaths per 100,000 were attributable to cumulative heatwave exposure (Table 4-2). Former smokers had an elevated mortality risk for the cumulative lag days 0 – 1 period, IRR: 1.03 (95% CI: 0.99, 1.08); AR: 586 (95% CI: -176, 1,373). Never smokers did not have increased mortality risks during heatwaves (Figure 4-3, Table S4-4).

Former smokers had the largest cold wave related mortality risk (cumulative lag day 0 – 7 IRR: 1.09 (95% CI: 1.02, 1.17); AR: 1,639 (95% CI: 328, 3,004). Current smokers also had an enhanced mortality risk over that same period, IRR: 1.07 (95% CI: 1.00, 1.14); AR: 1,008 (95% CI: -36, 2,093). Mortality risks among never smokers were attenuated and less statistically precise. Cold wave mortality risks were not statistically different comparing current and former smokers to never smokers (Figure 4-3, Table S4-4).

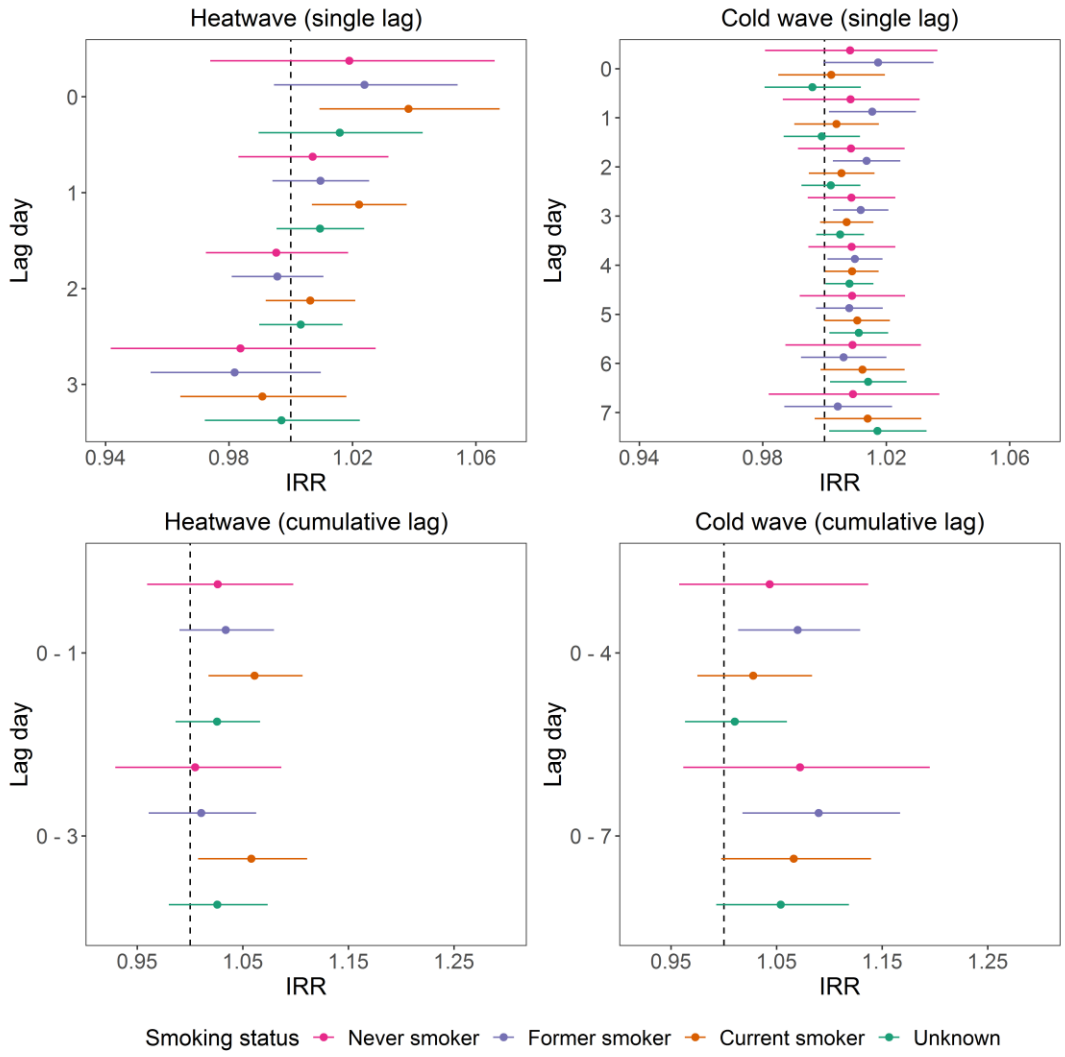

Figure 4-3: Adjusted incidence rate ratios (IRRs) for heat and cold wave associated mortality risk among patients with COPD stratified by smoking status. Single lag IRRs are presented for lag days 0 – 3 for heatwaves as well as cumulative lagged periods of lag days 0 – 1 and 0 – 3. For cold waves, single lag IRRs are presented for lag days 0 – 7 as well as cumulative lagged periods of lag days 0 – 4 and 0 – 7

Urbanicity

Urban patients had the largest heatwave associated mortality risk (cumulative lag day 0 – 1, IRR: 1.06 (95% CI: 1.04, 1.10); AR: 1,062 (95% CI: 576, 1,559). Patients living in rural and highly rural settings did not have associations between heatwaves and mortality (Figure 4-4, Table 4-2, Table S4-5). Urban patients had significantly greater heatwave associated mortality risk compared to rural patients for the cumulative lag days

0 – 1 period (Table S4-5). Cold wave related mortality risk was greatest among urban patients, cumulative lag 0 – 7, IRR: 1.07 (95% CI: 1.03, 1.12); AR: 1,261 (95% CI: 440, 2,105). Rural patients followed a similar pattern as urban patients, but with overall lower mortality risk (Figure 4-4, Table 4-2, Table S4-5). Estimates for highly rural patients were statistically imprecise due to small sample sizes (Table 4-2, Table S4-5).

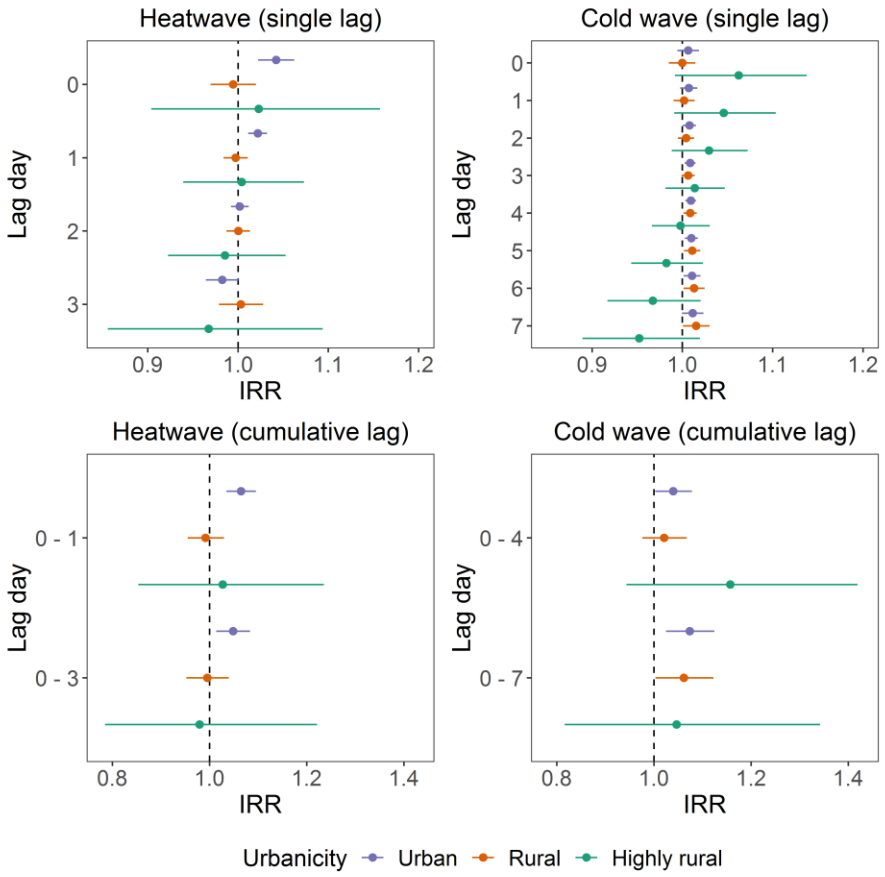

Figure 4-4: Adjusted incidence rate ratios (IRRs) for heat and cold wave associated mortality risk among patients with COPD stratified by urbanicity of patients' residence. Single lag IRRs are presented for lag days 0 – 3 for heatwaves as well as cumulative lagged periods of lag days 0 – 1 and 0 – 3. For cold waves, single lag IRRs are presented for lag days 0 – 7 as well as cumulative lagged periods of lag days 0 – 4 and 0 – 7

Sensitivity analyses

Our model results were robust against stratifying smoking status as a binary (never vs ever-smokers) vs a three-level categorization (never, former and current smokers), and the qualitative conclusions of our study did not change. The results of the

stratified analysis based on the number of additional underlying comorbidities were complex. Patients with COPD and one additional comorbidity had elevated heatwave associated mortality risk however these were attenuated compared to patients with no additional comorbidities (Table S4-6). Patients with 2 – 3 or 4+ comorbidities had no heatwave related mortality associations (Table S4-6). For cold waves, elevated mortality risks were seen in patients with 1 and 2 – 3 additional comorbidities yet these risks were also lower compared to patients with no additional comorbidities (Table S4-6). Patients with 4+ comorbidities did not have cold wave associated mortality risks (Table S4-6).

Discussion

We found heatwave associated mortality risks were greatest among patients with concurrent COPD and asthma. Patients with concurrent asthma and COPD diagnoses, also known as asthma-COPD overlap syndrome (ACOS) exacerbate more frequently, have more respiratory symptoms, and poorer quality of life compared to those with asthma or COPD alone[165–167]. Paradoxically, multiple studies found individuals with ACOS had better disease prognoses and lower mortality rates compared to those with COPD alone[168–172]. Our results are contradictory to previous work as we found individuals with potential ACOS had a higher mortality risk compared to those with COPD alone. Little is known on how COPD and asthma may synergize with each other and heighten sensitivity to extreme heat, however the mechanisms by which asthma and COPD affect the respiratory system may work in tandem to increase heat related mortality risk. Asthma and COPD are both characterized by chronic airway inflammation, whereas asthma has the added component of airway hypersensitivity accompanied by the chronic airflow obstruction of COPD[172]. Our findings suggest individuals with concomitant obstructive lung diseases are at increased risk to extreme heat and should be a target for clinical and public health interventions.

The lack of heatwave related mortality risk among patients with COPD and metabolic syndrome-associated diseases that included cardiovascular diseases, diabetes and obesity was unanticipated and does not align with previous research[126,136,173,174]. The primary cause of death associated with extreme heat often are cardiovascular in nature due in part to increased cardiac demand from vasodilation (a cooling mechanism for the

body) which is especially dangerous for elderly individuals and those with cardiac impairments[37]. While the metabolic syndrome-associated disease category included several related diseases, many of these patients had several comorbidities which may have restricted their ability to go outdoors and decreased their exposure. This is corroborated by our sensitivity analysis which illustrated a lack of associations between heatwaves and mortality among patients that had 2+ comorbidities. CKD also had no increased mortality risk from heatwaves contrary to previous work[126,159,175]. However, CKD is a broad diagnosis including people with milder forms of disease and those with end stage renal disease. It may be that only individuals with more severe kidney disease have a greater risk of heatwave related mortality.

Similar to heatwaves, our cold wave results found individuals with obstructive lung diseases had enhanced mortality risks, albeit results for those with concurrent COPD and asthma were less compelling. Cold wave related mortality among those with obstructive lung diseases may be driven by seasonal increases in viral respiratory infections, bacterial pneumonia or COPD exacerbations which are more common during the winter in temperate climates[132–134].

While attenuated compared to individuals with only COPD, patients with COPD and metabolic syndrome-associated diseases had an increased risk of death due to cold waves. There is a seasonal increase in cardiovascular related deaths during the winter, and recent meta-analyses have found the risk of cardiovascular related mortality due to cold waves ranged from a relative risk of 1.11 to 1.32[145,176]. Another meta-analysis found cold days accounted for 9.1% of cardiovascular deaths worldwide[177]. Other studies found associations between cold temperatures and increases in cardiovascular biomarkers including blood pressure, platelet counts, and serum low density lipoprotein cholesterol as well as inflammatory markers including C-reactive protein, interleukin-6 and plasma fibrogen which may increase the risk of adverse health events among those with underlying cardiovascular conditions[42,43].

We found a large public health burden of heat and cold wave associated mortality among current and former smokers with COPD. Smoking increases the progression of

COPD and is a potent oxidant which may heighten extreme weather mortality risk[178]. Smoking and heat may operate in unison with cardiovascular disease as smokers are at a heightened risk for these diseases compared to non-smokers, and extreme heat places large burdens on the cardiovascular system[37,179]. Cold wave related mortality among smokers with COPD may be related to seasonal trends in respiratory infections, COPD exacerbations and cardiovascular mortality[132,176]. Additionally, smokers are at a greater risk for venous thromboembolisms (VTE) which have seasonal peaks in the winter[180–183].. Seasonal patterns in VTE may be due to changes in coagulation factors, peripheral vasoconstriction, and decreased physical activity during the winter. In combination, smoking and cold waves may also increase risk of VTEs and subsequent mortality events in our cohort.

The UHI Increases temperatures In urban areas due to multiple causes including reduced vegetation and evapotranspiration, large amounts of impervious surfaces with low albedo and increased heat production via industrial, residential, and vehicular emissions[184]. These environmental conditions in urban settings can exacerbate health impacts of heatwaves as was seen in our study; patients residing in urban settings had greater heatwave associated mortality risk compared to patients residing in rural settings. However, the role of UHI in public health studies, while mechanistically intuitive, is not entirely clear. Several studies found the reverse with rural areas having a greater risk of adverse health events from extreme heat compared to urban areas[137,185–187]. The susceptibility in rural communities is thought to be driven by the lack of adaptive capacity for rural areas to cope with climate change rather than extremes in temperature alone[186]. Most large scale epidemiologic studies of extreme weather tend to focus exclusively on cities with far fewer focusing entirely on rural communities or comparing both urban and rural areas[107,108,188,189]. Unlike previous research, rural patients were well-represented in our study.

Our study was not without limitations. The study cohort was predominantly White race, male and older. Furthermore, some of our comorbidity and urbanicity strata had small sample sizes which, coupled with rare exposures of interest and a short study period, may have hampered our ability to detect differences in risks between subgroups.

Our comorbidity stratified analysis was limited by overall smaller sample sizes and by excluding 27.3% of the original cohort. Yet, to isolate specific diseases and their compounding effects on mortality risk with COPD, we believe our approach was the best compromise. There was also a large number of individuals with an unknown smoking status.

Conclusion

Patients with multiple comorbidities, smokers and those residing in urban settings had elevated heat and cold wave related mortality risks. Future research on extreme weather should consider investigating at-risk subgroups who are more susceptible than the general population to external environmental stressors. By understanding the risks climate change has on the most vulnerable members of society, more comprehensive and equitable climate change adaptation measures can be implemented.

Supplement

Table 4-S1: ICD-10 codes used to diagnose COPD as well as comorbidities within 1-year of the initial COPD medical encounter that occurred between 2016 – 2019 which was used to enroll patients into the study cohort

Comorbidity	ICD-10 codes
Asthma	J45.2, J35.3, J45.4, J45.5, J45.9
Chronic kidney disease	N18.1-N18.6, N18.9, E08.22, E09.22, E10.22, E11.22, E13.22, I12.0, I12.9, I13.0-I13.2, Z49.0, Z49.3
Coronary artery disease	I20.0, I20.1, I20.8, I20.9, I21.0-I21.4, I21.9, I21.A, I22.0, I22.1, I22.2, I22.8, I22.9, I23.0-I23.8, I24.0, I24.1, I24.8, I24.9, I25.1-I25.9
Congestive heart failure	I50.1-I50.4, I50.8, I50.9, I09.81, I11.0, I13.0, I13.2, I125.5, I142.0-I142.9, R57.0
COPD	J40, J41.0, J41.1, J41.8, J42, J43.0-J43.2, J43.8, J43.9, J44.0, J44.1, J44.9
Diabetes	E10.0, E10.1, E10.6, E10.8, E10.9, E11.0, E11.1, E11.6, E11.8, E11.9, E12.0, E12.1, E12.6, E12.8, E12.9, E13.0, E13.1, E13.6, E13.8, E13.9, E14.0, E14.1, E14.6, E14.8, E14.9 , E10.2-E10.5, E10.7, E11.2-E11.5, E11.7, E12.2-E12.5, E12.7, E13.2-E13.5, E13.7, E14.2-E14.5, E14.7
Lung cancer	C33, C34.0-C34.3, C34.8, C34.9, C39.0, C39.9, C45.0-C45.2, C45.7, C45.9, D02.1-D02.4, D38.0-D38.6, D49.1, J91.0
Obesity	E66.01, E66.9, Z68.3, Z68.4

Table 4-S2: Heat and cold wave exposure during event (mortality) days stratified by levels of comorbidities, smoking status and urbanicity

		Warm Season		
	Strata	Heatwave	Non-heatwave	Total
Variable	Total cohort	17,621 (9.6%)	166,104 (90.4%)	183,725
Smoking status	Current smoker	5,034 (9.5%)	48,114 (90.5%)	53,148
	Former smoker	4,805 (9.8%)	44,250 (90.2%)	49,055
	Never smoker	2,005 (9.7%)	18,767 (90.3%)	20,772
	Unknown	5,777 (9.5%)	54,973 (90.5%)	60,750
Additional comorbidities (1-year post index date)[A]	None (COPD only)	4,768 (9.7%)	44,332 (90.3%)	49,100
	Asthma	186 (11.3%)	1,453 (88.7%)	1,639
	Chronic kidney disease	546 (10.1%)	4,867 (89.9%)	5,413
	Lung cancer	574 (9.7%)	5,358 (90.3%)	5,932
	Metabolic syndrome	6,823 (9.5%)	64,983 (90.5%)	71,806
Urbanicity	Urban	11,339 (10.4%)	97,764 (89.6%)	109,103
	Rural	6,043 (8.4%)	65,564 (91.6%)	71,607
	Highly rural	239 (7.9%)	2,775 (92.1%)	3,014
		Cold Season		
		Cold wave	Non-cold wave	
	Total cohort	13,961 (7.2%)	179,859 (92.8%)	193,820
Smoking status	Current smoker	3,917 (7.1%)	50,923 (92.9%)	54,840
	Former smoker	3,721 (7.1%)	48,590 (92.9%)	52,311
	Never smoker	1,548 (7.1%)	20,394 (92.9%)	21,942
	Unknown	4,775 (7.4%)	59,952 (92.6%)	64,727
Additional comorbidities (within 1-year post index date)	None (COPD only)	3,645 (7.1%)	47,547 (92.9%)	51,192
	Asthma	102 (6.0%)	1,587 (94.0%)	1,689
	Chronic kidney disease	389 (6.9%)	5,274 (93.1%)	5,663
	Lung cancer	450 (7.5%)	5527 (92.5%)	5977
	Metabolic syndrome	5472 (7.2%)	70520 (92.8%)	75992
Urbanicity	Urban	8,256 (7.2%)	106,583 (92.8%)	114,839
	Rural	5,435 (7.2%)	70,275 (92.8%)	75,710
	Highly rural	270 (8.3%)	3,001 (91.7%)	3,271

[A]Comorbidity was diagnosed within 1 year of the initial COPD clinical encounter that occurred between 2016-2019 which was used to enroll patients into the initial study cohort. The totals presented in the comorbidity strata for the warm and cold seasons will not add up to the total

number of deceased patients in the cohort because patients were excluded if they had a mixture of comorbidities.

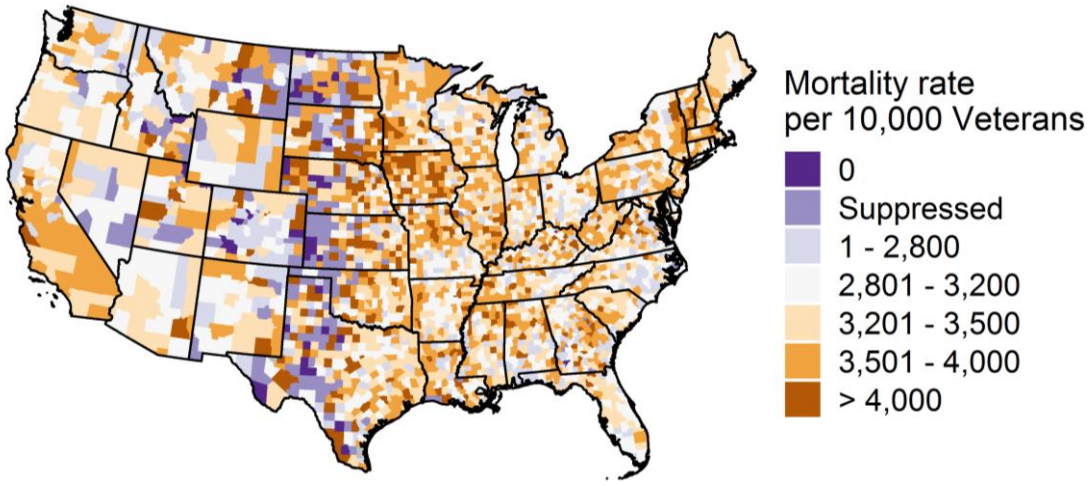

Figure S4-1: County level mortality rates for Veterans with COPD from 2016 – 2021. Counties with less than 20 Veterans had mortality rates suppressed due to unstable estimates. Gray shaded counties had no Veterans.

Table 4-S3: Incidence rate ratios (IRR) describing the association between heat and cold wave related mortality risk among patients stratified by comorbidities diagnosed within 1 year of the initial COPD medical encounter that occurred between 2016 – 2019

Exposure	**Strata (N)**	**Lag[A]**	**IRR (95% CI)**	**P value**
Heatwaves	COPD only (49,100)	0	1.04 (1.01, 1.07)	Referent
		1	1.02 (1.01, 1.04)	Referent
		2	1.01 (0.99, 1.02)	Referent
		3	0.99 (0.96, 1.02)	Referent
		0 – 1	1.07 (1.02, 1.11)	Referent
		0 – 3	1.07 (1.01, 1.12)	Referent
	Asthma (1,639)	0	1.12 (0.96, 1.30)	0.36
		1	1.08 (1.00, 1.18)	0.18
		2	1.05 (0.97, 1.14)	0.30
		3	1.02 (0.88, 1.18)	0.71
		0 – 1	1.21 (0.97, 1.52)	0.27
		0 – 3	1.30 (0.99, 1.70)	0.16
	Chronic kidney disease (5,413)	0	1.03 (0.95, 1.13)	0.88
		1	1.03 (0.98, 1.08)	0.88
		2	1.02 (0.98, 1.07)	0.55
		3	1.02 (0.93, 1.11)	0.58
		0 – 1	1.06 (0.93, 1.21)	0.96
		0 – 3	1.11 (0.95, 1.29)	0.65
	Lung cancer (5,932)	0	1.06 (0.97, 1.15)	0.69
		1	1.01 (0.97, 1.06)	0.63
		2	0.97 (0.93, 1.01)	0.08
		3	0.92 (0.85, 1.00)	0.11
		0 – 1	1.07 (0.95, 1.22)	0.93
		0 – 3	0.96 (0.83, 1.11)	0.18
	Metabolic syndrome (71,806)	0	1.01 (0.99, 1.04)	0.16
		1	1.01 (0.99, 1.02)	0.11
		2	1.00 (0.99, 1.01)	0.57
		3	1.00 (0.97, 1.02)	0.78
		0 – 1	1.02 (0.99, 1.06)	0.13
		0 – 3	1.02 (0.98, 1.06)	0.19
Cold waves	COPD only (51,192)	0	1.00 (0.98, 1.02)	Referent
		1	1.00 (0.99, 1.02)	Referent
		2	1.01 (1.00, 1.02)	Referent
		3	1.01 (1.00, 1.02)	Referent
		4	1.02 (1.01, 1.03)	Referent
		5	1.02 (1.01, 1.03)	Referent
		6	1.03 (1.01, 1.04)	Referent
		7	1.03 (1.02, 1.05)	Referent
		0 – 4	1.04 (0.99, 1.10)	Referent
		0 – 7	1.13 (1.06, 1.21)	Referent
	Asthma (1,689)	0	0.91 (0.83, 1.01)	0.08
		1	0.93 (0.86, 1.01)	0.08
		2	0.96 (0.90, 1.02)	0.11

		3	0.98 (0.94, 1.03)	0.24
		4	1.01 (0.96, 1.06)	0.69
		5	1.03 (0.97, 1.10)	0.74
		6	1.06 (0.98, 1.14)	0.45
		7	1.09 (0.99, 1.20)	0.31
		0 – 4	0.81 (0.60, 1.10)	0.11
		0 – 7	0.96 (0.66, 1.41)	0.42
	Chronic kidney disease (5,663)	0	1.00 (0.95, 1.06)	0.83
		1	1.00 (0.96, 1.05)	0.97
		2	1.00 (0.97, 1.03)	0.64
		3	1.00 (0.97, 1.02)	0.28
		4	1.00 (0.97, 1.02)	0.11
		5	0.99 (0.96, 1.03)	0.09
		6	0.99 (0.95, 1.03)	0.10
		7	0.99 (0.94, 1.04)	0.12
		0 – 4	1.00 (0.85, 1.18)	0.64
		0 – 7	0.97 (0.79, 1.20)	0.17
	Lung cancer (5,977)	0	1.03 (0.98, 1.09)	0.22
		1	1.02 (0.98, 1.07)	0.33
		2	1.02 (0.99, 1.05)	0.60
		3	1.01 (0.98, 1.04)	0.78
		4	1.00 (0.98, 1.03)	0.23
		5	0.99 (0.96, 1.03)	0.08
		6	0.99 (0.95, 1.03)	0.05
		7	0.98 (0.93, 1.03)	0.05
		0 – 4	1.09 (0.93, 1.27)	0.60
		0 – 7	1.04 (0.86, 1.27)	0.45
	Metabolic syndrome (75,992)	0	1.00 (0.99, 1.02)	0.61
		1	1.00 (0.99, 1.02)	0.87
		2	1.01 (1.00, 1.01)	0.68
		3	1.01 (1.00, 1.01)	0.20
		4	1.01 (1.00, 1.01)	0.04
		5	1.01 (1.00, 1.02)	0.02
		6	1.01 (1.00, 1.02)	0.02
		7	1.01 (0.99, 1.02)	0.03
		0 – 4	1.03 (0.98, 1.07)	0.68
		0 – 7	1.05 (0.99, 1.11)	0.09

[A]Single lag IRRs are presented for lag days 0 – 3 for heatwaves as well as cumulative lagged periods of lag days 0 – 1 and 0 – 3. For cold waves, single lag IRRs are presented for lag days 0 – 7 as well as cumulative lagged periods of lag days 0 – 4 and 0 – 7

Table 4-S4: Incidence rate ratios (IRR) describing the association between heat and cold wave related mortality risk among patients stratified by smoking status

Exposure	**Strata (N)**	**Lag[A]**	**IRR (95% CI)**	**P value**
Heatwaves	Never-smoker (20,772)	0	1.02 (0.97, 1.07)	Referent
		1	1.01 (0.98, 1.03)	Referent
		2	1.00 (0.97, 1.02)	Referent
		3	0.98 (0.94, 1.03)	Referent
		0 – 1	1.03 (0.96, 1.10)	Referent
		0 – 3	1.00 (0.93, 1.09)	Referent
	Former smoker (49,055)	0	1.02 (0.99, 1.05)	0.86
		1	1.01 (0.99, 1.03)	0.86
		2	1.00 (0.98, 1.01)	0.98
		3	0.98 (0.95, 1.01)	0.94
		0 – 1	1.03 (0.99, 1.08)	0.86
		0 – 3	1.01 (0.96, 1.06)	0.90
	Current smoker (53,148)	0	1.04 (1.01, 1.07)	0.49
		1	1.02 (1.01, 1.04)	0.31
		2	1.01 (0.99, 1.02)	0.43
		3	0.99 (0.96, 1.02)	0.78
		0 – 1	1.06 (1.02, 1.11)	0.41
		0 – 3	1.06 (1.01, 1.11)	0.27
	Unknown (60,750)	0	1.02 (0.99, 1.04)	0.91
		1	1.01 (1.00, 1.02)	0.87
		2	1.00 (0.99, 1.02)	0.56
		3	1.00 (0.97, 1.02)	0.60
		0 – 1	1.03 (0.99, 1.07)	0.99
		0 – 3	1.03 (0.98, 1.07)	0.65
Cold waves	Never-smoker (21,942)	0	1.01 (0.98, 1.04)	Referent
		1	1.01 (0.99, 1.03)	Referent
		2	1.01 (0.99, 1.03)	Referent
		3	1.01 (0.99, 1.02)	Referent
		4	1.01 (0.99, 1.02)	Referent
		5	1.01 (0.99, 1.03)	Referent
		6	1.01 (0.99, 1.03)	Referent
		7	1.01 (0.98, 1.04)	Referent
		0 – 4	1.04 (0.96, 1.14)	Referent
		0 – 7	1.07 (0.96, 1.20)	Referent
	Former smoker (52,311)	0	1.02 (1.00, 1.04)	0.59
		1	1.02 (1.00, 1.03)	0.60
		2	1.01 (1.00, 1.02)	0.63
		3	1.01 (1.00, 1.02)	0.72
		4	1.01 (1.00, 1.02)	0.90
		5	1.01 (1.00, 1.02)	0.93
		6	1.01 (0.99, 1.02)	0.83
		7	1.00 (0.99, 1.02)	0.77
		0 – 4	1.07 (1.01, 1.13)	0.63
		0 – 7	1.09 (1.02, 1.17)	0.80

	Current smoker (54,840)	0	1.00 (0.99, 1.02)	0.71
		1	1.00 (0.99, 1.02)	0.73
		2	1.01 (0.99, 1.02)	0.77
		3	1.01 (1.00, 1.02)	0.86
		4	1.01 (1.00, 1.02)	0.99
		5	1.01 (1.00, 1.02)	0.87
		6	1.01 (1.00, 1.03)	0.81
		7	1.01 (1.00, 1.03)	0.77
		0 – 4	1.03 (0.97, 1.08)	0.77
		0 – 7	1.07 (1.00, 1.14)	0.93
	Unknown (64,727)	0	1.00 (0.98, 1.01)	0.45
		1	1.00 (0.99, 1.01)	0.47
		2	1.00 (0.99, 1.01)	0.52
		3	1.01 (1.00, 1.01)	0.66
		4	1.01 (1.00, 1.02)	0.93
		5	1.01 (1.00, 1.02)	0.83
		6	1.01 (1.00, 1.03)	0.69
		7	1.02 (1.00, 1.03)	0.62
		0 – 4	1.01 (0.96, 1.06)	0.52
		0 – 7	1.05 (0.99, 1.12)	0.78

[A]Single lag IRRs are presented for lag days 0 – 3 for heatwaves as well as cumulative lagged periods of lag days 0 – 1 and 0 – 3. For cold waves, single lag IRRs are presented for lag days 0 – 7 as well as cumulative lagged periods of lag days 0 – 4 and 0 – 7

Table 4-S5: Incidence rate ratios (IRR) describing the association between heat and cold wave related mortality risk among patients stratified by urbanicity of patients' residence

Exposure	**Strata (N)**	**Lag[A]**	**IRR (95% CI)**	**P value**
Heatwaves	Urban (109,103)	0	1.04 (1.02, 1.06)	<0.01
		1	1.02 (1.01, 1.03)	<0.01
		2	1.00 (0.99, 1.01)	0.84
		3	0.98 (0.96, 1.00)	0.18
		0 – 1	1.06 (1.04, 1.10)	<0.01
		0 – 3	1.05 (1.01, 1.08)	0.06
	Rural (71,607)	0	0.99 (0.97, 1.02)	Referent
		1	1.00 (0.98, 1.01)	Referent
		2	1.00 (0.99, 1.01)	Referent
		3	1.00 (0.98, 1.03)	Referent
		0 – 1	0.99 (0.96, 1.03)	Referent
		0 – 3	1.00 (0.95, 1.04)	Referent
	Highly Rural (3,014)	0	1.02 (0.90, 1.16)	0.66
		1	1.00 (0.94, 1.07)	0.85
		2	0.99 (0.92, 1.05)	0.67
		3	0.97 (0.86, 1.09)	0.57
		0 – 1	1.03 (0.85, 1.24)	0.72
		0 – 3	0.98 (0.79, 1.22)	0.89
Cold waves	Urban (114,839)	0	1.01 (0.99, 1.02)	Referent
		1	1.01 (1.00, 1.02)	Referent
		2	1.01 (1.00, 1.02)	Referent
		3	1.01 (1.00, 1.01)	Referent
		4	1.01 (1.00, 1.02)	Referent
		5	1.01 (1.00, 1.02)	Referent
		6	1.01 (1.00, 1.02)	Referent
		7	1.01 (1.00, 1.02)	Referent
		0 – 4	1.04 (1.00, 1.08)	Referent
		0 – 7	1.07 (1.03, 1.12)	Referent
	Rural (75,710)	0	1.00 (0.99, 1.01)	0.49
		1	1.00 (0.99, 1.01)	0.50
		2	1.00 (1.00, 1.01)	0.53
		3	1.01 (1.00, 1.01)	0.65
		4	1.01 (1.00, 1.02)	0.88
		5	1.01 (1.00, 1.02)	0.89
		6	1.01 (1.00, 1.02)	0.76
		7	1.02 (1.00, 1.03)	0.69
		0 – 4	1.02 (0.98, 1.07)	0.53
		0 – 7	1.06 (1.00, 1.12)	0.76
	Highly Rural (3,271)	0	1.06 (0.99, 1.14)	0.13
		1	1.05 (0.99, 1.10)	0.18
		2	1.03 (0.99, 1.07)	0.31
		3	1.01 (0.98, 1.05)	0.77
		4	1.00 (0.97, 1.03)	0.50
		5	0.98 (0.94, 1.02)	0.19

		6	0.97 (0.92, 1.02)	0.11
		7	0.95 (0.89, 1.02)	0.09
		0 – 4	1.16 (0.94, 1.42)	0.31
		0 – 7	1.05 (0.82, 1.34)	0.84

[A]Single lag IRRs are presented for lag days 0 – 3 for heatwaves as well as cumulative lagged periods of lag days 0 – 1 and 0 – 3. For cold waves, single lag IRRs are presented for lag days 0 – 7 as well as cumulative lagged periods of lag days 0 – 4 and 0 – 7

Table 4-S6: Incidence rate ratios (IRR) describing the association between heat and cold wave related mortality risk among patients stratified by the number of additional comorbidities a patient had within 1 year of their initial COPD medical encounter that occurred between 2016 – 2019

Exposure	**Strata (N)**	**Lag[A]**	**IRR (95% CI)**	**P value**
Heatwaves	0 additional comorbidities (49,100)	0	1.04 (1.01, 1.07)	Referent
		1	1.02 (1.01, 1.04)	Referent
		2	1.01 (0.99, 1.02)	Referent
		3	0.99 (0.96, 1.02)	Referent
		0 – 1	1.07 (1.02, 1.11)	Referent
		0 – 3	1.07 (1.01, 1.12)	Referent
	1 additional comorbidity (51,659)	0	1.03 (1.00, 1.06)	0.61
		1	1.01 (1.00, 1.03)	0.29
		2	1.00 (0.98, 1.01)	0.23
		3	0.98 (0.95, 1.01)	0.49
		0 – 1	1.04 (1.00, 1.09)	0.47
		0 – 3	1.02 (0.97, 1.07)	0.18
	2-3 additional comorbidities (63,596)	0	1.01 (0.98, 1.03)	0.07
		1	1.01 (0.99, 1.02)	0.08
		2	1.01 (0.99, 1.02)	0.89
		3	1.01 (0.98, 1.03)	0.42
		0 – 1	1.01 (0.97, 1.05)	0.07
		0 – 3	1.03 (0.98, 1.07)	0.25
	4+ additional comorbidities (19,370)	0	1.03 (0.99, 1.08)	0.76
		1	1.01 (0.98, 1.03)	0.25
		2	0.98 (0.96, 1.01)	0.07
		3	0.96 (0.91, 1.00)	0.20
		0 – 1	1.04 (0.97, 1.11)	0.53
		0 – 3	0.98 (0.90, 1.06)	0.07
Cold waves	0 additional comorbidities (N = 51,192)	0	1.00 (0.98, 1.02)	Referent
		1	1.00 (0.99, 1.02)	Referent
		2	1.01 (1.00, 1.02)	Referent
		3	1.01 (1.00, 1.02)	Referent
		4	1.02 (1.01, 1.03)	Referent
		5	1.02 (1.01, 1.03)	Referent
		6	1.03 (1.01, 1.04)	Referent
		7	1.03 (1.02, 1.05)	Referent
		0 – 4	1.04 (0.99, 1.10)	Referent
		0 – 7	1.13 (1.06, 1.21)	Referent
	1 additional comorbidity (54,145)	7	1.00 (0.98, 1.02)	0.82
		1	1.00 (0.99, 1.02)	0.93
		2	1.00 (0.99, 1.01)	0.54
		3	1.00 (1.00, 1.01)	0.17
		4	1.01 (1.00, 1.01)	0.05
		5	1.01 (1.00, 1.02)	0.03
		6	1.01 (0.99, 1.02)	0.04
		7	1.01 (0.99, 1.03)	0.06

		0 – 4	1.02 (0.96, 1.07)	0.54
		0 – 7	1.04 (0.97, 1.11)	0.08
	2-3 additional comorbidities (67,690)	0	1.01 (1.00, 1.03)	0.19
		1	1.01 (1.00, 1.02)	0.35
		2	1.01 (1.00, 1.02)	0.79
		3	1.01 (1.00, 1.02)	0.41
		4	1.01 (1.00, 1.01)	0.05
		5	1.00 (0.99, 1.01)	0.01
		6	1.00 (0.99, 1.01)	0.01
		7	1.00 (0.99, 1.02)	0.01
		0 – 4	1.05 (1.00, 1.10)	0.79
		0 – 7	1.06 (1.00, 1.12)	0.15
	4+ additional comorbidities (20,793)	0	1.00 (0.97, 1.03)	0.94
		1	1.00 (0.98, 1.02)	0.81
		2	1.00 (0.98, 1.02)	0.46
		3	1.00 (0.99, 1.02)	0.15
		4	1.00 (0.99, 1.02)	0.05
		5	1.00 (0.98, 1.02)	0.04
		6	1.00 (0.98, 1.02)	0.05
		7	1.00 (0.98, 1.03)	0.07
		0 – 4	1.00 (0.92, 1.09)	0.46
		0 – 7	1.01 (0.91, 1.12)	0.08

[A]Single lag IRRs are presented for lag days 0 – 3 for heatwaves as well as cumulative lagged periods of lag days 0 – 1 and 0 – 3. For cold waves, single lag IRRs are presented for lag days 0 – 7 as well as cumulative lagged periods of lag days 0 – 4 and 0 – 7

Chapter 5: Compound drought and heatwave effects on mortality risk in United States Veterans with chronic obstructive pulmonary disease

Background: Compound extreme weather events are the co-occurrence of harmful weather conditions that jointly exacerbate human health risks beyond any single event alone. Both drought and heatwaves are extreme weather events associated with adverse health, but their combined impact is poorly understood.

Methods: We designed a case-crossover study to estimate heatwave associated mortality modified by drought status in 183,725 Veterans (2016 – 2021) with chronic obstructive pulmonary disease (COPD) using conditional logistic regression with distributed lag models for single and cumulative lag exposure. Droughts were categorized as both binary and categorical metrics, and we also explored the timing of heatwaves as a risk factor.

Results: Heatwaves are amplified during drought conditions, and the percentage of mortality events attributable to heatwaves during severe drought was 9.91% (95% CI: -1.01, 20.63).

Discussion: Our results demonstrate that compound extreme weather conditions may substantially increase health risks and present a growing human health threat under climate change.

Introduction

A growing number of studies are evaluating the public health impacts of climate change. Yet, climate hazards such as heatwaves, wildfires, and drought seldom occur in isolation and may exist as either compounding events, occurring at the same time in the same place[190,191], or cascading events, occurring one after the other without normal conditions in between[192]. While the frequency of compounding climate events is expected to increase under climate change[1,190,193–195], little work exists from a public health perspective describing the additive health risks of compound climate events.

Extreme heat has severe public health implications with increases in morbidity and mortality particularly for vulnerable individuals living with climate sensitive diseases including chronic respiratory illnesses[125]. Prior research on individuals with chronic obstructive pulmonary disease (COPD), a chronic inflammatory lung disease characterized by obstructed airflow, found increased risk of morbidity and mortality associated with extreme heat exposure[54,58,139]. While unknown, plausible biological pathways relating extreme heat and COPD include fluid loss, impaired pulmonary perfusion, and airway inflammation[44]. Individuals with COPD tend to have diagnoses of other chronic diseases including cardiovascular diseases that are known to increase vulnerability to extreme heat[37]. COPD also acts as a systemic disorder, hastening the progression of other comorbidities and worsening overall health[20].

Drought is a slow onset, spatially defuse climate hazard with both direct and indirect effects on infectious and non-infectious diseases[196]. Drought research in public health is nascent, but studies have examined drought effects on mortality[197], mental health[198], respiratory[199–201] and cardiovascular diseases[200,201]. As a geographically broad weather event, droughts can synergize with other environmental exposures resulting in a worsening of existing environmental hazards. Previous work found drought conditions were strongly correlated with increased ambient ozone air pollution[202], and drought may degrade air quality via increases in dust or by exacerbating other disasters such as wildfires[196,203]. Other research found an increase in the frequency of compound drought and heatwave events which is likely to continue or worsen under predicted climate change scenarios[204–206]. In temperate regions of the world, droughts can increase the

severity of heatwaves particularly during anticyclonic activity[196]. High pressure systems with clear skies in combination with increased temperatures during the summer can linger over land masses for an extended period of time[196]. In addition, the lack of soil moisture attributed to drought may increase the frequency of surface temperature anomalies[196]. Thus, public health research on the impacts of compound drought and heatwave events on climate sensitive diseases, including respiratory related outcomes, is needed.

We hypothesize compound drought and heatwave events will increase the risk of mortality in a population of highly susceptible individuals diagnosed with a chronic respiratory disease. Using data from the Veterans Health Administration (VHA) on people diagnosed with COPD from 2016 to 2021, we designed a case-crossover study to estimate the risk of all-cause mortality due to heatwaves during periods with and without drought. We further investigated if the timing of the heatwave during the warm season (early vs late) had disparate mortality responses with respect to drought conditions. Our study will demonstrate the modification of heatwaves by drought conditions and potential impacts on adverse health outcomes.

Methods

Study cohort

We acquired electronic health data from a population of Veterans diagnosed with COPD who died between 2016 and 2021 during the warm season (April – September) in the United States (N = 183,725). These Veterans were between the ages of 35 and 100 at age of initial COPD diagnosis and had a minimum of two clinical encounters with an International Classification of Diseases 9th or 10th revision codes for COPD (ICD-9: 490, 491.XX, 492.XX, 496 or ICD-10: J40, J41.X, J42, J43.X, J44.X) between 2016 and 2019[110]. Data including age, self-reported gender and race, and geocoded residential addresses of Veterans were obtained from electronic health data stored in the VHA Veteran Enrollee files, Corporate Data Warehouse[111].

Weather data

We assigned daily weather data (mean ambient temperature, total precipitation, mean wind speed and mean specific humidity) to geocoded residential locations by

spatially overlaying these locations with gridded climatological data for the warm season of the year. GridMet, a highly resolved gridded climatological dataset with a spatial resolution of 4x4km, was used to assign daily weather exposure[112]. Heatwaves were defined as $\geq$2 consecutive days with a mean ambient daily temperature exceeding the 90th percentile of mean ambient warm season daily temperature based on a 30-year reference distribution (1992 – 2021) at each Veteran's geocoded home location.

Drought data

We defined drought using two separate data sources that measure drought differently: the United States Drought Monitor (USDM) and the Standardized Precipitation-Evapotranspiration Index (SPEI)[207,208]. The USDM is a collaborative effort of governmental agencies that blend physical climate data (precipitation, streamflow, soil moisture, etc.), drought impacts, and on-the-ground expert observations to classify drought conditions for North America on a weekly basis[208]. USDM values include no drought, abnormally dry (D0) and four levels of drought: moderate drought (D1), severe drought (D2), extreme drought (D3), and exceptional drought (D4)[208]. SPEI is an extension of the Standardized Precipitation Index (SPI) that uses precipitation and potential evapotranspiration data to classify drought, thereby capturing the impact of increased temperature on water demand[209]. SPEI data is globally available at several timescales from 1 to 48-months.

We acquired weekly USDM data at the county level from the USDM program, and the 12-month SPEI index at a spatial resolution of 5km and a monthly temporal resolution from the National Center for Environmental Information[209]. The 12-month SPEI timescale captures longer-term deviations in precipitation and evapotranspiration compared to shorter term timescales (e.g. 1 or 3-month timescales). We classified droughts on a month-to-month basis using both a binary and a categorical definition of drought.

To convert weekly USDM into monthly data, we expanded the weekly data into a daily time series assuming each day had the same USDM value during a given week. Next, we assigned a single county-level USDM value for each day (no drought, D0, D1,

D2, D3 or D4) using the USDM category with the largest affected land area per county per day (highest value chosen in the presence of ties). The daily USDM data were collapsed into simplified binary and categorical definitions. The binary definition included no drought (no drought and D0) and drought (D1 to D4). The categorical definition included no drought, moderate drought (D1 to D2) and severe drought (D3 to D4). The daily data were aggregated to the monthly level where each month was assigned the most frequent daily USDM drought category (for binary and categorical definitions respectively) in that month. For SPEI, we applied a zonal mean to calculate the mean SPEI values in each county per month. The raw SPEI values were converted to USDM equivalent values for ease of comparison[210], and these USDM equivalent values were then converted into binary and categorical drought definitions described above.

Study design

We used a time stratified case-crossover study design to determine if heatwave associated mortality risk is modified by drought conditions in a nationwide population of Veterans with COPD. In a case-crossover approach, each Veteran's date of death is matched with referent days of the same day of week, month and year as the date of death allowing us to quantify if the risk of dying is greater during extreme weather conditions (e.g. heatwave or heatwave during drought) compared to normal conditions. A strength of this self-matched study design is that each person is compared to themselves and it controls for time-invariant, seasonal and day of week confounding by design[92,97,104]. We additionally adjusted for time varying confounders including daily precipitation, specific humidity, wind speed, and holiday status, including all federally recognized holidays and Easter.

Statistical analyses

Distributed lag models (DLM) with conditional logistic regression were developed to estimate incidence rate ratios (IRR) of single lag and cumulative lagged associations between heatwaves and mortality during both drought and non-drought conditions[92]. Precipitation and wind speed were adjusted for in statistical models as linear terms, specific humidity was expressed as a natural cubic spline term with five degrees of freedom and holiday status was a binary term.

Our primary analysis evaluated the effect of heatwaves on all-cause mortality modified by drought status using our USDM definition with stratified data analyses. We stratified the data for 1) binary drought, 2) categorical drought, and 3) early (April to June) and late (July to September) season heatwaves. Stratification by heatwave timing was only completed for the binary drought definition. As a secondary analysis, we repeated the stratified data analyses and timing evaluation using the SPEI drought definition.

Heatwave effects were estimated at each single lag day from 0 to 3 days (i.e. day of death to 3 days prior), as well as the cumulative (i.e. additive) effect across the lagged period of 0 to 1 and 0 to 3 days. The percentage of mortality events attributable to heatwave exposure during the different drought conditions (AR%) was calculated for the cumulative lagged periods following Equation 5-1.

$$AR\% = \frac{(IRR - 1)}{IRR} * 100$$

Equation 5-1: Attributable risk (%) calculation

Z-tests were used to compare differences of stratum specific effects at each lag day and cumulative lag period[121]. All analyses were completed in R statistical software (version 4.1)[122], and the DLM models were built using the *dlnm* R package[164].

Sensitivity analyses

First, we defined droughts using a duration criterion similar to Berman et al., 2017, where drought events could only be considered if a county was in the USDM D1 category or above for a sustained period of at least 5 consecutive months, otherwise a county would be classified as not experiencing a drought event[200]. This analysis enabled us to restrict our assessment to only persistent drought events and was completed for both USDM and SPEI binary drought definitions. In a second sensitivity analysis, we defined drought conditions using weekly USDM data. This was completed for the binary USDM drought definition where individuals in our study were partitioned into strata of drought based on exposure during their week of mortality. In a third sensitivity analysis, we assessed potential confounding from ambient air pollution exposure by including daily

concentrations of fine particulate matter ($PM_{2.5}$) into our model of binary drought (USDM) for a subset of Veterans living within a 10km radius of an EPA regulatory monitor site (N = 20,735)[211].

Ethics Statement

This study was approved by the institutional review boards at the Minneapolis VA Health Care System and the University of Minnesota.

Results

Descriptive statistics

Our study cohort included 183,725 Veterans with COPD who died during the warm season between 2016 to 2021 (Figure S5-1). Of these Veterans with COPD, the mean age was 76.9 years, and they were predominantly male and of White race (Table 5-1).

Table 5-1: Demographic summary of Veterans with COPD who died during the warm season (April – September), 2016 to 2021

Baseline Characteristic	
Age (years), mean (SD)	76.9 (10.1)
Gender, frequency (%)	
Male	179,850 (97.9%)
Female	3,872 (2.1%)
Transgender	3 (<1%)
Race, frequency (%)	
White	145,575 (79.2%)
Black	20,987 (11.4%)
American Indian / Alaska Native	1,609 (<1%)
Asian American / Pacific Islander	1720 (<1%)
Missing	13,834 (7.5%)

There was a pattern of higher mortality rates among Veterans exposed to both drought and heatwaves which increased as droughts became more severe (Table 5-2). Among Veterans exposed to heatwaves during severe drought conditions, 15.3% of Veterans died compared to 9% of Veterans who died during heatwaves under non-drought conditions (Table 5-2). Higher mortality rates under simultaneous heatwave and

drought conditions were also observed when stratifying the data by timing of heatwaves in the warm season of the year (Table S5-1). Patterns in mortality were similar for droughts defined using SPEI (Table 5-2).

Table 5-2: Frequency of deceased Veterans with COPD stratified by heatwave and drought status on day on death (USDM and SPEI)

Drought Index	Heatwave status	Drought classification			
		No drought	Any drought	Moderate drought	Severe drought
USDM	Non-heatwaves (N, %)	145,336 (91.0%)	20,768 (86.3%)	16,369 (86.8%)	4,399 (84.7%)
	Heatwaves (N, %)	14,336 (9.0%)	3,285 (13.7%)	2,489 (13.2%)	796 (15.3%)
	Total	159,672	24,053	18,858	5,195
SPEI	Non-heatwaves (N, %)	129,127 (91.5%)	36,977 (87.0%)	25,760 (87.6%)	11,217 (85.6%)
	Heatwaves (N, %)	12,072 (8.5%)	5,549 (13.0%)	3,661 (12.4%)	1,888 (14.4%)
	Total	141,199	42,526	29,421	13,105

Among days of mortality in our cohort, both heatwave and drought exposure days were hotter than days with only heatwave exposure (Table 5-3). Heatwaves had an average temperature of 27.81°C during non-drought periods but had an average temperature of 28.35°C during drought conditions (USDM binary drought) (Table 5-3). Heatwaves also lasted longer during drought conditions with an average of 4.85 days in the absence of drought and 6.41 days for heatwaves during drought (Table 5-3). These differences in heatwave temperature and duration were more pronounced when comparing heatwaves that occurred during severe drought to no drought. Heatwaves during drought were also hotter and longer than heatwaves during non-drought conditions when comparing exposure based on timing of heatwaves in the warm season of the year (early vs late) (Table S5-2). Drought as defined by SPEI similarly accentuated the effects of heatwave, with the exception that duration increased from moderate to severe drought categories unlike USDM where little change was seen (Table 5-3). In addition, there were spatial heterogeneities in both heatwave temperature and duration changes during drought

conditions with some areas of the United States having heatwaves that were colder and shorter during drought compared to non-drought conditions (Figure S5-2).

Table 5-3: Mean heatwave temperature and duration on days of Veteran mortality stratified by USDM and SPEI binary and categorical drought categories

Drought Index	Heatwave status / duration	Drought classification			
		No drought	Any drought	Moderate drought	Severe drought
USDM	Non-heatwave mean temperature °C (SD)	20.39 (6.46)	21.15 (6.04)	21.01 (6.01)	21.71 (6.14)
	Heatwave mean temperature °C (SD)	27.81 (2.71)	28.35 (4.27)	28.09 (4.15)	29.16 (4.54)
	Heatwave mean duration days (SD)	4.85 (3.14)	6.41 (5.56)	6.47 (5.95)	6.25 (4.12)
SPEI	Non-heatwave mean temperature °C (SD)	20.32 (6.39)	21.09 (6.46)	20.79 (6.54)	21.77 (6.20)
	Heatwave mean temperature °C (SD)	27.52 (2.57)	28.74 (3.81)	28.63 (3.58)	28.97 (4.21)
	Heatwave mean duration days (SD)	4.69 (2.92)	6.13 (4.99)	5.66 (3.93)	7.06 (6.48)

Heatwave associated mortality during drought and non-drought conditions

We observed a pattern of increased mortality risk during heatwaves under drought conditions, although, the estimates were less precise, and stratum specific differences did not exclude the null at the 95% confidence level. The cumulative heatwave effect during drought was greatest across the lagged period of days 0 to 1 with an IRR: 1.08 (95% CI: 1.03, 1.14) (Figure 5-1). Among Veterans exposed to heatwaves during drought conditions in the cumulative lag day 0 to 1 exposure period, 7.41% (95% CI: 2.91, 12.28) of deaths were attributable to heatwaves (Table 5-4). Heatwave related mortality risks increased as the severity of drought increased from moderate to severe. The cumulative effect of heatwaves across the entire 3-day lag period during severe drought had an IRR:

1.11 (95% CI: 0.99, 1.26), AR%: 9.91% (95% CI:-1.01, 20.63) compared to IRR: 1.02 (95% CI: 0.99, 1.05) when no drought was present (Figure 5-1, Table S5-3).

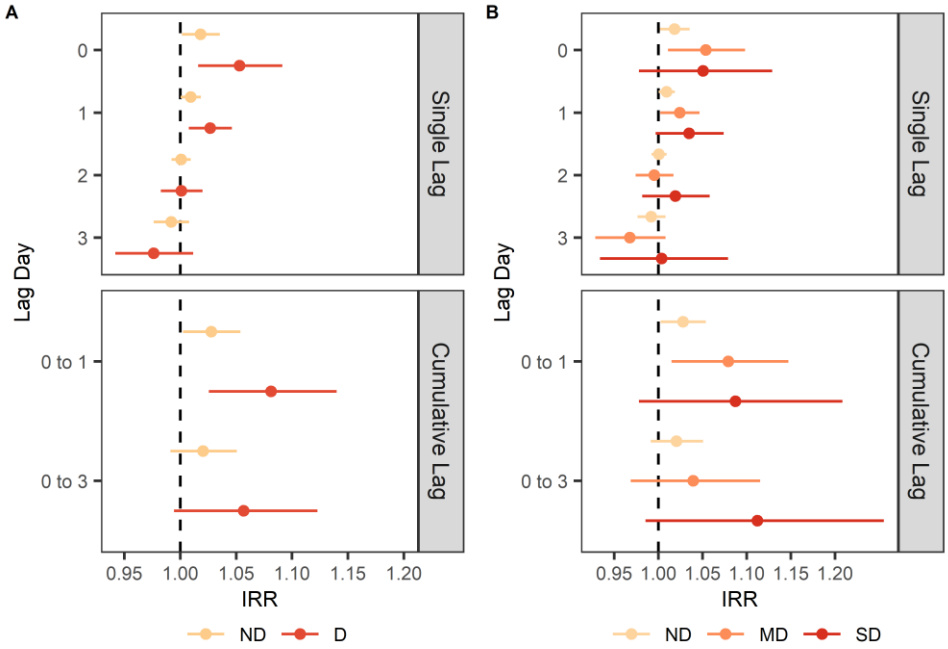

Figure 5-1: Adjusted incidence rate ratios (IRR) describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary (A) and categorical (B) USDM drought definitions. ND = No drought, D = Drought, MD = Moderate drought, SD = Severe drought

Table 5-4: Attributable risk (%) for the cumulative heatwave effects (lag day 0 to 1 and lag day 0 to 3) stratified by USDM drought status (binary and categorical) and by timing of heatwaves in the warm season of the year

Strata	AR% (95% CI) Cumulative lag 0 to 1	AR% (95% CI) Cumulative lag 0 to 3
No drought	2.91 (0.00, 4.76)	1.96 (-1.01, 4.76)
Any drought	7.41 (2.91, 12.28)	5.66 (-1.01, 10.71)
Moderate drought	7.41 (1.96, 13.04)	3.85 (-3.09, 10.71)
Severe drought	8.26 (-2.04, 17.36)	9.91 (-1.01, 20.63)
Heatwave timing		
Early (No Drought)	9.09 (3.85, 13.79)	5.66 (-1.01, 12.28)
Early (Drought)	8.26 (-3.09, 18.03)	8.26 (-5.26, 20.00)
Late (No Drought)	0.99 (-1.01, 3.85)	0.99 (-2.04, 3.85)
Late (Drought)	7.41 (1.96, 13.04)	4.76 (-2.04, 10.71)

Heatwave associated mortality during drought and non-drought conditions stratified by timing of heatwaves in the warm season

There was a pattern of heatwaves during drought conditions in the latter half of the warm season resulting in a larger mortality risk than heatwaves during non-drought periods (Figure 5-2, Table 5-4, Table S5-4), although the estimates were less precise, and stratum specific differences did not exclude the null at the 95% confidence level. The cumulative mortality risk over lag days 0 to 1 was IRR: 1.08 (95% CI: 1.02, 1.15) for late season heatwaves during drought compared to IRR: 1.01 (95% CI: 0.98, 1.04) for late season heatwaves during non-drought periods (Figure 5-2, Table S4). This difference in risk was reflected in the AR% estimates, AR%: 7.41% (95% CI: 1.96, 13.04) vs AR%: 0.99% (95% CI: -1.01, 3.85). There were no differences in heatwave associated mortality risk comparing drought and non-drought periods in the early warm season (Table 5-4, Table S5-4).

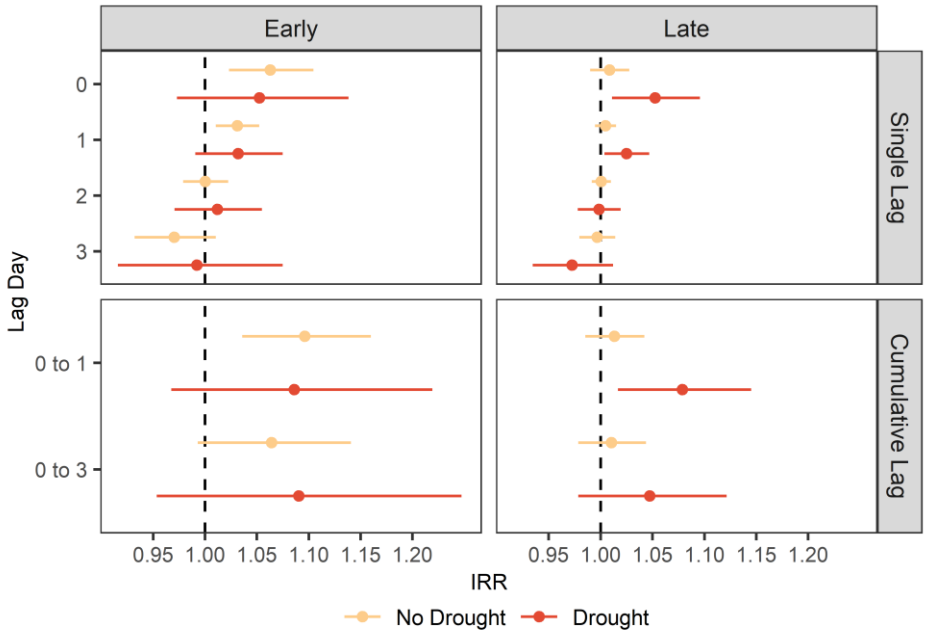

Figure 5-2: Adjusted incidence rate ratios (IRR) describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary USDM drought definitions and timing of heatwaves in the warm season of the year (early = April to June and late = July to September)

Heatwave associated mortality during drought and non-drought conditions defined by SPEI

We found similar results for heatwave associated mortality stratified by binary drought, categorical drought, and timing of heatwaves in the year when using SPEI to define droughts (Tables S5-5 to S5-7, Figures S5-3 to S5-4). In general, effect estimates were slightly attenuated compared to results using USDM defined droughts (Tables S5-5 to S5-7, Figures S5-3 to S5-4).

Sensitivity analyses

Our sensitivity analysis using a 5-month duration criterion to define drought events found heatwave associated mortality risks during drought were larger compared to month-to-month drought definitions (Figure S5-5). The cumulative lag day 0 to 1 IRR for heatwaves during drought events was IRR: 1.12 (95% CI: 1.06, 1.19), a 4% increase in mortality risk compared to our primary results using monthly drought exposure. We found no differences between heatwave associated mortality risk during drought and non-

drought periods using SPEI comparing droughts defined on a monthly basis vs the 5-month duration criterion (Figure S5-5). When defining drought exposure using weekly rather than monthly USDM data, we found no differences in heatwave associated mortality risk compared to monthly USDM analysis results (Figure S5-6). Our models were robust to potential confounding bias by ambient air pollution. In a model adjusted for $PM_{2.5}$ among Veterans who lived within 10km of EPA air monitors, the cumulative lag 0 to 1 IRR for heatwaves during drought was IRR: 1.16 (95% CI: 1.03, 1.32) compared to IRR: 1.14 (95% CI: 1.06, 1.23) in a model not adjusted for $PM_{2.5}$ in this same population. This was less than a 2% change in the magnitude of the effect estimate and does not change the qualitative conclusions of our study.

Discussion

Our nationwide evaluation showed a pattern of hotter and longer duration heatwaves occurring during drought conditions compared to heatwaves during non-drought conditions. We estimated an increased heatwave associated mortality risk during drought compared to non-drought periods that intensified with increasing drought severity among Veterans with COPD. Heatwave associated mortality risks were also greater during drought conditions in the late warm season compared to heatwaves under non-drought conditions. To our knowledge, this is the first nationwide study to assess and demonstrate the public health impacts of compound heat and drought events.

Climate change is anticipated to worsen existing environmental hazards such as heatwaves, droughts, wildfires, floods and air quality, and vulnerable populations including those with underlying comorbidities may be disproportionately impacted[1]. An increase in climate induced adverse health events may also overburden existing healthcare infrastructures. One study estimated extreme weather events and climate associated diseases in 2012 alone cost the United States $10 billion in healthcare related costs[212]. Compound and cascading climate hazards are critical to consider as they have the potential to induce greater economic costs and loss of life than any single climate event alone. In North America, the summer of 2023 had several compounding climate disasters including extreme heat, drought and wildfires. The devastating 2023 wildfire in Maui, Hawaii notably occurred after a rapid three-week flash drought, a phenomenon of

drought and heat intensification that amplifies vegetation dryness and heightens conditions for severe wildfire events[213]. The public health impacts of these compounding events and their long-term economic and societal effects have yet to be quantified but are essential to uncover so governments can better prepare to adapt and mitigate against the increasing threat of compounding climate extremes.

Drought and heat are a notable compound climate hazard for North America which has an historical record of pan-continental droughts and is experiencing a trend of increasing summer temperatures[214,215]. Compound drought and heatwave events are hypothesized to emerge due to complex land-atmosphere feedback loops. As soil and vegetation become desiccated, evapotranspiration declines and the air becomes drier which reduces the likelihood of precipitation and favors the genesis of meteorological droughts[216]. Meanwhile, as evapotranspiration declines, a larger fraction of incoming solar radiation warms the environment which increases atmospheric heat that may generate a heatwave or amplify its intensity[216]. Changes in heatwave intensity and duration may explain the increased mortality risk we observed for heatwaves during drought compared to non-drought conditions. Our cohort of older individuals all have a diagnosis of a chronic respiratory disease that may additionally heighten their sensitivity to adverse health effects from extreme heat[37,38,45].

The attribution of greater heatwave associated mortality risk to late season drought conditions differs from previous work on heatwaves alone. Prior research identified the initial heatwaves of the season having greater mortality risk under the hypothesis that the population has yet to physiologically acclimatize to warmer summer temperatures[135,217]. This can place individuals at greater susceptibility to extreme heat. Our results were somewhat contrary to these previous findings. While early season heatwaves tended to induce larger mortality risks compared to late season heatwaves, there were no differences in early season heatwave associated mortality during drought and non-drought conditions. However, there was a relatively large difference in late season heatwave associated mortality comparing drought to non-drought conditions. Our data show similar increases in mean heatwave temperature comparing drought and non-drought conditions for both early and late season heatwaves. Yet, late season heatwaves

tended to last longer on average than early season heatwaves particularly during drought conditions. Therefore, it may be that the extended duration of late season heatwaves during drought conditions may be driving the higher mortality risk. As climate change extends warm seasons across North America, the frequency of both early and late season heatwaves will likely increase in the near future[218].

Several limitations should be considered when interpreting our results. The generalizability of our study was limited, in part by, the demographic composition of our COPD Veterans cohort that was predominantly male, older and of White race. The extent to which these demographic factors affected the results is unknown. Despite having a relatively large study cohort, our study period was short which contributed to the rarity of compound drought and heatwave events. With fewer Veterans simultaneously exposed to heatwaves and drought conditions, the precision of our estimates was affected and prohibited evaluations by subgroups including age, gender and race, which may reveal additional health disparities of importance. Additionally, the spatial scale for our drought data was relatively coarse at the county level. However, drought is a spatially defuse climate hazard that affects large geographic areas so it is unclear how much exposure misclassification would be reduced by using more spatially resolved drought data and if this misclassification would change the conclusions of our study.

Conclusion

Compound weather extremes of heatwaves and drought placed people with existing respiratory disease at greater risk of death than people experiencing heatwaves alone. Furthermore, these effects were more apparent in late season heatwaves occurring under drought conditions. These results support the need to understand the burdens of compound climate hazards more fully as climate change will cause these events to become increasingly frequent in the future. Developing an understanding of the public health impacts of complex climate events is needed for optimal climate change mitigation and adaptation strategies.

Supplement

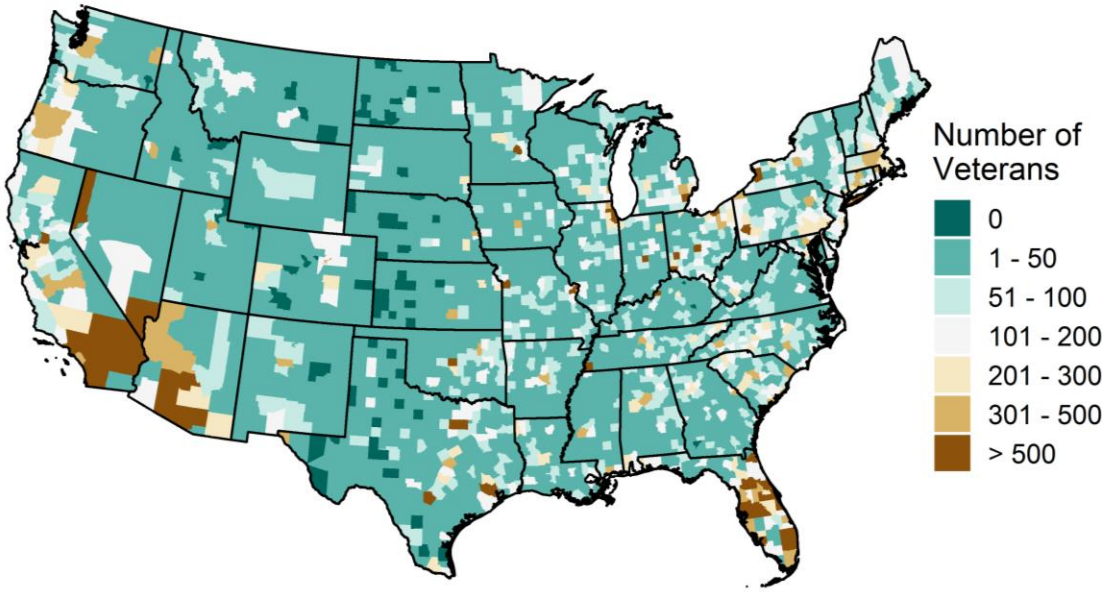

Figure S5-1: County level distribution of deceased Veterans diagnosed with COPD during the warm season (April to September), 2016 to 2021

Table 5-S1: Frequency of deceased Veterans with COPD stratified by heatwave status, drought status, and timing of heatwaves in the warm season on day on death (USDM and SPEI)

Drought index	Timing	Heatwave status	Drought classification	
			No Drought	Drought
USDM	Early	Non-heatwave, N (%)	78,293 (97.1%)	10,378 (94.6%)
		Heatwave, N (%)	2,366 (2.9%)	593 (5.4%)
		Total	80,659	10,971
	Late	Non-heatwave, N (%)	67,043 (84.9%)	10,390 (79.4%)
		Heatwave, N (%)	11,970 (15.1%)	2,692 (20.6%)
		Total	79,013	13,082
SPEI	Early	Non-heatwave, N (%)	67,987 (97.3%)	20,684 (95.1%)
		Heatwave, N (%)	1,899 (2.7%)	1,060 (4.9%)
		Total	69,886	21,744
	Late	Non-heatwave, N (%)	61,140 (85.7%)	16,293 (78.4%)
		Heatwave, N (%)	10,173 (14.3%)	4,489 (21.6%)
		Total	71,313	20,782

Table 5-S2: Mean heatwave temperature and duration on days of Veteran mortality stratified by USDM and SPEI binary and categorical drought categories and timing of heatwaves in the warm season

Drought index	Timing	Heatwave status	Drought classification	
			No Drought	Drought
USDM	Early	Non-heatwave mean temperature °C (SD)	17.95 (6.94)	19.79 (6.39)
		Heatwave mean temperature °C (SD)	27.60 (2.68)	29.03 (4.04)
		Heatwave mean duration days (SD)	4.00 (2.32)	4.86 (3.22)
	Late	Non-heatwave mean temperature °C (SD)	23.25 (4.36)	22.52 (5.34)
		Heatwave mean temperature °C (SD)	27.85 (2.71)	28.20 (4.30)
		Heatwave mean duration days (SD)	5.02 (3.25)	6.75 (5.90)
SPEI	Early	Non-heatwave mean temperature °C (SD)	17.87 (6.92)	19.13 (6.76)
		Heatwave mean temperature °C (SD)	27.44 (2.46)	28.70 (3.77)
		Heatwave mean duration days (SD)	3.85 (2.20)	4.76 (2.99)
	Late	Non-heatwave mean temperature °C (SD)	23.04 (4.34)	23.57 (5.06)
		Heatwave mean temperature °C (SD)	27.54 (2.59)	28.75 (3.82)
		Heatwave mean duration days (SD)	4.84 (3.01)	6.46 (5.31)

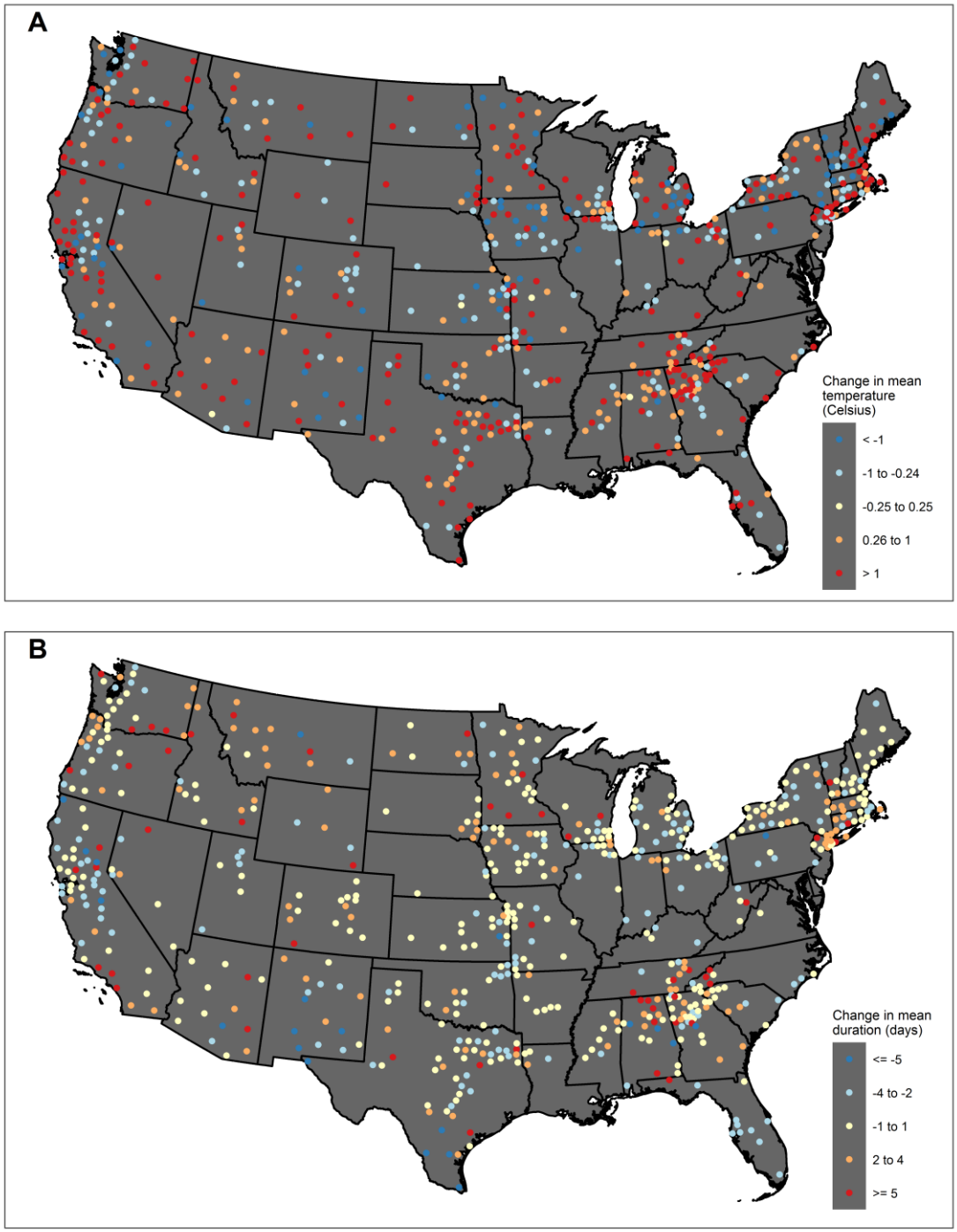

Figure S5-2: Absolute change in mean temperature (A) and mean duration (B) of heatwaves comparing heatwaves that occurred during drought conditions to non-drought conditions on days of mortality events among United States Veterans with COPD. Dots represent county centroids (N = 622 counties that had Veterans with heatwave exposure during drought and non-drought conditions)

Table 5-S3: Adjusted incidence rate ratios describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary and categorical USDM drought definitions

Strata	Lag	IRR (95% CI)	P value
No drought (N = 159,672)	0	1.02 (1.00, 1.04)	Ref
	1	1.01 (1.00, 1.02)	Ref
	2	1.00 (0.99, 1.01)	Ref
	3	0.99 (0.98, 1.01)	Ref
	0 to 1	1.03 (1.00, 1.05)	Ref
	0 to 3	1.02 (0.99, 1.05)	Ref
Any drought (N = 24,053)	0	1.05 (1.02, 1.09)	0.10
	1	1.03 (1.01, 1.05)	0.11
	2	1.00 (0.98, 1.02)	0.97
	3	0.98 (0.94, 1.01)	0.42
	0 to 1	1.08 (1.03, 1.14)	0.09
	0 to 3	1.06 (0.99, 1.12)	0.31
Moderate drought (N = 18,858)	0	1.05 (1.01, 1.10)	0.13
	1	1.02 (1.00, 1.05)	0.23
	2	1.00 (0.97, 1.02)	0.66
	3	0.97 (0.93, 1.01)	0.27
	0 to 1	1.08 (1.02, 1.15)	0.15
	0 to 3	1.04 (0.97, 1.12)	0.63
Severe drought (N = 5,195)	0	1.05 (0.98, 1.13)	0.40
	1	1.03 (1.00, 1.07)	0.20
	2	1.02 (0.98, 1.06)	0.35
	3	1.00 (0.93, 1.08)	0.76
	0 to 1	1.09 (0.98, 1.21)	0.31
	0 to 3	1.11 (0.99, 1.26)	0.18

Table 5-S4: Adjusted incidence rate ratios describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary USDM drought definitions and timing of heatwaves in the warm season

Strata (N)	Lag	IRR (95% CI)	P value[A]
Early season, no drought (N = 80,659)	0	1.06 (1.02, 1.10)	Ref
	1	1.03 (1.01, 1.05)	Ref
	2	1.00 (0.98, 1.02)	Ref
	3	0.97 (0.93, 1.01)	Ref
	0 to 1	1.10 (1.04, 1.16)	Ref
	0 to 3	1.06 (0.99, 1.14)	Ref
Early season, drought N = (10,971)	0	1.05 (0.97, 1.14)	0.82
	1	1.03 (0.99, 1.07)	0.97
	2	1.01 (0.97, 1.05)	0.63
	3	0.99 (0.92, 1.07)	0.63
	0 to 1	1.09 (0.97, 1.22)	0.89
	0 to 3	1.09 (0.95, 1.25)	0.75
Late season, no drought (N = 79,013)	0	1.01 (0.99, 1.03)	Ref
	1	1.00 (0.99, 1.01)	Ref
	2	1.00 (0.99, 1.01)	Ref
	3	1.00 (0.98, 1.01)	Ref
	0 to 1	1.01 (0.99, 1.04)	Ref
	0 to 3	1.01 (0.98, 1.04)	Ref
Late season, drought (N = 13,082)	0	1.05 (1.01, 1.10)	0.06
	1	1.03 (1.00, 1.05)	0.09
	2	1.00 (0.98, 1.02)	0.85
	3	0.97 (0.93, 1.01)	0.27
	0 to 1	1.08 (1.02, 1.15)	0.06
	0 to 3	1.05 (0.98, 1.12)	0.35

[A]Early season no drought is the referent compared to early season drought and late season no drought is the referent compared to late season drought estimates.

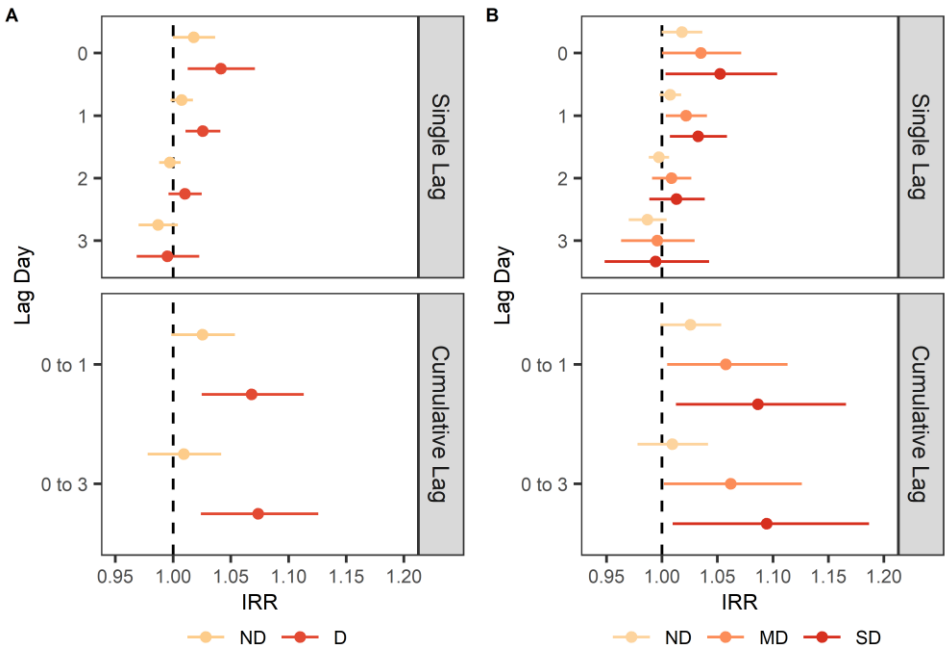

Figure S5-3:Adjusted incidence rate ratios (IRR) describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary (A) and categorical (B) SPEI drought definitions. ND = No drought, D = Drought, MD = Moderate drought, SD = Severe drought

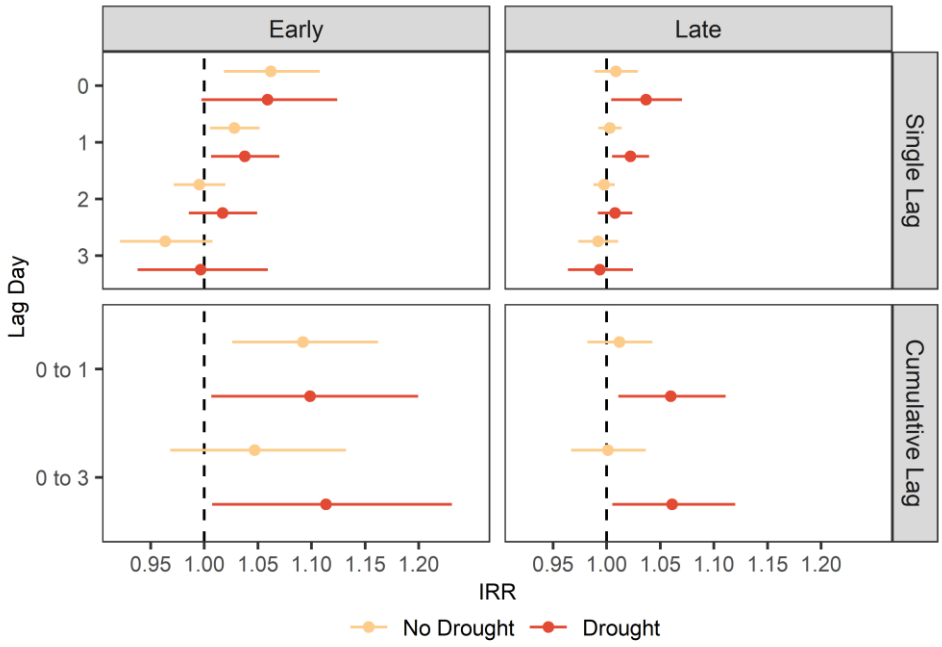

Figure S5-4: Adjusted incidence rate ratios (IRR) describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary SPEI drought definitions and timing of heatwaves in the warm season of the year (early = April to June and late = July to September)

Table 5-S5: Adjusted incidence rate ratios describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary and categorical SPEI drought definitions

Strata (N)	Lag	IRR (95% CI)	P value
No drought (N = 141,199)	0	1.02 (1.00, 1.04)	Ref
	1	1.01 (1.00, 1.02)	Ref
	2	1.00 (0.99, 1.01)	Ref
	3	0.99 (0.97, 1.00)	Ref
	0 to 1	1.03 (1.00, 1.05)	Ref
	0 to 3	1.01 (0.98, 1.04)	Ref
Any drought (N = 42,526)	0	1.04 (1.01, 1.07)	0.18
	1	1.03 (1.01, 1.04)	0.05
	2	1.01 (1.00, 1.02)	0.13
	3	1.00 (0.97, 1.02)	0.62
	0 to 1	1.07 (1.02, 1.11)	0.11
	0 to 3	1.07 (1.02, 1.13)	0.03
Moderate drought (N = 29,421)	0	1.04 (1.00, 1.07)	0.40
	1	1.02 (1.00, 1.04)	0.18
	2	1.01 (0.99, 1.03)	0.26
	3	1.00 (0.96, 1.03)	0.65
	0 to 1	1.06 (1.00, 1.11)	0.30
	0 to 3	1.06 (1.00, 1.13)	0.13
Severe drought (N = 13,105)	0	1.05 (1.00, 1.10)	0.20
	1	1.03 (1.01, 1.06)	0.07
	2	1.01 (0.99, 1.04)	0.23
	3	0.99 (0.95, 1.04)	0.78
	0 to 1	1.09 (1.01, 1.17)	0.13
	0 to 3	1.09 (1.01, 1.19)	0.07

Table 5-S6: Attributable risk (%) for the cumulative heatwave effects (lag day 0 to 1 and lag day 0 to 3) stratified by SPEI drought status (binary and categorical) and by timing of heatwaves in the warm season of the year

Strata	AR% (95% CI) Cumulative lag 0 to 1	AR% (95% CI) Cumulative lag 0 to 3
No drought	2.91 (0.00, 4.76)	0.99 (-2.04, 3.85)
Drought	6.54 (1.96, 9.91)	6.54 (1.96, 11.5)
Moderate drought	5.66 (0.00, 9.91)	5.66 (0.00, 11.50)
Severe drought	8.26 (0.99, 14.53)	8.26 (0.99, 15.97)
Heatwave timing		
Early (No Drought)	8.26 (2.91, 13.79)	4.76 (-3.09, 11.50)
Early (Drought)	9.09 (0.99, 16.67)	9.91 (0.99, 18.70)
Late (No Drought)	0.99 (-2.04, 3.85)	0.00 (-3.09, 3.85)
Late (Drought)	5.66 (0.99, 9.91)	5.66 (0.99, 10.71)

Table 5-S7: Adjusted incidence rate ratios describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary SPEI drought definitions and timing of heatwaves in the warm season

Strata (N)	Lag	IRR (95% CI)	P value[A]
Early season, no drought (N = 69,886)	0	1.06 (1.02, 1.11)	Ref
	1	1.03 (1.01, 1.05)	Ref
	2	1.00 (0.97, 1.02)	Ref
	3	0.96 (0.92, 1.01)	Ref
	0 to 1	1.09 (1.03, 1.16)	Ref
	0 to 3	1.05 (0.97, 1.13)	Ref
Early season, drought (N = 21,744)	0	1.06 (1.00, 1.12)	0.94
	1	1.04 (1.01, 1.07)	0.63
	2	1.02 (0.99, 1.05)	0.29
	3	1.00 (0.94, 1.06)	0.38
	0 to 1	1.10 (1.01, 1.20)	0.91
	0 to 3	1.11 (1.01, 1.23)	0.34
Late season, no drought (N = 71,313)	0	1.01 (0.99, 1.03)	Ref
	1	1.00 (0.99, 1.01)	Ref
	2	1.00 (0.99, 1.01)	Ref
	3	0.99 (0.97, 1.01)	Ref
	0 to 1	1.01 (0.98, 1.04)	Ref
	0 to 3	1.00 (0.97, 1.04)	Ref
Late season, drought (N = 20,782)	0	1.04 (1.00, 1.07)	0.06
	1	1.02 (1.01, 1.04)	0.09
	2	1.01 (0.99, 1.02)	0.85
	3	0.99 (0.96, 1.02)	0.27
	0 to 1	1.06 (1.01, 1.11)	0.06
	0 to 3	1.06 (1.01, 1.12)	0.35

[A]Early season no drought is the referent compared to early season drought and late season no drought is the referent compared to late season drought estimates.

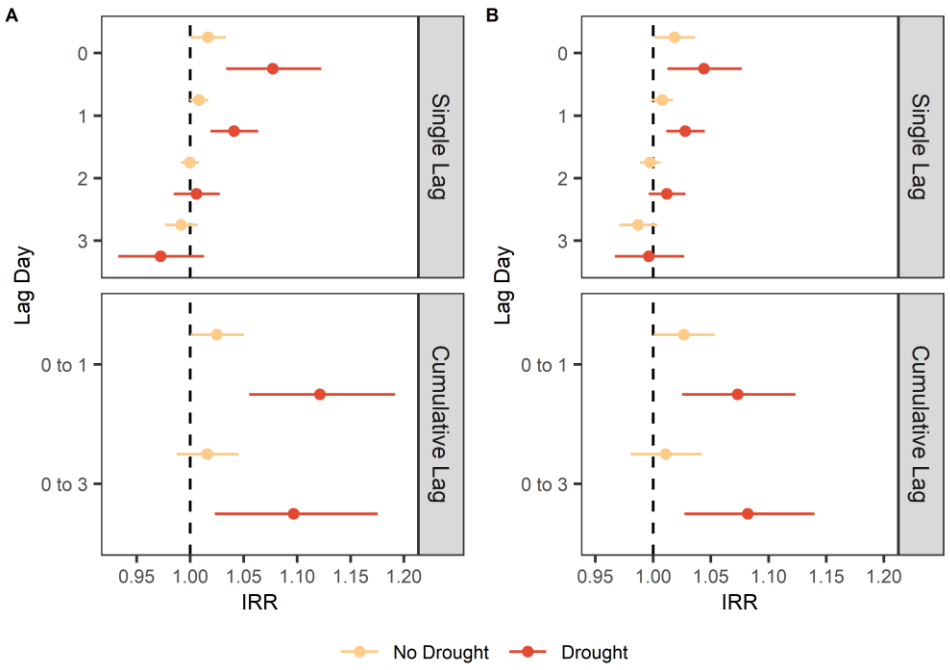

Figure S5-5: Adjusted incidence rate ratios (IRR) describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary A) USDM and B) SPEI drought definition where a drought needed to be at least 5 consecutive months of at least D1 or higher

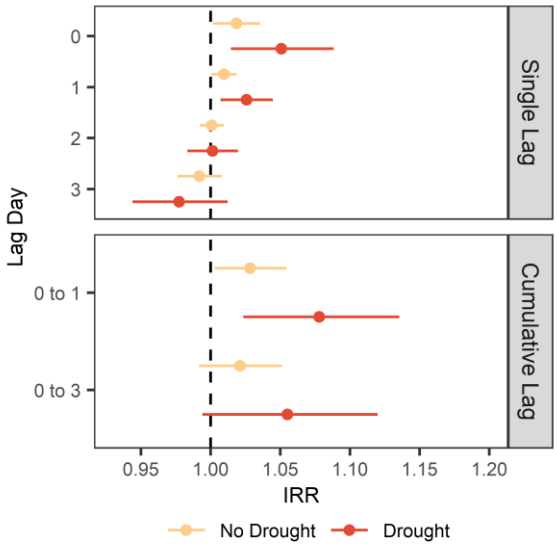

Figure S5-6: Adjusted incidence rate ratios (IRR) describing the association between heatwaves and all-cause mortality among Veterans with COPD stratified by binary USDM drought definition where a drought exposure was defined using weekly USDM data

Chapter 6: Conclusion

Contributions to public health

The overarching goal of this dissertation was to enumerate the magnitude of risk heat and cold waves had on mortality among a population of individuals living with a chronic respiratory disease. Identification of at-risk subgroups within this population by individual characteristics (age, sex, race, ethnicity, comorbidities, smoking status, and urbanicity) were explored to differentiate mortality risk severity and move beyond the average risk estimate of the entire population. Furthermore, the impact of compounding climate hazards (droughts and heatwaves) was investigated as a novel public health exposure that will become more commonplace under climate change.

Chapter 3, as the initial study of this dissertation, provided estimates of heat and cold wave associated mortality risk in the entire population of patients with COPD on both the multiplicative and additive scales. Not only was chapter 3 one of the few individual level climate and health studies, but it was also one of the first nationwide individual level studies to examine heat and cold wave mortality risks in a population of individuals who all had a diagnosis of COPD. This study moves the literature forward by providing individual level estimates of heat and cold wave mortality risk for people with COPD unlike the currently available ecological studies. Furthermore, the public health burdens of heat and cold waves were provided in the form of attributable risks. Methodologists have known about the public health benefits of additive measures of associations for decades however current research and public health practice is lagging in the adoption of these measures. The methods and findings of this study can be used to inform future individual level climate and health studies of other respiratory diseases. Furthermore, chapter 3 can serve as a push for other researchers to present additive measures of association which clearly demonstrate the public health burden of climate change by providing the number of excess injuries, illnesses or deaths that will be incurred by extreme weather events.

Chapter 4 extended the work of chapter 3 by examining other less commonly explored effect measure modifiers of additional comorbidities, smoking status and urbanicity. The results from chapter 4 show high promise in developing precise climate

change vulnerability profiles for individuals who are living with multiple chronic diseases, tobacco exposure and living in urban vs rural settings. Classical effect measure modifiers of age, sex and race, while important, are well-studied in environmental epidemiology. However, as chapter 4 indicated, there are other critical characteristics of individuals that amplify susceptibility to extreme weather. An emphasis of less recognized individual characteristics is needed to develop a full picture of climate change vulnerability for populations susceptible to climate change.

Chapter 5 was among the first nationwide studies to enumerate the public health risks of compounding climate hazards (drought and heatwaves). While a nascent field, climate and health epidemiology is developing at a modest pace and recognition of compounding climate hazards is gaining recognition amongst researchers. The summer of 2023 was a clear indicator for what the future of climate change may hold with several extreme weather events occurring at the same time. The United States was simultaneously affected by wildfire smoke, drought and extreme heat in the summer of 2023. Individually, all of these climate hazards have been shown to increase the risk of morbidity and mortality in the population, however it has yet to be shown what the added risk of adverse health events is when all three of these hazards occur simultaneously. If the results from chapter 5 are any indication of potential effects, it may be found that risk of adverse health events was increased by several folds during the summer of 2023.

Future research directions

The importance of individual level assessments in climate and health research is invaluable and cannot be understated. The paucity of these types of studies is understandable, individual level health data is challenging to acquire. However, without individual level studies, the field of climate and health epidemiology cannot move forward in identifying the most vulnerable members of society who would benefit most from climate change mitigation and adaptation strategies. Future research using individual level health data from health systems that include members of the civilian population should be completed in the near future. Additive measures of association are also needed to understand the public health burden of climate change and to properly

identify which segments of the population are most at-risk and would benefit most from public health interventions.

Furthermore, there should be an emphasis on studying populations with specific comorbidities. Studies of the general population are an average over the heterogeneities in risk that may exist depending upon which comorbidities or lack thereof that individuals have. A “one size fits all” approach to climate change mitigation is not suitable as it ignores the nuances in risk of adverse health events that are driven by individual level characteristics. Similar to how physicians are pursuing precision medicine as a way to best treat patients, so too should public health seek to develop precision public health. Precise vulnerability profiles can be developed using several strata of underlying effect measure modifiers to create a set of risk estimates related to extreme weather exposure and adverse health events that can be used to guide public health practitioners and policy makers to develop more effective and targeted intervention strategies.

Finally, the recognition of compounding and cascading climate hazards must be realized in climate and health epidemiology. The frequency of these complex hazards is anticipated to increase, and the public health impacts of these events are likely to be several folds greater than an individual extreme weather event on its own. Compounding extreme heat and wildfire smoke or cascading drought and extreme rainfall are two examples of these complex climate hazards that could be investigated in future research. New developments in epidemiological study designs and statistical methods may also be needed to measure public health impacts of complex climate hazards.

Climate change is here. Regardless of race, sex, creed, origin or political affiliation, all nations and members of society will be affected in some shape or form by climate change. It is the role of public health scientists to enumerate the risks of disease associated with climate related hazards and to identify groups of individuals who may be at heightened susceptibility compared to others. Additionally, researchers should consider advocating the results of their work to make real world changes in policy and behavior such that the population-level burden of climate change is minimized. This work is

important not only for the present day but for the future generations of children who will live in a world entirely shaped by our actions or lack thereof.

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Chapter 7: Technical appendix

```
# Austin Rau
# 8/17/2023
# This file provides snippets of code and functions used to
# 1) extract daily GridMet data to Veteran point locations
# 2) create 30 year warm and cold season percentiles
# 3) create heat and cold wave variables
# 4) create a case crossover dataet
# 5) automate a DLM model
################################################################################
library(sf)
library(tidyverse)
library(lubridate)
library(stars) # fast extract of rasters
library(slider) # for moving averages
library(survival) # for conditional logistic model
library(splines) # for natural cubic splines
library(raster)
library(ncdf4)
library(rts) # raster package for time series data
################################################################################
copd <- readRDS("./output/copd_analytic_sample_updated_exclusion_criteria.rds")

# create a list of counties to iterate over
my_counties <- unique(copd$county_fips)

################################################################################
# create a list of gridmet weather files
tmmx_list <- list.files("./data/gridmet", pattern = "tmmx_*", full.names = TRUE)

tmmn_list <- list.files("./data/gridmet", pattern = "tmmn_*", full.names = TRUE)

pr_list <- list.files("./data/gridmet", pattern = "pr_*", full.names = TRUE)

sph_list <- list.files("./data/gridmet", pattern = "sph_*", full.names = TRUE)

vs_list <- list.files("./data/gridmet", pattern = "vs_*", full.names = TRUE)


# read each weather data in its own variable as a list
tmmx <- map(tmmx_list, read_ncdf, var = "air_temperature")

tmmn <- map(tmmn_list, read_ncdf, var = "air_temperature")

pr <- map(pr_list, read_ncdf, var = "precipitation_amount")

sph <- map(sph_list, read_ncdf, var = "specific_humidity")

vs <- map(vs_list, read_ncdf, var = "wind_speed")
```

```
#############################################################################
#
# Function to extract Gridmet data to points that does not crop the rasters
# based on bounding boxes of VA points
#############################################################################
#
extract.gridmet.no.bbox <- function(county_id, in_df){

 # This function will extract Gridmet weather data to veteran points for a given county

 # This function requires a string containing a 5 digit state-county FIPS code
 # and a dataframe containing the VA COPD dataset

 # This function assumes you have the Gridmet weather rasters already read into R
 # using the variable naming conventions in this function

 # tmmn, tmmx, pr, vs and sph should be variable names for gridmet raster objects that
 # you read into environment

 start_time <- Sys.time()

 # filter to veterans of a specific county
 county <- in_df %>%
  filter(county_fips == county_id & DeceasedFlag == "Y")

 print(paste("Starting with county", county_id, "at", Sys.time()))

 # turn to spatial points
 county_pts <- st_as_sf(county, coords = c("ptGISLongitude", "ptGISLatitude"), crs = 4326)

 # trim data to just patient ID
 county_pts <- county_pts %>%
  dplyr::select(patientsid)

 # project points to CRS of Gridmet data
 county_pts <- county_pts %>%
  st_transform(crs = st_crs(tmmx[[1]]))

 ######################################
 # extract values to points
 tmmx_extract <- map(tmmx, st_extract, at = county_pts)

 tmmn_extract <- map(tmmn, st_extract, at = county_pts)

 pr_extract <- map(pr, st_extract, at = county_pts)

 sph_extract <- map(sph, st_extract, at = county_pts)

 vs_extract <- map(vs, st_extract, at = county_pts)
```

```
####################################
# turn results into a tibble
tmmx_tbl <- map(tmmx_extract, as_tibble)

tmmn_tbl <- map(tmmn_extract, as_tibble)

pr_tbl <- map(pr_extract, as_tibble)

sph_tbl <- map(sph_extract, as_tibble)

vs_tbl <- map(vs_extract, as_tibble)

####################################
# bind the rows of the results for a long dataset
tmmx_tbl <- tmmx_tbl %>%
  bind_rows()

tmmn_tbl <- tmmn_tbl %>%
  bind_rows()

pr_tbl <- pr_tbl %>%
  bind_rows()

sph_tbl <- sph_tbl %>%
  bind_rows()

vs_tbl <- vs_tbl %>%
  bind_rows()

# rename tmax and tmin columns to avoid duplicate names
tmmx_tbl <- tmmx_tbl %>%
  rename("tmax" = air_temperature)

tmmn_tbl <- tmmn_tbl %>%
  rename("tmin" = air_temperature)

####################################
# bind all the weather datasets into one
gridmet_all_tbl <-
  tmmx_tbl %>%
  bind_cols(tmmn_tbl) %>%
  bind_cols(pr_tbl) %>%
  bind_cols(sph_tbl) %>%
  bind_cols(vs_tbl) %>%
  # drop all geometry columns
  select(-starts_with("geometry")) %>%
  # rename columns and only keep one day column
  select("day" = day...2, tmax, tmin, "precip" = precipitation_amount,
         specific_humidity, wind_speed)
####################################
```

```
  # add column for patient ID

  # how the 'stars' package works is that it returns a dataframe for each person
  # for an entire raster layer then repeats going through all people for the next raster.

  # so what you need to do is make a vector whose length is the same as
  # the number of rows in the gridmet_all_tbl and repeat the person IDs from the VA data

  # figure out number of times you need to repeat the veteran's IDs
  reps <- nrow(gridmet_all_tbl) / nrow(county)

  # create vector of repeating IDs
  ids <- rep(county$patientsid, times = reps)

  # Add the IDs as a new column
  gridmet_all_tbl$patientsid <- ids

  ######################################
  # convert all weather data to numeric
  gridmet_all_tbl$tmax <- as.numeric(gridmet_all_tbl$tmax)

  gridmet_all_tbl$tmin <- as.numeric(gridmet_all_tbl$tmin)

  gridmet_all_tbl$precip <- as.numeric(gridmet_all_tbl$precip)

  gridmet_all_tbl$specific_humidity <- as.numeric(gridmet_all_tbl$specific_humidity)

  gridmet_all_tbl$wind_speed <- as.numeric(gridmet_all_tbl$wind_speed)

  # save out the dataset
  saveRDS(gridmet_all_tbl,
          paste0("./data/veteran_weather_data/", "veterans_meteo_county_", county_id,
"_2015_2021.rds"))

  end_time <- Sys.time()

  diff <- difftime(end_time, start_time, units = c("mins"))

  print(paste("Time to complete", diff, "minutes"))

  print(paste("Completed with", county_id, "at", Sys.time()))


}

#############################################################################
# Extract 2015-2021 gridmet data to county points and store as dataframe per each county

the_start_time <- Sys.time()
```

```
# iterate over each county and extract weather data
for(i in seq_along(my_counties)){
  extract.gridmet.no.bbox(county_id = my_counties[[i]], copd)
}

the_end_time <- Sys.time()

################################################################################
# The following code shows the general process for creating
# 30-year warm and cold season percentiles for point locations with GridMet data
################################################################################
# Function for compiling 30-years of weather data for cold and warm seasons
################################################################################
weather.compiler.30years <- function(in_dates_df, in_months, in_files){
  # This function will compile 30-years of weather data for 1992 - 2021
  # for a specific range of months and save it out as a raster stack

  # This function requires:
  # a dataframe with two columns. One for year and one for month-year pasted together
  # a vector of months as integers defining time period of interest and
  # a list of gridmet files to iterate over


  # start time for function
  start_time <- Sys.time()

  # print the months being used to filter raster
  print(paste("These months are being extracted from Gridmet data", in_months))


  # print file names being used
  print(paste("These files are being used", in_files))


  # create vectors for 10 3 year chunks to supply into list that you will iterate over
  # the year range is closed on the right interval
  chunk1 <- make.vector(in_dates_df, months_list = in_months, lower_year = 1992, upper_year =
1995)

  chunk2 <- make.vector(in_dates_df, months_list = in_months, lower_year = 1995, upper_year =
1998)

  chunk3 <- make.vector(in_dates_df, months_list = in_months, lower_year = 1998, upper_year =
2001)

  chunk4 <- make.vector(in_dates_df, months_list = in_months, lower_year = 2001, upper_year =
2004)

  chunk5 <- make.vector(in_dates_df, months_list = in_months, lower_year = 2004, upper_year =
2007)
```

```
  chunk6 <- make.vector(in_dates_df, months_list = in_months, lower_year = 2007, upper_year =
2010)

  chunk7 <- make.vector(in_dates_df, months_list = in_months, lower_year = 2010, upper_year =
2013)

  chunk8 <- make.vector(in_dates_df, months_list = in_months, lower_year = 2013, upper_year =
2016)

  chunk9 <- make.vector(in_dates_df, months_list = in_months, lower_year = 2016, upper_year =
2019)

  # last chunk needs to include 2021
  chunk10 <- make.vector(in_dates_df, months_list = in_months, lower_year = 2019, upper_year
= 2022)

  # month-years to subset from rts

  # insert chunk vectors into list
  years_vec <- list(chunk1, chunk2, chunk3, chunk4, chunk5, chunk6, chunk7, chunk8,
                    chunk9, chunk10)

  print(paste("These years are being used", years_vec))

#############################################################################
  # For loop mechanism

  # index positions of files for 3 year chunks
  file_idx <- list(c(1:3), c(4:6), c(7:9), c(10:12), c(13:15), c(16:18), c(19:21),
                   c(22:24), c(25:27), c(28:30))

  # For loop 10, 3 year chunks that you will turn into one raster brick
  out_rast_brick <- list()

  ##############################
  for(i in seq_along(file_idx)){

    # make small subset
    files_sub <- in_files[file_idx[[i]]]

    # open the files
    grids <- map(files_sub, nc_open)

    # this is a list of grid files, need to go through each list element

    # gather geographic and time elements from data
    lon <- map(grids, ncvar_get, varid = "lon")

    lat <- map(grids, ncvar_get, varid = "lat")
```

```
  # this is days since 1900-01-01
  time <- map(grids, ncvar_get, varid = "day")

  # get the temperature data from the array for each gridmet item in list
  temp_array <- map(grids, ncvar_get, varid = "air_temperature")

  # check which value was used for missing data
  fill_value <- map(grids, ncatt_get, varid = "air_temperature", attname = "_FillValue")

  fill_value


################################################################################
  # Replace NA values and create raster brick

  # Convert missing value cells to NA
  for(j in seq_along(temp_array)){
    temp_array[[j]][temp_array == fill_value$value] <- NA
  }


  # create a raster brick list
  # Set X axis using latitude and Y axis using longitude
  r_brick_list <- list()


  for(j in seq_along(temp_array)){
    r_brick_list[[j]] <- brick(temp_array[[j]],
                               xmn=min(lat[[j]]), xmx=max(lat[[j]]),
                               ymn=min(lon[[j]]), ymx=max(lon[[j]]),
                               crs=CRS("+proj=longlat +ellps=WGS84 +datum=WGS84 +no_defs+
towgs84=0,0,0"))
  }


  # remove original temperature array to save memory
  rm(temp_array)


  # since the data is not oriented correctly, need to transpose it
  r_brick_list <- map(r_brick_list, t)

  # we know that time in the time matrix is days since 1900-01-01
  # Change the values of the time matrix into the actual 2018 dates they represent
  time <- map(time, as_date, origin = "1900-01-01")

  # set Z values equal to the time
  for(k in seq_along(r_brick_list)){
    r_brick_list[[k]] <- setZ(r_brick_list[[k]], time[[k]])
```

```
  }

#############################################################################
##
  # create on large raster brick from list of raster bricks
  r_brick <- brick(r_brick_list)

  # check that time is still correct
  getZ(r_brick)

  # unlist the time data, it does not retain the original date information
  time2 <- unlist(time)

  # turn the data back into date format, need to use new origin date of
  # 1970-01-01 since this is R's origin date for date data
  time3 <- as_date(time2, origin = "1970-01-01")

  time3

  # create a raster time series
  my_obj <- rts(r_brick, time = time3)

  # subset on time
  my_sub <- subset(my_obj, years_vec[[i]])

  # turn back into raster stack
  my_sub_stack <- stack(my_sub@raster)

  # add the raster brick to your empty list
  out_rast_brick[[i]] <- my_sub_stack
 }

#############################################################################
 # turn this list of raster bricks into one large raster brick
 merged_brick <- brick(out_rast_brick)

 # print the time it took to run it
 end_time <- Sys.time()

 difference <- difftime(end_time, start_time, units = "mins")

 print(paste("Total processing time", round(difference), "minutes"))

 # return the final raster brick
 return(merged_brick)

}
```

```
################################################################################
# 30-year and 20-year definition files
################################################################################
# get list of temperature files (min temperature)
files_tmin <- list.files("Z:/rauxx087/drought_project/data/gridmet",
                         pattern = "tmmn_*", full.names = TRUE)

# get list of files for max temp
files_tmx <- list.files("Z:/rauxx087/drought_project/data/gridmet",
                        pattern = "tmmx_*", full.names = TRUE)

# exclude some files (only want 1992 - 2021 for 30-year definition)
files_tmin_30year <- files_tmin[c(3:32)]

files_tmax_30year <- files_tmx[c(3:32)]

################################################################################
# Create warm and cold season defintions
################################################################################
# create a vector of cold season months

# Oct - Mar definition
cold_months <- c(10, 11, 12, 1, 2, 3)

######################
# create a vector of warm season months

# Apr - Sept definition
warm_months <- c(4, 5, 6, 7, 8, 9)


################################################################################
# 30 year definition pre-prep
################################################################################

# create a sequence of dates from 1992 to 2021 (the 30 year time period)
date_seq_30_years <- seq(as.Date("1992/01/01"), as.Date("2021/12/31"), "months")

# turn to dataframe
date_seq_30_years <- as.data.frame(date_seq_30_years)

# change name of column
names(date_seq_30_years) <- c("month_year")

# create a month column
date_seq_30_years$month <- month(date_seq_30_years$month_year)

# trim off days from month year column
date_seq_30_years$month_year <- substr(date_seq_30_years$month_year, 1, 7)
```

```
#############################################################################
# 30-year cold and warm season processing
# This was run using Tmax and Tmin data from GridMet then I had to take the average
# of the 2 to calculate a Tmean 30 year percentile for each point location
#############################################################################
# Cold season definition  (Oct-Mar)
#####################################################################
# Tmin (this takes 1.5 hours)
cold_season_30_year_tmin <- weather.compiler.30years(in_dates_df = date_seq_30_years,
                                    in_months = cold_months, in_files = files_tmin_30year)


# check number of layers (days) in raster brick
# This is 30 years of data from 6 months that are about 182 days in length
# The number of layers should be really close to 30*182 = 5,460 (not accounting for leap days)
# There are 8 leap years in 1992 - 2021 so total layers should be 5,468
nlayers(cold_season_30_year_tmin)



# write out raster (this takes ~30min)
raster::writeRaster(cold_season_30_year_tmin,
                    filename = "./data/cold_season_oct_mar_min_temp_1992_2021.tif",
                    # can add overwrite = TRUE argument
                    format = "GTiff")

#####################################################################
# Warm season (Apr - Sept)
#####################################################################
# Tmax
warm_season_30_year_tmax <- weather.compiler.30years(in_dates_df = date_seq_30_years,
                                    in_months = warm_months,
                                    in_files = files_tmax_30year)

# check that number of layers (days) is correct
# should be 183*30 = 5490
nlayers(warm_season_30_year_tmax)

# write out raster (this takes ~30min)
raster::writeRaster(warm_season_30_year_tmax,
                    filename = "./data/warm_season_apr_sept_max_temp_1992_2021.tif",
                    format = "GTiff")
#############################################################################
#
# Heatwave function
#############################################################################
#
```

```
# This function will calculate heatwaves and 1, 2 and 3 day lagged heatwave sequences
outputting
# an ID for each heatwave event and an indicator of whether a day was part of a heatwave
sequence

heatwave.gen <- function(df, temp_var, ptile_var, season_var,
                         seq_id_var, seq_day_var,heatwave_var, lag1_var,
                         lag2_var, lag3_var, lag4_var, lag5_var, lag6_var, lag7_var){

  # This function requires
  # 1) a dataframe with daily weather data, 30 and 20 year seasonal (warm / cold)
  #       percentile cutoffs and variables indicating season of year (warm vs cold)
  # 2) a column indicating which temperature variable to use to make heatwave definition
  # 3) a column indicating the percentile threshold value to which the temperature variable will
  #       be compared against. choices include 20 and 30 year reference distribution cutoffs
  # 4) a column indicating season of year
  # this column should designate cold or warm season of year
  # 5) a string indicating the name you want to assign the output variable that will hold the unique
  #       ID for each heatwave event
  # 6) a string indicating the name you want to assign the output variable that will hold the number
of
  #       days a heatwave event lasted
  # 7) a string indicating the name you want to assign the output variable that will indicate
whether a
  #      a day was part of a heatwave event or not
  # 8) a string indicating the name you want to assign the output variable that will hold lag 1 - 7
day heatwave
  #       information


  # check day's eligibility for heatwave by ensuring it is a warm season day
  # and that the day's temperature exceeds the percentile cutoff for warm season reference
distribution
  df$eligible_day <- ifelse(df[[season_var]] == "warm season" &
                            df[[temp_var]] > df[[ptile_var]], "eligible day", "not eligible day")

  ########################
  # find all heatwave days
  df <- df %>%
    # arrange by patient and date
    arrange(patientsid, date) %>%
    # group by patient and by heatwave ID
    # This code will count the number of times values are repeated from row to row
    # in the sequence (i.e. was there 3 times in which 'heatwave eligible day' occurred?)
    group_by(patientsid,
             seq_id = with(rle(eligible_day), rep(seq_along(lengths),
                                                  lengths))) %>%
    # create variable that is number of times a sequence of an event occurred
    mutate(counter = seq_along(seq_id)) %>%
    # calculate total number of days per sequence of events
```

```
  mutate(seq_day = n()) %>%
  ungroup()

 ########################
 # create an indicator variable to note if a day was heatwave eligible and belonged
 # to a string of at least 2+ days
 df[["heatwave"]] <- ifelse(df$eligible_day == "eligible day" &
                            df$seq_day >= 2, "heatwave", "non heatwave")

 ########################
 # Calculate 1, 2 and 3 day lags for heatwaves
 # Shift the heat/cold wave time series down by 1, 2, or 3 days grouped by each patient

 # arrange by patient and date
 # group by patient
 df <- df %>%
   arrange(patientsid, date) %>%
   group_by(patientsid) %>%
   # shift the heatwave column down 1 - 7 days
   mutate(heat_lag1 = lag(heatwave, n = 1),
          heat_lag2 = lag(heatwave, n = 2),
          heat_lag3 = lag(heatwave, n = 3),
          heat_lag4 = lag(heatwave, n = 4),
          heat_lag5 = lag(heatwave, n = 5),
          heat_lag6 = lag(heatwave, n = 6),
          heat_lag7 = lag(heatwave, n = 7))

 # copy dataframe as new variable
 res <- df

 # rename columns at the end and drop unneeded columns
 res <- res %>%
   # use the {{}} :=  notation to allow dplyr to read string inputs as symbols
   rename({{seq_id_var}} := seq_id, {{seq_day_var}} := seq_day,
          {{heatwave_var}} := heatwave, {{lag1_var}} := heat_lag1,
          {{lag2_var}} := heat_lag2, {{lag3_var}} := heat_lag3,
          {{lag4_var}} := heat_lag4, {{lag5_var}} := heat_lag5,
          {{lag6_var}} := heat_lag6, {{lag7_var}} := heat_lag7) %>%
   select(-counter, -eligible_day)


 return(res)
}


#############################################################################
#
# Coldwave function
#############################################################################
#
```

```
# This function will calculate coldwaves and 1, 2 and 3 day lagged coldwave sequences
outputting
# an ID for each coldwave event and an indicator of whether a day was part of a coldwave
sequence

coldwave.gen <- function(df, temp_var, ptile_var, season_var,
                         seq_id_var, seq_day_var,coldwave_var, lag1_var,
                         lag2_var, lag3_var, lag4_var, lag5_var, lag6_var, lag7_var){

  # This function requires
  # 1) a dataframe with daily weather data, 30 and 20 year seasonal (warm / cold)
  #       percentile cutoffs and variables indicating season of year (warm vs cold)
  # 2) a column indicating which temperature variable to use to make coldwave definition
  # 3) a column indicating the percentile threshold value to which the temperature variable will
  #       be compared against. choices include 20 and 30 year reference distribution cutoffs
  # 4) a column indicating season of year
  #       this column should designate cold or warm season of year
  # 5) a string indicating the name you want to assign the output variable that will hold the unique
  #       ID for each coldwave event
  # 6) a string indicating the name you want to assign the output variable that will hold the number
of
  #       days a coldwave event lasted
  # 7) a string indicating the name you want to assign the output variable that will indicate
whether a
  #       a day was part of a coldwave event or not
  # 8) a string indicating the name you want to assign the output variable that will hold lag 1-7 day
coldwave


  # check day's eligibility for coldwave by ensuring it is a cold season day
  # and that the day's temperature is below the percentile cutoff for cold season reference
distribution
  df$eligible_day <- ifelse(df[[season_var]] == "cold season" &
                            df[[temp_var]] < df[[ptile_var]], "eligible day", "not eligible day")

  ########################
  # find all coldwave days
  df <- df %>%
    # arrange by patient and date
    arrange(patientsid, date) %>%
    # group by patient and by coldwave ID
    # This code will count the number of times values are repeated from row to row
    # in the sequence (i.e. was there 3 times in which 'coldwave eligible day' occurred?)
    group_by(patientsid,
             seq_id = with(rle(eligible_day), rep(seq_along(lengths),
                                                  lengths))) %>%
    # create variable that is number of times a sequence of an event occurred
    mutate(counter = seq_along(seq_id)) %>%
    # calculate total number of days per sequence of events
    mutate(seq_day = n()) %>%
```

```
  ungroup()

  ########################
  # create an indicator variable to note if a day was coldwave eligible and belonged
  # to a string of at least 2+ days
  df[["coldwave"]] <- ifelse(df$eligible_day == "eligible day" &
                       df$seq_day >= 2, "coldwave", "non coldwave")

  ########################
  # Calculate 1, 2 and 3 day lags for coldwaves
  # Shift the heat/cold wave time series down by 1, 2, or 3 days grouped by each patient

  # arrange by patient and date
  # group by patient
  df <- df %>%
    arrange(patientsid, date) %>%
    group_by(patientsid) %>%
    # shift the coldwave column down 1, 2 and 3 days
    mutate(cold_lag1 = lag(coldwave, n = 1),
           cold_lag2 = lag(coldwave, n = 2),
           cold_lag3 = lag(coldwave, n = 3),
           cold_lag4 = lag(coldwave, n = 4),
           cold_lag5 = lag(coldwave, n = 5),
           cold_lag6 = lag(coldwave, n = 6),
           cold_lag7 = lag(coldwave, n = 7))

  # copy dataframe as new variable
  res <- df

  # rename columns at the end and drop unneeded columns
  res <- res %>%
    # use the {{}} :=  notation to allow dplyr to read string inputs as symbols
    rename({{seq_id_var}} := seq_id, {{seq_day_var}} := seq_day,
           {{coldwave_var}} := coldwave, {{lag1_var}} := cold_lag1,
           {{lag2_var}} := cold_lag2, {{lag3_var}} := cold_lag3,
           {{lag4_var}} := cold_lag4, {{lag5_var}} := cold_lag5,
           {{lag6_var}} := cold_lag6, {{lag7_var}} := cold_lag7) %>%
    select(-counter, -eligible_day)

  return(res)
}


##############################################################################
#
# Function to make all heat/cold wave variables and rolling mean variables in one loop
##############################################################################
#

variable.gen <- function(weather_files, clim_files, ptile_files){
```

```
# This will iterate over lists of county specific VA weather files and compute
# 1,2 and 3 day rolling averages for weather data and different heat/cold wave
# definitions

# This function requires
# 1) a list of 2015-2021 daily weather datasets
# 2) a list of 1991-2020 daily climatology datasets
# 3) a list of 1992-2021 and 2002-2021 warm/cold season percentile datasets
# where each of these lists are in the same order for which county appears
# and these datasets are county specific veteran-point extracted datasets


# create loop structure
for(i in seq_along(weather_files)){

  start_time <- Sys.time()

  # read in county specific RDS files
  weather <- readRDS(weather_files[[i]])

  clim <- readRDS(clim_files[[i]])

  ptile <- readRDS(ptile_files[[i]])

  # get county name
  county <- weather_files[[i]]

  county_id <- substr(county, start = 51, stop = 55)

  ########################################################

  # turn day column of weather dataframe into ymd format
  weather$date <- ymd(weather$day)

  # use yday() function to create a column for calendar day (1 to 365)
  # to join on for climatology data
  weather$day_of_year <- yday(weather$date)

  # create a variable for year
  weather$year <- year(weather$date)

  # calcualte month variable
  weather$month <- month(weather$date)

  # create a day column
  weather$day <- day(weather$date)

  # create a variable to indicate leap years
  weather$leap_year <- ifelse(weather$year %in% c(2016, 2020), "leap year", "not leap year")
```

```
  # for years that are leap years, you need to adjust the day_of_year variable
  # so that December 31st is day 365. This is needed so that when you join temperature
climatology
  # data, the matches are correct and leap days are missing data
  weather$day_of_year <- ifelse(weather$leap_year == "leap year" &
                          weather$month %in% c(3, 4, 5, 6, 7, 8, 9, 10, 11, 12),
                        # subtract 1 off of day_of_year for months march - dec
                        weather$day_of_year - 1,
                        # set leap days to missing for day_of_year variable
                        ifelse(weather$day == 29 & weather$month == 2, NA,
                             # leave january and rest of february day_of_year variable alone
                             weather$day_of_year))


  # calculate daily tmean variable for weather data
  weather$tmean <- (weather$tmax + weather$tmin) / 2

  # join dataframes together
  all_dat <- weather %>%
    # daily climatology
    left_join(clim, by = c("patientsid", "day_of_year")) %>%
    # warm / cold percentiles
    left_join(ptile, by = c("patientsid")) %>%
    # drop day of year column
    select(-day_of_year)

  ##########################################################
  # Calculate derived variables

  # tmean temperature anomaly
  all_dat$tmean_anomaly <- all_dat$tmean - all_dat$tmean_normal

  # tmax temperature anomaly
  all_dat$tmax_anomaly <- all_dat$tmax - all_dat$tmax_normal

  # tmin temperature anomaly
  all_dat$tmin_anomaly <- all_dat$tmin - all_dat$tmin_normal

  # calculate meteorological season variable
  all_dat$season <- ifelse(all_dat$month %in% c(12, 1, 2), "winter",
                    ifelse(all_dat$month %in% c(3, 4, 5), "spring",
                         ifelse(all_dat$month %in% c(6, 7, 8), "summer", "fall")))

  # create variable for cold/warm season definition
  # primary cold = Oct - Mar
  # primary warm = Apr - Sept
  all_dat$warm_cold_season_primary <- ifelse(all_dat$month %in% c(10, 11, 12, 1, 2, 3),
                                      "cold season", "warm season")
```

```
  # create a variable to indicate if it is early, mid or late warm/cold season
  all_dat$warm_cold_season_primary_timing <- ifelse(
    all_dat$warm_cold_season_primary == "cold season" & all_dat$month %in% c(10, 11),
    "early cold season",
    ifelse(all_dat$warm_cold_season_primary == "cold season" & all_dat$month %in% c(12, 1),
           "mid cold season",
           ifelse(all_dat$warm_cold_season_primary == "cold season" & all_dat$month %in% c(2,
3),
                  "late cold season",
                  ifelse(all_dat$warm_cold_season_primary == "warm season" & all_dat$month
%in% c(4, 5),
                         "early warm season",
                         ifelse(all_dat$warm_cold_season_primary == "warm season" & all_dat$month
%in% c(6, 7),
                                "mid warm season", "late warm season")))))

  ########################################################
  # prep data for rolling calculations

  # group data by patient and arrange in ascedning order for date (day variable)
  all_dat <- all_dat %>%
    # group by patient ID
    group_by(patientsid) %>%
    # sort data by date and patient ID
    arrange(patientsid, date)

  # calculate 1, 2 and 3 day rolling average lags for all weather and temp anomaly variables
  # make sure rolling lags include day of (so lag day 1 is rolling mean of day 0 and day 1)

  weather_vars <- c("tmean", "tmax", "tmin", "precip", "specific_humidity", "wind_speed",
                    "tmean_anomaly", "tmin_anomaly", "tmax_anomaly")

  for(i in seq_along(weather_vars)){

    all_dat <- all_dat %>%
      moving.avg(in_col = weather_vars[[i]])

  }

  ########################################################
  # Heatwave calcuation
  ########################################################
  # Mean temperature; Apr - Sept; 1992 - 2021; 95th percentile
  all_dat <- all_dat %>%
    heatwave.gen(temp_var = "tmean", ptile_var =
"warm_season_apr_sept_mean_temp_95th_ptile_1992_2021",
                 season_var = "warm_cold_season_primary",
                 seq_id_var = "heatwave_id_apr_sept_1992_2021_tmean_95_ptile",
```

```
                seq_day_var = "heatwave_days_apr_sept_1992_2021_tmean_95_ptile",
                heatwave_var = "heatwave_indicator_apr_sept_1992_2021_tmean_95_ptile",
                lag1_var = "heatwave_indicator_apr_sept_1992_2021_tmean_95_ptile_lag1",
                lag2_var = "heatwave_indicator_apr_sept_1992_2021_tmean_95_ptile_lag2",
                lag3_var = "heatwave_indicator_apr_sept_1992_2021_tmean_95_ptile_lag3",
                lag4_var = "heatwave_indicator_apr_sept_1992_2021_tmean_95_ptile_lag4",
                lag5_var = "heatwave_indicator_apr_sept_1992_2021_tmean_95_ptile_lag5",
                lag6_var = "heatwave_indicator_apr_sept_1992_2021_tmean_95_ptile_lag6",
                lag7_var = "heatwave_indicator_apr_sept_1992_2021_tmean_95_ptile_lag7")


    # Mean temperature; Apr - Sept; 1992 - 2021; 90th percentile
    all_dat <- all_dat %>%
      heatwave.gen(temp_var = "tmean", ptile_var =
"warm_season_apr_sept_mean_temp_90th_ptile_1992_2021",
                season_var = "warm_cold_season_primary",
                seq_id_var = "heatwave_id_apr_sept_1992_2021_tmean_90_ptile",
                seq_day_var = "heatwave_days_apr_sept_1992_2021_tmean_90_ptile",
                heatwave_var = "heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile",
                lag1_var = "heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag1",
                lag2_var = "heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag2",
                lag3_var = "heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag3",
                lag4_var = "heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag4",
                lag5_var = "heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag5",
                lag6_var = "heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag6",
                lag7_var = "heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag7")

    ################################################
    # Mean temperature; Apr - Sept; 2002 - 2021; 95th percentile
    all_dat <- all_dat %>%
      heatwave.gen(temp_var = "tmean", ptile_var =
"warm_season_apr_sept_mean_temp_95th_ptile_2002_2021",
                season_var = "warm_cold_season_primary",
                seq_id_var = "heatwave_id_apr_sept_2002_2021_tmean_95_ptile",
                seq_day_var = "heatwave_days_apr_sept_2002_2021_tmean_95_ptile",
                heatwave_var = "heatwave_indicator_apr_sept_2002_2021_tmean_95_ptile",
                lag1_var = "heatwave_indicator_apr_sept_2002_2021_tmean_95_ptile_lag1",
                lag2_var = "heatwave_indicator_apr_sept_2002_2021_tmean_95_ptile_lag2",
                lag3_var = "heatwave_indicator_apr_sept_2002_2021_tmean_95_ptile_lag3",
                lag4_var = "heatwave_indicator_apr_sept_2002_2021_tmean_95_ptile_lag4",
                lag5_var = "heatwave_indicator_apr_sept_2002_2021_tmean_95_ptile_lag5",
                lag6_var = "heatwave_indicator_apr_sept_2002_2021_tmean_95_ptile_lag6",
                lag7_var = "heatwave_indicator_apr_sept_2002_2021_tmean_95_ptile_lag7")


    # Mean temperature; Apr - Sept; 2002 - 2021; 90th percentile
    all_dat <- all_dat %>%
      heatwave.gen(temp_var = "tmean", ptile_var =
"warm_season_apr_sept_mean_temp_90th_ptile_2002_2021",
                season_var = "warm_cold_season_primary",
```

```
                seq_id_var = "heatwave_id_apr_sept_2002_2021_tmean_90_ptile",
                seq_day_var = "heatwave_days_apr_sept_2002_2021_tmean_90_ptile",
                heatwave_var = "heatwave_indicator_apr_sept_2002_2021_tmean_90_ptile",
                lag1_var = "heatwave_indicator_apr_sept_2002_2021_tmean_90_ptile_lag1",
                lag2_var = "heatwave_indicator_apr_sept_2002_2021_tmean_90_ptile_lag2",
                lag3_var = "heatwave_indicator_apr_sept_2002_2021_tmean_90_ptile_lag3",
                lag4_var = "heatwave_indicator_apr_sept_2002_2021_tmean_90_ptile_lag4",
                lag5_var = "heatwave_indicator_apr_sept_2002_2021_tmean_90_ptile_lag5",
                lag6_var = "heatwave_indicator_apr_sept_2002_2021_tmean_90_ptile_lag6",
                lag7_var = "heatwave_indicator_apr_sept_2002_2021_tmean_90_ptile_lag7")


    ########################################################
    # Coldwave calculation
    ########################################################
    # Mean temp; Oct - Mar; 1992 - 2021; 5th percentile
    all_dat <- all_dat %>%
      coldwave.gen(temp_var = "tmean", ptile_var =
"cold_season_oct_mar_mean_temp_5th_ptile_1992_2021",
                season_var = "warm_cold_season_primary",
                seq_id_var = "coldwave_id_oct_mar_1992_2021_tmean_5_ptile",
                seq_day_var = "coldwave_days_oct_mar_1992_2021_tmean_5_ptile",
                coldwave_var = "coldwave_indicator_oct_mar_1992_2021_tmean_5_ptile",
                lag1_var = "coldwave_indicator_oct_mar_1992_2021_tmean_5_ptile_lag1",
                lag2_var = "coldwave_indicator_oct_mar_1992_2021_tmean_5_ptile_lag2",
                lag3_var = "coldwave_indicator_oct_mar_1992_2021_tmean_5_ptile_lag3",
                lag4_var = "coldwave_indicator_oct_mar_1992_2021_tmean_5_ptile_lag4",
                lag5_var = "coldwave_indicator_oct_mar_1992_2021_tmean_5_ptile_lag5",
                lag6_var = "coldwave_indicator_oct_mar_1992_2021_tmean_5_ptile_lag6",
                lag7_var = "coldwave_indicator_oct_mar_1992_2021_tmean_5_ptile_lag7")

    # Mean temp; Oct - Mar; 1992 - 2021; 10th percentile
    all_dat <- all_dat %>%
      coldwave.gen(temp_var = "tmean", ptile_var =
"cold_season_oct_mar_mean_temp_10th_ptile_1992_2021",
                season_var = "warm_cold_season_primary",
                seq_id_var = "coldwave_id_oct_mar_1992_2021_tmean_10_ptile",
                seq_day_var = "coldwave_days_oct_mar_1992_2021_tmean_10_ptile",
                coldwave_var = "coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile",
                lag1_var = "coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag1",
                lag2_var = "coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag2",
                lag3_var = "coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag3",
                lag4_var = "coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag4",
                lag5_var = "coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag5",
                lag6_var = "coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag6",
                lag7_var = "coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag7")

    ############################################
    # Mean temp; Oct - Mar; 2002 - 2021; 5th percentile
    all_dat <- all_dat %>%
```

```
    coldwave.gen(temp_var = "tmean", ptile_var =
"cold_season_oct_mar_mean_temp_5th_ptile_2002_2021",
                 season_var = "warm_cold_season_primary",
                 seq_id_var = "coldwave_id_oct_mar_2002_2021_tmean_5_ptile",
                 seq_day_var = "coldwave_days_oct_mar_2002_2021_tmean_5_ptile",
                 coldwave_var = "coldwave_indicator_oct_mar_2002_2021_tmean_5_ptile",
                 lag1_var = "coldwave_indicator_oct_mar_2002_2021_tmean_5_ptile_lag1",
                 lag2_var = "coldwave_indicator_oct_mar_2002_2021_tmean_5_ptile_lag2",
                 lag3_var = "coldwave_indicator_oct_mar_2002_2021_tmean_5_ptile_lag3",
                 lag4_var = "coldwave_indicator_oct_mar_2002_2021_tmean_5_ptile_lag4",
                 lag5_var = "coldwave_indicator_oct_mar_2002_2021_tmean_5_ptile_lag5",
                 lag6_var = "coldwave_indicator_oct_mar_2002_2021_tmean_5_ptile_lag6",
                 lag7_var = "coldwave_indicator_oct_mar_2002_2021_tmean_5_ptile_lag7")

  # Mean temp; Oct - Mar; 2002 - 2021; 10th percentile
  all_dat <- all_dat %>%
    coldwave.gen(temp_var = "tmean", ptile_var =
"cold_season_oct_mar_mean_temp_10th_ptile_2002_2021",
                 season_var = "warm_cold_season_primary",
                 seq_id_var = "coldwave_id_oct_mar_2002_2021_tmean_10_ptile",
                 seq_day_var = "coldwave_days_oct_mar_2002_2021_tmean_10_ptile",
                 coldwave_var = "coldwave_indicator_oct_mar_2002_2021_tmean_10_ptile",
                 lag1_var = "coldwave_indicator_oct_mar_2002_2021_tmean_10_ptile_lag1",
                 lag2_var = "coldwave_indicator_oct_mar_2002_2021_tmean_10_ptile_lag2",
                 lag3_var = "coldwave_indicator_oct_mar_2002_2021_tmean_10_ptile_lag3",
                 lag4_var = "coldwave_indicator_oct_mar_2002_2021_tmean_10_ptile_lag4",
                 lag5_var = "coldwave_indicator_oct_mar_2002_2021_tmean_10_ptile_lag5",
                 lag6_var = "coldwave_indicator_oct_mar_2002_2021_tmean_10_ptile_lag6",
                 lag7_var = "coldwave_indicator_oct_mar_2002_2021_tmean_10_ptile_lag7")


  ########################################################
  saveRDS(all_dat, file =
paste0("./data/veteran_heat_cold_wave_data/veterans_heat_cold_wave_county_",
                        county_id, "_2015_2021.rds"))

  end_time <- Sys.time()

  diff <- difftime(end_time, start_time, units = c("mins"))

  print(paste("Time to complete", diff, "minutes"))

  print(paste("Completed with", county_id, "at", Sys.time()))

 }
}


##############################################################################
# Heatwave / Coldwave variable generation
```

```
################################################################################
# create 3 lists of files
# 1) list of daily 2015-2021 weather data
# 2) 30-year daily climatology data for 1991 - 2020
# 3) heat/cold percentile values data for 1992 - 2021 and 2002 - 2021


# Need to ensure that each of these lists is in the same order
# Iterate through each list (county by county), join the dataframes
# together and calculate new variables
weather_list <- list.files("./data/veteran_weather_data", full.names = TRUE)


clim_list <- list.files("./data/veteran_climate_normals", full.names = TRUE)


ptile_list <- list.files("./data/veteran_heat_cold_percentiles", full.names = TRUE)


# check that ordering of files is correct
head(weather_list, n = 5)

head(clim_list, n = 5)

head(ptile_list, n = 5)


# use variable.gen function to create final dataframes (takes 4 days)
variable.gen(weather_list, clim_list, ptile_list)
################################################################################
#
# Case crossover dataframe function
################################################################################
#

cco.gen <- function(in_file, copd_df, holiday_df){

  # This function will create a time stratified and bidirectional case crossover dataset
  # for a given county

  # This function requires a full file name including path to a county specific dataset of
  # veteran weather data (heatwave and coldwaves)
  # a dataframe of the original copd cohort being used
  # a vector of holidays from 2015-2021

  start_time <- Sys.time()

  # read in heat/cold wave file
  ext_weather_dat <- readRDS(in_file)
```

```
# from the county specific heat/cold wave file name, get the 5 digit county fips code
in_fips <- substr(in_file, start = 67,stop = 71)

# filter the COPD data to county that matches file name
my_dat <- copd_df %>%
  filter(county_fips == in_fips)


# get day of week, month and year for death date column
my_dat$death_dow <- wday(my_dat$DeathDate)

my_dat$death_month <- month(my_dat$DeathDate)

my_dat$death_year <- year(my_dat$DeathDate)


# join the data for single county to its weather data file
joined_dat <- ext_weather_dat %>%
  left_join(my_dat, by = c("patientsid"))

# create a weekday column for the weather data
joined_dat$dow <- wday(joined_dat$date)


# time stratified days are same week day, month and year as death date
joined_dat$time_strat_day <- ifelse(joined_dat$year == joined_dat$death_year &
                                    joined_dat$month == joined_dat$death_month &
                                    joined_dat$dow == joined_dat$death_dow &
                                    joined_dat$date != joined_dat$DeathDate,
                                  "control day",
                                  ifelse(joined_dat$date == joined_dat$DeathDate, "event day", "not
eligible"))



# bidirectional days are +/- 7, 14 days around event day
# create columns to indicate these eligible days
joined_dat$death_date_plus7 <- joined_dat$DeathDate + 7

joined_dat$death_date_plus14 <- joined_dat$DeathDate + 14

joined_dat$death_date_minus7 <- joined_dat$DeathDate - 7

joined_dat$death_date_minus14 <- joined_dat$DeathDate - 14


# mark eligible control days as days that are +/- 7, 14 days
joined_dat$bidirectional_day <- ifelse(
  joined_dat$date == joined_dat$death_date_plus7 |
    joined_dat$date == joined_dat$death_date_plus14 |
```

```
    joined_dat$date == joined_dat$death_date_minus7 |
    joined_dat$date == joined_dat$death_date_minus14,
  "control day",
  ifelse(joined_dat$date == joined_dat$DeathDate,
         "event day", "not eligible"))

##############################
# create a holiday indicator variable
joined_dat$holiday <- ifelse(
  joined_dat$date %in% holiday_df, "Holiday", "Non Holiday")


# create a birth month and birth day column
joined_dat$day_of_birth <- day(joined_dat$BirthDate)

joined_dat$month_of_birth <- month(joined_dat$BirthDate)


# create a column to signify if case or control day was on their birth date
joined_dat$birth_day_month <- ifelse(joined_dat$day == joined_dat$day_of_birth &
                                       joined_dat$month == joined_dat$month_of_birth,
                                     "birthday", "not birthday")

# drop columns not needed
joined_dat <- joined_dat %>%
  select(-starts_with("death_date_plus"), -starts_with("death_date_minus"))


# create a dataset for time stratified design
time_strat_dat <- joined_dat %>%
  filter(time_strat_day %in% c("event day", "control day"))

# create a dataset for bidirectional design
bidirec <- joined_dat %>%
  filter(bidirectional_day %in% c("event day", "control day"))


# save out each design type
saveRDS(time_strat_dat, file = paste0("./data/veteran_county_cco_data/veterans_cco_county_",
                                      in_fips, "_time_stratified_2015_2021.rds"))

saveRDS(bidirec, file = paste0("./data/veteran_county_cco_data/veterans_cco_county_",
                               in_fips, "_bidirectional_2015_2021.rds"))

end_time <- Sys.time()

diff <- difftime(end_time, start_time, units = c("mins"))

print(paste("Time to complete", diff, "minutes"))
```

```
  print(paste("Completed with county", in_fips, "at", Sys.time()))

}
################################################################################
# Create county level time stratified and bi-directional datasets for extreme weather
################################################################################

# create a function that will do this and then loop thru each county
my_files <- list.files("./data/veteran_heat_cold_wave_data", full.names = TRUE)


# iterate over each county and make county level dataset for case crossover
for(i in seq_along(my_files)){

  cco.gen(my_files[[i]], copd_df = copd, holiday_df = holidays)

}

################################################################################
#
# Function to run a DLM model for heat and cold waves
################################################################################
#
dlm.iter <- function(df, event_type, stratum_var, stratum_value, stratum_label){

  # This function will create a DLM model and calculate lag specific and cumulative effects
  # for heat and cold waves
  # Lag 0 - 1 and 0 - 3 for heat
  # Lag 0 - 4 and 0 - 7 for cold
  # This function requires
  # 1) a dataframe
  # 2) a string denoting the exposure of interest (heatwave or coldwave)
  # 3) the name of the variable you want to do stratified analysis of
  # 4) The value of the strata you want to filter out of your input data
  #    e.g. TobaccoCurrentUse == "Smoker"
  # 5) a label to give for the stratum in the output dataset

  # Turn your stratum variable into a symbol
  stratum_var_sym <- sym(stratum_var)

  if(event_type == "heatwave"){

    # Create the subset dataset base on the input value to filter
    sub_df <- df %>%
      filter(!!stratum_var_sym == stratum_value)

    # grab the heatwave variables for the cross-basis
    heat_vars <- sub_df %>%
      dplyr::select(heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile,
                    heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag1,
```

```
            heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag2,
            heatwave_indicator_apr_sept_1992_2021_tmean_90_ptile_lag3)

# Create the cross-basis
cb <- crossbasis(heat_vars, lag = c(0,3), argvar = list(fun = "lin"),
             arglag = list(fun = "lin"))

# Model for heatwaves
mod <- clogit(time_strat_day ~ cb + precip + wind_speed + holiday +
          ns(specific_humidity, 5) + strata(patientsid), data = sub_df)

# Predictions by 1 unit of lag day for exposure
pred <- crosspred(cb, mod, at = 0:1, bylag = 1, cumul = TRUE)

# Create empty lists to hold the lag specific estimates and the SEs
lags_df <- list()

se_df <- list()

# vector of lag days to iteratively grab estimates for
lag_days <- c(0, 1, 2, 3)

# iterate over the lag days and grab their estimates and standard errors
for(i in seq_along(lag_days)){

  # run crossreduce for ith lag day
  reduced_mod <- crossreduce(cb, mod, type = "lag", value = lag_days[[i]], at = 1)

  # unexponentiated point estimate
  est <- reduced_mod$fit

  # unexponentiated SE
  se <- reduced_mod$se

  # Add ith elements to lists
  lags_df[[i]] <- est

  se_df[[i]] <- se

}

# bind the lag and SE lists into dataframes
lags_df <- bind_rows(lags_df)

se_df <- bind_rows(se_df)

res <- lags_df %>%
  bind_cols(se_df)

# create a column to hold lag day value
```

```
res$lag <- lag_days

# change column names
names(res) <- c("estimate", "se", "lag")

# change lag to character
res$lag <- as.character(res$lag)


# Grab 0-1 cumulative effects
pred_cumfit <- as.data.frame(pred$cumfit)

# Unexponentiated estimate for lag 0 - 1 effect is the 2nd column, 2nd row cell value
cumul_est <- pred_cumfit[2,2]

# same location for unexponentiated se
pred_se <- as.data.frame(pred$cumse)

cumul_se <- pred_se[2,2]

# add values as new row
res <- res %>%
  dplyr::add_row(estimate = cumul_est, se = cumul_se, lag = "0 - 1")


# Overall Cumulative effect RR unexponentiated stored in allfit and allse
# Values stored in 2nd index of allfit variable
# Insert as new row
res <- res %>%
  dplyr::add_row(estimate = pred$allfit[2], se = pred$allse[2], lag = "0 - 3")


# Then create exponentiated estimates and CIs
res$exp_estimate <- exp(res$estimate)

# lower CI
res$lower_ci <- exp(res$estimate - (1.96*res$se))


# upper CI
res$upper_ci <- exp(res$estimate + (1.96*res$se))

# Make the lag days an ordered factor
res$lag <- factor(res$lag, levels = c("0", "1", "2", "3", "0 - 1", "0 - 3"))


# add string for stratum type
res$strata <- stratum_label

# add column for sample size
```

```
sample <- length(unique(sub_df$patientsid))

res$sample_size <- sample

# add an exposure column
res$exposure <- "Heatwave"

print("Done!")

return(res)} else{

 # Create the subset dataset base on the input value to filter
 sub_df <- df %>%
  filter(!!stratum_var_sym == stratum_value)

 # grab the cold wave variables for the cross-basis
 cold_vars <- sub_df %>%
  dplyr::select(coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile,
                coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag1,
                coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag2,
                coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag3,
                coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag4,
                coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag5,
                coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag6,
                coldwave_indicator_oct_mar_1992_2021_tmean_10_ptile_lag7)

 # Create the cross-basis
 cb <- crossbasis(cold_vars, lag = c(0,7), argvar = list(fun = "lin"),
                  arglag = list(fun = "lin"))

 # Model for cold waves
 mod <- clogit(time_strat_day ~ cb + precip + wind_speed + holiday +
                specific_humidity + strata(patientsid), data = sub_df)

 # Predictions by 1 unit of lag day for exposure
 pred <- crosspred(cb, mod, at = 0:1, bylag = 1, cumul = TRUE)

 # Create empty lists to hold the lag specific estimates and the SEs
 lags_df <- list()

 se_df <- list()

 # vector of lag days to iteratively grab estimates for
 lag_days <- c(0, 1, 2, 3, 4, 5, 6, 7)

 # iterate over the lag days and grab their estimates and standard errors
 for(i in seq_along(lag_days)){

  # run crossreduce for ith lag day
  reduced_mod <- crossreduce(cb, mod, type = "lag", value = lag_days[[i]], at = 1)
```

```
  # unexponentiated point estimate
  est <- reduced_mod$fit

  # unexponentiated SE
  se <- reduced_mod$se

  # Add ith elements to lists
  lags_df[[i]] <- est

  se_df[[i]] <- se

}

# bind the lag and SE lists into dataframes
lags_df <- bind_rows(lags_df)

se_df <- bind_rows(se_df)

res <- lags_df %>%
  bind_cols(se_df)

# create a column to hold lag day value
res$lag <- lag_days

# change column names
names(res) <- c("estimate", "se", "lag")

# change lag to character
res$lag <- as.character(res$lag)


# Grab 0-4 cumulative effects
pred_cumfit <- as.data.frame(pred$cumfit)

# Unexponentiated estimate for lag 0 - 4 effect is the 5th column, 2nd row cell value
cumul_est <- pred_cumfit[2,5]

# same location for unexponentiated se
pred_se <- as.data.frame(pred$cumse)

cumul_se <- pred_se[2,5]

# add values as new row
res <- res %>%
  dplyr::add_row(estimate = cumul_est, se = cumul_se, lag = "0 - 4")


# Overall Cumulative effect RR unexponentiated stored in allfit and allse
# Values stored in 2nd index of allfit variable
```

```
    # Insert as new row
    res <- res %>%
      dplyr::add_row(estimate = pred$allfit[2], se = pred$allse[2], lag = "0 - 7")


    # Then create exponentiated estimates and CIs
    res$exp_estimate <- exp(res$estimate)

    # lower CI
    res$lower_ci <- exp(res$estimate - (1.96*res$se))


    # upper CI
    res$upper_ci <- exp(res$estimate + (1.96*res$se))

    # Make the lag days an ordered factor
    res$lag <- factor(res$lag, levels = c("0", "1", "2", "3", "4", "5", "6", "7", "0 - 4", "0 - 7"))

    # add string for stratum type
    res$strata <- stratum_label

    # add column for sample size
    sample <- length(unique(sub_df$patientsid))

    res$sample_size <- sample

    # add an exposure column
    res$exposure <- "Cold wave"

    print("Done!")

    return(res)
  }
}
```