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The impact of meteorological factors and air pollution on adverse birth outcomes

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THE IMPACT OF METEOROLOGICAL FACTORS AND AIR POLLUTION ON ADVERSE BIRTH OUTCOMES

by

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DEDICATION

This dissertation is dedicated to my parents, Steven and Denise Butler,

and to my little brothers, Stevie and TJ.

Thank you for your unwavering love and support.

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THE IMPACT OF METEOROLOGICAL FACTORS AND AIR POLLUTION ON ADVERSE BIRTH OUTCOMES

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ABSTRACT

The human health impacts of anthropogenic climate change continue to intensify. Perhaps most concerning is the rapid rise in ambient temperature, with 10 of the hottest years ever recorded having occurred over the last 15 years (IPCC, 2018; NASA, 2019). A robust literature has accumulated characterizing an extensive list of adverse health effects of heat exposure, identifying a number of groups particularly vulnerable (Ebi et al., 2018). The most recent group identified as highly vulnerable to heat exposure is expectant mothers (Bekkar et al., 2020; Chersich et al., 2020). A consistent relationship has been observed between increased ambient temperature and adverse pregnancy events, including increase in preterm delivery (PTD), small for gestational age, and stillbirth (Bekkar et al., 2020; Chersich et al., 2020) .

Utilizing birth records and fetal death records from 2000-2004, we carried out two case-crossover studies assessing the impact of ambient temperature on preterm delivery and stillbirth across the contiguous United States, where 1 in 10 births results in a preterm delivery and 1 in 160 births results in a stillborn fetus. Our aim was to assess how increased temperature, singularly and in combination with air pollution exposure, impacts the odds of experiencing a preterm delivery or stillbirth (Aims 1 and 2). Our third aim,

performed with a case-control study, expanded on the exploration of air pollution exposure, examining how traffic related air pollution (measured by maternal residential proximity to major roadways) impacts placental-associated stillbirth (Aim 3).

We identified significantly increased odds of preterm delivery and stillbirth associated with a 10-degree Fahrenheit increase in average apparent temperature in the week preceding delivery for babies delivered in the warm season (May – October) and the meteorological summer (June – August). These increases were strongest in the Southern half of the United States and modified by maternal race/ethnicity for both preterm delivery and stillbirth. The increased odds were independent of air pollution exposure (ozone and $PM_{2.5}$), which had no impact on the odds of preterm delivery or stillbirth. Furthermore, we did not observe a meaningful increase in overall odds of placental-associated stillbirth with increased proximity of the maternal residence to major roads.

These studies contribute to the growing literature on the vulnerability of pregnant women to heat exposure and enhance the understanding of environmental risk factors of preterm birth and stillbirth, a chronically understudied health outcome.

TABLE OF CONTENTS

LIST OF TABLES

LIST OF FIGURES

LIST OF ABBREVIATIONS

aOR	adjusted odds ratio
AQS	Air Quality System
ASOS	Atmospheric Surface Observing System
CI	confidence interval
cOR	crude odds ratio
DOD	Department of Defense
EPA	Environmental Protection Agency
FAA	Federal Aviation Administration
MADPH	Massachusetts Department of Public Health
MI	multiple imputation
NCHS	National Center for Health Statistics
NOAA	National Oceanic and Atmospheric Administration
NOx	nitrogen oxides
NVSS	National Vital Statistics System
NWS	National Weather Service
O3	ozone
OR	odds ratio
PCE	tetrachloroethylene (aka perchloroethylene)
PM2.5	particulate matter sized 2.5 microns in diameter
PTD	preterm delivery
RIDOH	Rhode Island Department of Health

SGA	small for gestational age
TIGER	Topologically Integrated Geographic Encoding and Referencing System
TRAP	traffic-related air pollution

CHAPTER 1. INTRODUCTION

The Growing Health Burden of Anthropogenic Climate Change

Currently, 197 countries are signed on to the Paris Climate Accord, a landmark climate agreement formed in 2015 to address climate change and its present and future negative impacts. The primary aim of the commitment is to substantially reduce greenhouse gas emissions to limit the global rise in temperature in this century to 2-degrees Celsius above pre-industrial levels (NRDC, 2020). Five years after conception of the Accord, we are failing to make meaningful progress. Global carbon dioxide emissions continue to rise steadily with no tangible or convincing sustained reductions, and the rise in global average temperature is at 1.2 ºC. Ten of the hottest years on record have occurred since 2005, with the top 5 since 2015, and 2019 and 2020 emerging as the two hottest years ever recorded (Watts et al., 2020; NASA, 2019).

The environmental, economic, and human health impacts of the changing climate are catastrophic. The Intergovernmental Panel on Climate Change repeatedly warns about increasing global warming, increase in extreme weather events, rising sea levels, diminishing Arctic sea ice, increase in drought and wildfire, growing food insecurity, and other consequences (IPCC, 2018). The human health impacts of climate change are profound and multifactorial, arising from displacement, hunger, increased heat exposure, international conflict from resource scarcity, and loss of life from extreme events (IPCC, 2018; Ebi et al. 2018; Watts et al., 2020). While scientists continue to characterize the litany of ways in which climate change effects human health, the physiologic danger of increasing ambient temperatures emerges as particularly concerning. A robust literature has characterized the effects of heat stress on humans, noting associations with increased ambient temperature and cardiovascular disease, respiratory disease, overall increased mortality, emergency room hospitalizations, mental health problems, allergic responses, and the spread of vector born infectious disease (Cui et al., 2014, Anderson et al., 2013; Limaye et al., 2018, Vaidyanathan, et al., 2019; Upperman et al., 2017; Ogen et al., 2017). Public health officials have consistently identified children under 5 years of age, elderly individuals over 65, the immunocompromised and outdoor workers as vulnerable groups who are at increased risk of experiencing an adverse health event from heat stress (Watts et al., 2020; Weir, 2002).

In 2019, vulnerable groups were exposed to an additional 475-million heatwave events globally (a metric defined as one person over 65 years of age experiencing a given heat wave). In the past two decades, there has been a 53.7% increase in heat related mortality in the population older than 65 (Watts et al., 2020). The dangers of heat exposure as we near the later stages of life are established, but a newer literature also identifies increased vulnerability at the most nascent stage of life — pregnancy. In a growing body of research, a relationship has been observed between increased ambient temperature and adverse pregnancy events, including increase in preterm delivery, small for gestational age (SGA) or low birthweight, and occurrence of stillbirth (Bekkar et al., 2020).

A systematic review of the US literature published in 2020, found that 9 out of 10 studies examining heat exposure and birth outcomes showed statistically significant positive associations. Of these studies, five examined preterm delivery (PTD) and four found positive associations (a 10-degree increase in apparent temperature associated with increased odds of PTD ranging from eight to 22%) (Bekkar et al., 2020). In 2017, a global systematic review, titled “Heat Exposure and Maternal Health in the Face of Climate Change,” identified 14 out of 17 studies where heat was significantly correlated with increased risk or rate of preterm birth (Kuehn et al., 2017). In the US and globally there have been fewer studies of maternal heat stress with stillbirth as a primary outcome. Still, a consistent association is observed, with two studies in the US and three additional outside the US, identifying an increased risk of stillbirth with increased maternal ambient temperature exposure (Basu et al., 2016; Ha et al., 2017; Wang et al., 2013; Fakuda et al., 2014; Strand et al., 2012).

Air Pollution: A Persistent Public Health Crisis

To achieve the greenhouse gas reduction objectives of the Paris Accord, we must adopt cleaner and renewable sources of energy. With this, will come a significant reduction in air pollution and a subsequent improvement of global public health. Air pollution is one of the greatest public health crises of our time, responsible for killing an estimated 7 million people worldwide every year (WHO, 2014). Of these deaths, 4.2 million are attributable to ambient (outdoor) air pollution (WHO, 2014). Air pollution leads to premature death primarily through increased mortality from stroke, heart disease, lung cancer, chronic obstructive pulmonary disease, and acute respiratory infections (WHO, 2014). As is the case for heat exposure, a growing and consistent literature is emerging identifying pregnant women as highly vulnerable to adverse health effects of air pollution exposure (Ha et al., 2014).

There is growing epidemiologic evidence of associations between ambient air pollution exposure and adverse outcomes and pregnancy complications including preterm birth, low birthweight, stillbirth, preeclampsia, and gestational diabetes. One of the greatest sources of ambient air pollution is fuel combustion from motor vehicles (cars, trucks, and heavy-duty vehicles). Traffic-related air pollution (TRAP) is comprised of a number of air pollutants including carbon monoxide, carbon dioxide, hydrocarbons, nitrogen oxides, particulate matter, mobile-source air toxics (such as benzene, formaldehyde, acetaldehyde, 1,3,-butadiene, and lead), and secondary-by-products such as ozone and nitrates (HEI, 2010). Certain components of TRAP, like particulate matter, nitrogen oxides, and ozone have been more frequently studied in the context of exposure during pregnancy, compared to other component contaminants. Exposure to fine particulate matter (PM 2.5) has been associated with increased risk of preterm birth and low birth weight. Exposure to nitrogen oxides (NOx) have been associated with gestational diabetes and preeclampsia. Exposure to ozone (O3) has been associated with increased risk of stillbirth, low birth weight, and maternal hypertension (Bekkar et al., 2020).

It is common practice in environmental health to study TRAP using a proxy measure, residential proximity to major roadways. Studies using road proximity metrics have identified positive associations with low placental weight, low birth weight, and small for gestational age (Yorifuji et al., 2012; Brauer et al., 2008; Hannam et al., 2013).

Environmental Exposures in the Context of Maternal Fetal Health

While maternal fetal health indicators are improving worldwide, certain adverse pregnancy events remain prevalent in both developed and developing nations (WHO, 2010). The rate of preterm birth, defined as gestational age less than 37 weeks completed gestation, remains high. The estimated global preterm birth rate is about 10.6%, slightly higher than the US rate of 1 in 10 pregnancies (CDC, 2020). Worldwide, approximately one million neonatal deaths occur every year as a result of complications arising from preterm birth (March of Dimes, 2020). Furthermore, surviving preterm infants face long-term adverse health outcomes including vision and hearing impairment, chronic lung disease, chronic cardiovascular ill health, and neurodevelopmental and behavioral disorders (March of Dimes, 2012).

The annual societal economic burden of preterm birth in the US is about 26.2 billion dollars, and the first-year medical costs of a preterm baby are, on average, ten times that of a full term infant (IOM, 2007). In the US, significant racial disparities persist for preterm birth, with the highest risk among Non-Hispanic Black mothers — about 14% compared to 9% among Non-Hispanic White mothers. Preterm birth-related mortality is also three times higher in premature Black infants compared to premature White infants (Burris et al., 2019).

While the rate of preterm delivery in the United States closely reflects the worldwide numbers, that is not the case for stillbirth. In 2019, the global rate of stillbirth is about fourteen per 1,000 total births and in the United States, it is about three per 1,000 total births. The high numbers of stillbirth in some countries (as high as twenty-eight per 1,000 total births in parts of sub-Saharan Africa) highlights the need for more study in to the etiology of stillbirth, which is often described as the “neglected tragedy” due to the lack of public health emphasis and paucity of etiologic studies. In the US, racial disparities in stillbirth exceed those for preterm delivery, with Non-Hispanic Black mothers twice as likely to experience a stillbirth compared to Non-Hispanic White mothers (WHO, 2020).

For both preterm delivery and stillbirth, some risk factors have been established, yet the etiologic cause of the adverse outcome is unknown in about 50% of cases. For spontaneous preterm delivery known risk factors include maternal age (adolescence or advanced maternal age), multiple pregnancies, maternal infection, maternal underlying chronic conditions, genetic risks, previous preterm labor, and nutritional and lifestyle factors (NICHD, 2020). For stillbirth, risk factors are not as well understood but smoking, obesity, advanced age, lower education, and inadequate prenatal care have been shown to be associated in different studies to stillbirth (Goldenberg et al., 2011; Lawn et al., 2016; Stillbirth Collaborative Research Network, 2011). An early study of occupational exposure to environmental chemicals identified that women in metal-electrical-chemical industries and women with low-level exposure to pesticides were at increased risk of experiencing a miscarriage or stillbirth (Goulet et al., 1991).

With the cause of preterm delivery and stillbirth unknown in half of cases, we must explore potential environmental factors contributing to these outcomes. As mentioned above, both increased maternal heat stress and air pollution exposure have been implicated as potential contributors. In an international review, 15 out of 17 studies identified a statistically significant positive association between increased maternal ambient temperature exposure and preterm delivery (Kuehn et al., 2017). Five of these 15 studies were conducted in US populations, with three in California, one in Massachusetts, and one conducted at 12 different US clinical sites (Basu et al., 2010; Basu, et al., 2017; Avalos et al., 2017; Kloog et al., 2015; Ha et al., 2017) For the studies conducted in California, a 10-degree increase in average apparent temperature in the week preceding the delivery was associated with an increased risk of preterm delivery of 8.6% and 22.1% (both studies examining births in the warm season) (Basu et al., 2010; Basu et al., 2017; Avalos et al., 2017). These studies utilized a case-crossover design and found no confounding of air pollution on the relationship between heat exposure and preterm delivery. Additionally, they identified racial/ethnic differences in vulnerability. In the first of the California studies conducted by Basu et al., in 2010, a case-crossover study of over 58,000 preterm deliveries in 16 California counties found an 8.6% increased risk of preterm delivery in the warm season, with the greatest risk for younger mothers and Black or Asian mothers (Basu, et al., 2010). Later, in 2017, Basu and colleagues conducted another case-crossover study of over 14,000 preterm deliveries in Northern California and identified an 11.6% increased odds and identified greatest risk for mothers who were younger, Black, Hispanic, underweight, using Medicaid, smokers, or having a pre-existing or gestational diabetes or hypertension (Basu et al., 2017). In the Massachusetts study of heat and preterm delivery, Kloog and colleagues utilized a cross-sectional design examining data on 473,977 births in Massachusetts and found a slight decrease (0.26%) in gestational age when looking at temperature exposure across the entire pregnancy (Kloog et al., 2015).

In contrast to these three studies which were limited to single states, a fourth case-crossover study published by Ha and colleagues in 2017 utilized data from 12 US clinical sites (locations in: CA, DC, DE, FL, IL, IN, OH, MA, MD, NY, TX, UT). This study examined the impacts of extreme ambient heat and cold at multiple points during pregnancy on preterm birth. For the week before the delivery, they observed a 5-degree Fahrenheit increase in heat was associated with a 12 to 16% increased odds of early delivery in the warm season (Ha et al., 2017). Most recently, in 2019, Sun et al. utilized a retrospective cohort study of 32 million US singleton births and identified that days of extreme heat, but not extreme cold, were associated with increased risk of preterm birth in the contiguous US (Sun et al., 2019).

The research on maternal ambient heat exposure and stillbirth is sparser than that of preterm delivery and low birth weight, once again reflecting the "neglected tragedy" (Bekkar et al., 2020). Three studies conducted in the United States have identified positive associations. In a 2016 case-crossover study, Basu et al. observed that a 10-degree increase in average apparent temperature in the week prior to the delivery was associated with a 10.4% increased risk of stillbirth in the warm season in California. They observed the association to be independent of air pollution exposure and greatest among Hispanic women (Basu et al., 2016). In 2017 Ha et al. published data on 987 stillbirths from 12 clinical sites across the US (locations in: CA, DC, DE, FL, IL, IN, OH, MA, MD, NY, TX, UT) and observed a 6% increase in risk was associated with every 1-

degree Celsius increase in apparent temperature in the week prior to the delivery (Ha et al., 2017). In 2019, Rammah et al. reported a 45% increased risk of stillbirth with a 10-degree Fahrenheit increase in apparent temperature in the week preceding the delivery for deliveries occurring from May to September in Harris County, Texas. They also found these associations to be independent of air pollution exposure and identified the greatest risks among Hispanic and Non-Hispanic Black women. Rammah et al. also evaluated stillbirths caused by placental abruption and found that this group had a 93% increased odds associated with a 10-degree increase in apparent temperature in the week leading up to the delivery (Rammah et al., 2019).

There are a greater number of studies characterizing the impacts of maternal air pollution exposure on adverse pregnancy outcomes than there are maternal heat exposure (Bekkar et al., 2020). Still, some questions remain about air pollution and pregnancy, in part due to the diversity and ubiquity of air pollution sources and constituents and the inconsistent findings in the literature. While traffic related air pollution has several dangerous constituents that have been examined in isolation, studying TRAP as a whole is a good representation of a women's actual mixture of air pollutant exposures experienced from mobile sources. We are aware of five studies conducted in the United States which examined air pollution and stillbirth. Findings have varied substantially depending on the pollutant, the window of exposure, and the exposure assessment techniques utilized. None of these studies utilized road proximity metrics to assess TRAP. The most frequently assessed air pollutant has been PM2.5. One study by Ebisu and colleagues in 2018 identified a 23% increased odds of stillbirths caused by inadequate fetal growth with every IQR increase in total PM2.5 across the pregnancy (Ebisu et al., 2018). In 2015 Green et al. observed a 6% increased odds of stillbirth with a 10 ug/m3 increase in PM 2.5 exposure across the whole pregnancy (Green et al., 2015). Also in 2015, DeFranco et al. observed that high exposure to PM2.5 in the third trimester (defined as 16.22 ug/m3) was associated with a 42% increased risk of stillbirth but exposure in the first or second trimester had no effect (DeFranco, et al., 2015).

Potential Biological Mechanisms

The biological mechanisms by which these environmental exposures may influence pregnancy are different for heat stress and air pollution and differ by pregnancy outcome. It has been postulated that maternal heat stress effects preterm delivery through two processes: general reduced thermoregulatory capacity and dehydration. When the human body experiences heat stress, it diverts blood away from the vital organs to the surface of the skin in an effort to cool down (Basu et al., 2010; Bouchama et al., 2002). Increased weight gain and the physiological burden of the fetus, combined with increased plasma blood volume, may hinder a women's thermoregulatory capacity making her more vulnerable to heat stress. This maternal physiologic stress may lead to premature rupture of membranes, triggering preterm delivery (Kuehn et al., 2017). Dehydration from heat stress may trigger the release of labor inducing hormones prostaglandin and oxytocin. Extreme dehydration could restrict uterine blood flow causing fetal distress (Avalos et al., 2017; Stan et al., 2002; Bouchama et al., 2002; Astrand et al., 2003).

The biological mechanisms that trigger preterm delivery are also relevant for stillbirth in cases where stillbirth is a result of a premature delivery at a gestational age that is incompatible with extrauterine life. Other mechanisms by which heat stress may impact stillbirth include lowering amniotic fluid volume, damaging or degrading the placenta, or causing a placental abruption (Bakkar et al., 2020; Stan et al., 2002; Ha et al., 2018; Prada et al., 1998; Browne et al., 2015; Li et al., 2003; He et al., 2018)

A number of biological mechanisms have been hypothesized for air pollution impact and adverse pregnancy outcomes, including systemic inflammation and oxidative stress, endothelial dysfunction, decrease in DNA methylation, systemic changes in hematocrit and blood viscosity, and disturbances to hemodynamic responses (Wesselink et al., 2017; Hettfleish et al., 2017; Kannan et al., 2006; de Melo et al., 2014; Slama et al., 2008; Veras et al., 2008).

Dissertation Objectives

Informed by the previous research, the overall objective of the dissertation was to investigate the role of two important environmental factors affecting pregnancy — maternal heat stress and air pollution. This was achieved through the exploration of three specific aims:

1. Examine maternal exposure to increased ambient temperature as a potential trigger of spontaneous preterm delivery (*Chapter 2*)

2. Examine maternal exposure to increased ambient temperature as a potential trigger of stillbirth (*Chapter 3*)

3. Examine the association between maternal residential proximity to major roadways and placental-associated stillbirth (*Chapter 4*)

In *Chapter* 2, we explore the first aim using US birth record data for almost one million preterm deliveries occurring in the contiguous United States between 2000 and 2004. Linking the maternal residence county with meteorological data from the National Oceanic and Atmospheric Administration (NOAA) Atmospheric Surface Observing System (ASOS) and utilizing a case-crossover design, we were able to examine a large, heterogeneous population of women across the climactically diverse country of the US. Our large sample size granted us the ability to identify particular regions and subgroups of the population at greater risk, adding to the previous literature.

In *Chapter 3*, we use similar methodology to examine meteorological triggers of stillbirth. Instead of birth records, fetal death records were used to ascertain data for stillbirths occurring in the contiguous United States from 2000 to 2004. Because of the lower incidence of stillbirth, the case numbers were much smaller than in chapter 2, yet the overall sample size of over 40,000 stillbirth cases makes this study one of the largest etiologic studies of stillbirth conducted in the US to date. Like in chapter 2, the large, heterogeneous sample granted us the ability to address some limitations of the previous literature.

In *Chapter 4*, we diverge from the previously utilized methods and use a case-control study design to assess the relationship between residential proximity to major roadways and placental-associated stillbirth. By restricting the case definition to placental-associated stillbirths, we improve upon the outcome classification typically used in studies of all-cause stillbirth. To the best of our knowledge, this study contributes the first exploration of maternal residential roadway proximity and stillbirth.

In *Chapter 5,* we summarize the findings of the three aims and discuss the limitations of this work. We explore the public health relevance of these findings, consider the findings in relation to the ongoing COVID-19 crisis, and suggest directions for future studies of heat stress and air pollution on pregnancy outcomes in the global context.

CHAPTER 2. ACUTE IMPACT OF TEMPERATURE ON PRETERM DELIVERY IN THE US

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Abstract

In the face of rising temperatures from anthropogenic climate change, it is imperative that we identify populations at high risk for adverse health effects from heat stress. While often missing from designations of heat-health high risk groups, pregnant women have emerged as a subgroup uniquely vulnerable to increasing ambient temperatures. We utilized a case-crossover design to examine the impact of a 10-degree increase in average apparent temperature in the week preceding birth among 968,529 women with preterm deliveries occurring across the contiguous US from January 1, 2000 through December 31, 2004. We observed a statistically significant increased risk of preterm deliveries occurring in the warm season (May 1 to Oct 31) and the meteorological summer (June 1 to August 31), Odds Ratio = 1.04 (95% Confidence Interval 1.03 – 1.05) and Odds Ratio = 1.15 (95% CI 1.14 – 1.16), respectively. The odds were higher in the Southern half of the US compared to Northern half of the US, and among Non-Hispanic Black mothers and Hispanic mothers than Non-Hispanic White mothers. As the frequency and intensity of hot days continues to rise in the US and globally, additional studies of increasing ambient temperature and adverse pregnancy outcomes are warranted.

Introduction

Climate change impacts continue to intensify across the US and worldwide. The Intergovernmental Panel on Climate Change warns about increasing global warming, increase in extreme weather events, rising sea levels, and diminishing Arctic sea ice, among other consequences (IPCC, 2018). The World Health Organization, the US National Climate Assessment, and the Lancet Countdown have characterized the many adverse health effects of climate change impacts (WHO, 2018; Ebi et al., 2018; Watts et al., 2019).

Perhaps most threatening to human health is the rapid rise in ambient temperature across the globe, with 10 of the hottest years ever recorded having occurred since 2005, and 2019 and 2020 emerging as the top two hottest years on record (NASA, 2019). A robust literature has characterized the effects of heat stress on humans, noting associations with increased ambient temperature and cardiovascular disease, respiratory disease, overall increased mortality, emergency room hospitalizations, mental health problems, allergic responses, and spread of vector born infectious disease (Cui et al., 2014, Anderson et al., 2013; Limaye et al., 2018, Vaidyanathan, et al., 2019; Upperman et al., 2017; Ogen et al., 2017). It is crucial that we identify specific populations who are most vulnerable to the effects of heat stress.

Typically, in the face of an oncoming extreme heat event, municipalities, weather forecasting professionals, and public health departments warn of the enhanced heat stress vulnerability of children under 5 years of age, elderly individuals over 65, the immunocompromised, and outdoor workers (Weir, 2002). However, an additional group has emerged in the literature deserving of the highly vulnerable designation – expectant mothers. In a growing body of literature, a consistent relationship has been observed between increased ambient temperature and adverse pregnancy events, including increase in preterm delivery, small for gestational age (SGA) or low birthweight, and occurrence of stillbirth (Bekkar et al., 2020; Kuehn et al., 2017).

The present study was undertaken to assess the impact of ambient temperature on preterm delivery across the US. Utilizing data on nearly one million preterm births, we assessed the role of ambient temperature in the week preceding the delivery to determine if increased temperature triggers spontaneous preterm birth. Given the large sample size and expansive geographic area under study, we are able to examine particularly sensitive subgroups of pregnant women and differences in risk among climactic regions of the US.

Preterm delivery is defined as birth occurring before 37 weeks of completed gestation (CDC, 2020). Globally, an estimated 15 million preterm deliveries occur every year and preterm birth is the second leading cause of mortality in children under the age of 5 years old (March of Dimes, 2012). Approximately one million neonatal deaths occur every year as a result of complications arising from preterm birth. Furthermore, surviving preterm infants face long-term adverse health outcomes including vision and hearing impairment, chronic lung disease, chronic cardiovascular ill health, and neurodevelopmental and behavioral disorders (March of Dimes, 2020).

In 2018, a Lancet update on preterm birth rates found that since 2000, rates of preterm births were increasing in 26 nations, and decreasing in only 12 (Chawanpaiboon et al., 2019). In the US, about 1 in 10 babies are born preterm. The annual societal economic burden of preterm birth in the US is about 26.2 billion dollars, and the first-year medical costs of a preterm baby are, on average, ten times that of a full term infant (IOM, 2007). In the US, significant racial disparities persist for preterm birth, with the highest risk among Non-Hispanic Black mothers — about 14% compared to 9% among Non-Hispanic White mothers. Preterm birth-related mortality is also three times higher in premature Black infants compared to premature White infants (Burris et al., 2019). It is important to note that these persistent racial disparities, and those in other maternal-infant health indicators, arise not from differences in innate biological risk but instead are a consequence of historic and present, deeply entrenched, systemic racism. This is further complicated by implicit racial bias in the provision of healthcare to Black women and their babies (Burris et al., 2019; Taylor, 2020; NICHQ, 2020).

Preterm births fall into two categories, spontaneous preterm birth (spontaneous onset of premature labor) or provider-initiated preterm birth (medically induced for fetal or maternal indications). Established risk factors for spontaneous preterm birth include maternal age (adolescence or advanced maternal age), multiple pregnancies (twins or higher), maternal infection (e.g., urinary tract infection, HIV, malaria), maternal underlying chronic conditions (e.g., diabetes, hypertension), genetic risks (e.g., family history of incompetent cervix), previous preterm labor, and nutritional and lifestyle factors (e.g., undernutrition, obesity, smoking, excessive alcohol consumption) (NICHD, 2020).

Despite this long list of established risk factors, the cause of spontaneous preterm birth is unknown in about 50% of cases (IOM, 2007). Several studies of environmental factors have identified associations between air pollution and increased preterm birth, including carbon monoxide, nitrous oxides, and particulate matter (Mendola et al., 2019). More recently, a methodologically diverse group of studies suggests that extreme ambient temperature is also associated with decreased gestational length. While associations have been observed for cold stress (Bruckner et al., 2014) and heat stress, there is stronger evidence that increased ambient temperatures are associated with preterm birth and other adverse pregnancy outcomes (Bekkar et al., 2020, Kuehn et al., 2017).

A recent systematic review published by Bekkar et al., found that 9 out of 10 studies examining heat exposure and birth outcomes in the US showed statistically significant associations. Of these studies, five examined preterm delivery, of which four found positive, associations (a 10 degree increase in apparent temperature associated with an increased odds of PTD ranging from 8 to 22% for warm season deliveries) (Bekkar et al., 2020). In 2017 Kuehn and McCormick, published a global systematic review, titled “Heat Exposure and Maternal Health in the Face of Climate Change,” which identified 14 out of 17 studies where heat was significantly correlated with increased risk or rate of preterm birth (Kuehn et al., 2017).

In an effort to build upon these findings and address some limitations of the previous work, the present study examines ambient temperature in the week leading up to the delivery as a potential trigger for spontaneous preterm birth in the contiguous US over a 5-year period from 2000 to 2004. This study combines preterm birth data from the US

National Center for Health Statistics (NCHS) with meteorological data from the National Oceanic and Atmospheric Association (NOAA) Automated Surface Observing System (ASOS), and air pollutant data from the Environmental Protection Agency (EPA) Air Quality System (AQS) in a case-crossover design of almost one million expectant mothers.

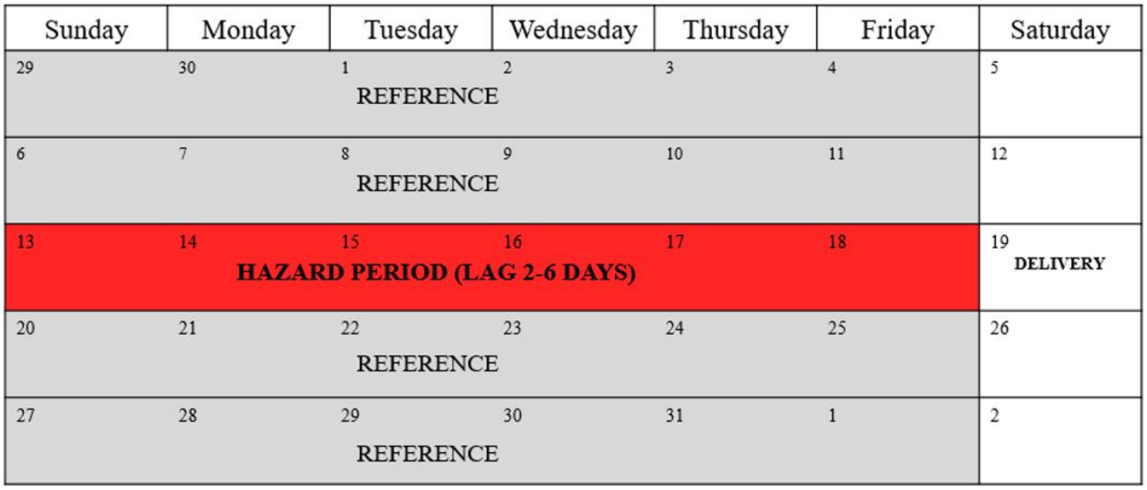
Methods

Study Design

The study utilizes a bi-directional case-crossover design with a hazard lag period of 2-6 days and a four to one hazard to reference ratio. First introduced by Malcolm Maclure and Murray Mittleman in the late 1980s, the case-crossover design is a method for studying transient effects on the risk of acute events (Maclure, 1991). The design resembles a retrospective nonrandomized crossover study and is ideal for the study of time-varying factors like weather and air pollution as triggers of acute events. Since the initial use of this design to study behaviors and activities that triggered acute myocardial infarction, it has been used a number of times to study exposures during a critical window of time before a woman gives birth (Mittleman et al., 1995; Avalos et al., 2017; Basu et al., 2010; Basu et al., 2017; Rammah et al., 2019). The case-crossover design was used by Avalos, Basu, Rammah, and others, to study weather-related triggers of preterm birth, stillbirth, and placental abruption (Avalos et al., 2017; Basu et al., 2010; Basu et al., 2017; Rammah et al., 2019).

In this design, the mother serves as her own control, eliminating the threat of confounding by non-time dependent maternal factors. Comparisons are made between a hazard period immediately before an acute event and appropriate reference periods. Based on previous findings and the biologically relevant window for preterm delivery resulting from an acute exposure, we assigned a hazard period of one week prior to the delivery (Basu et al., 2010; Ha et al., 2017). Thus, considering the delivery date as day 1, the hazard period encompasses days 2 to 6. We assigned four reference periods for comparison within 30 days of the delivery date. Each reference period was also one week in length and consisted of the same days of the week as the hazard period to avoid potential confounding by day of the week. We balanced the design with two reference periods before the hazard period and two reference periods after the hazard period. Figure 2.1 depicts an example of the hazard and reference periods for a preterm delivery occurring on July 19, 2003.

Figure 2.1 Depiction of hazard and reference period assignment for example delivery date July 19, 2003.

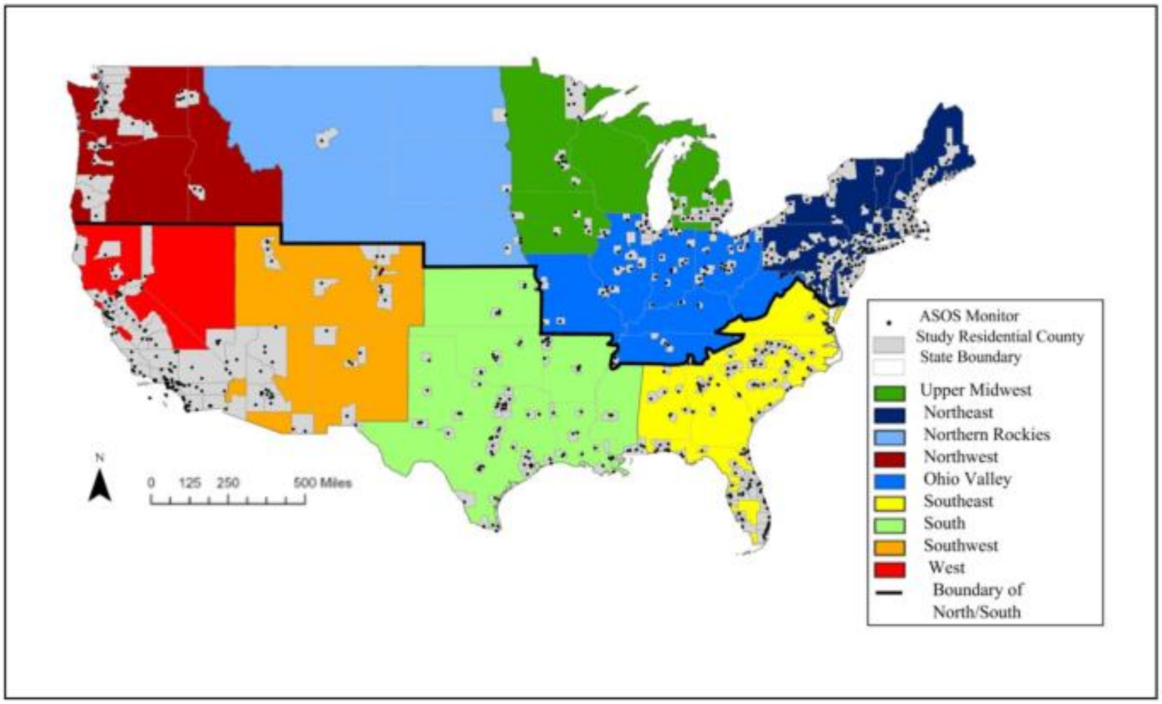


Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
29 REFERENCE	30	1	2	3	4	5
6 REFERENCE	7	8	9	10	11	12
13 HAZARD PERIOD (LAG 2-6 DAYS)	14	15	16	17	18	19 DELIVERY
20 REFERENCE	21	22	23	24	25	26
27 REFERENCE	28	29	30	31	1	2

Study Population

We utilized data on live births occurring from January 1, 2000 through December 31, 2004 to US residents derived from the NCHS, Vital Statistics System (NVSS) birth record files. NCHS NVSS natality data are limited to births occurring to U.S. resident mothers residing in a county with a population greater than 100,000 people. We restricted the analysis to mothers residing in the contiguous US, excluding counties in Alaska, Hawaii, and Puerto Rico. The publicly available data from NCHS NVSS does not contain the exact date of birth from the birth record so we imputed the date of delivery using year and month of birth, gestational age, date of the mother's last menstrual period, and day of the week of the delivery. Thus, we were limited to studying mothers with complete data for these variables. This methodology was previously used by Sun et al. to study preterm delivery and markers of fetal growth (Sun et al., 2019). Additional exclusion criteria included incomplete data for maternal residence state and county and discordance with the Alexander criteria (a fetal growth curve that eliminates implausible combinations of gestational age and birthweight from the data (Alexander et al., 1996). We excluded preterm births born before 20 weeks gestation, medically induced preterm births, multiple pregnancies, and the presence of birth defects or chromosomal anomalies as noted on the birth record. The final criteria for inclusion into the study was the presence of at least one ASOS weather monitoring station within the maternal residence county boundary. The final analytical sample was based on 968,529 preterm deliveries across 401 US counties. Figure 2.2 depicts the geographic distribution of the study population.

Figure 2.2 Distribution of study population across the United States, NOAA US Climate Regions, and location of ASOS Weather monitors relevant to the geographic area of the study population.



Outcome assessment

Data on gestational age was ascertained from the clinical estimate of gestation at the time of delivery as recorded on the birth record. Preterm birth was defined as gestation less than 37 weeks. Additionally, we assessed infants born very preterm (28 – 32 weeks’ gestation) and extremely preterm (less than 28 weeks’ gestation). In addition, other maternal characteristics were extracted from the birth records including race/ethnicity, education, age in years, access to prenatal care, cigarette smoking in pregnancy, parity, and sex of the fetus. Because we utilized de-identified, publicly available data, the study was determined to be exempt from formal review by the Institutional Review Board at the Boston University Medical Campus.

Exposure assessment

Meteorological variables were ascertained from the NOAA Automated Surface Observing System (ASOS). This automated observing network is located at airports across the US and provides essential observations for the National Weather Service (NWS), the Federal Aviation Administration (FAA), and the Department of Defense (DOD). ASOS stations take minute-by-minute observations and are monitored for quality control 24-hours a day. We downloaded raw observations for air temperature, dew point, and relative humidity from weather stations across the US from January 1, 2000 through December 31, 2004. We then calculated 24-hour daily averages, 24-hour daily minimums, and 24-hour daily maximums for each of these three meteorological factors: air temperature, dew point, relative humidity. In addition to air temperature, we also assessed apparent temperature, a combination of humidity and air temperature that allows better assessment of how a person feels when experiencing heat stress. Multiple techniques exist for calculating apparent temperature (Anderson et al., 2013). We utilized the following formula to be consistent with other environmental health studies of heat stress: apparent temperature = (-2.653 + (0.994 * Air Temperature Celsius) + (0.0153 * Dew Point Celsius^2)). Apparent temperature was also assessed as 24-hour average daily apparent temperature, 24-hour daily minimum apparent temperature, and 24-hour daily maximum apparent temperature.

Data on maternal residence county was then linked to the appropriate weather station(s). If a maternal residence county had a single weather station within the county boundary, the values from that station were assigned. If a maternal residence county had multiple stations within the county, data were averaged across stations.

To assess effect modification by air pollution, data for particulate matter size 2.5 microns in diameter ($PM_{2.5}$) and ozone were ascertained from the (EPA) Air Quality System (AQS) monitoring stations. In the case of $PM_{2.5}$, the 24-hour daily average was downloaded from AQS. In the case of ozone, we use the average 8-hour daily maximum.

We used ArcGIS Pro (ESRI, Redlands, CA) to map the study population and all monitoring stations and to link the maternal residence county to the appropriate station(s) for all exposure variables.

Statistical analysis

We calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) using univariate conditional logistic regression with the exposure of interest (e.g., daily average apparent temperature) as a linear term and preterm birth as a binary variable (Y/N) applied to each study period (hazard period = Y, reference period = N). To assess effect measure modification, we stratified by the third factor in separate models (all Table 2.1 Characteristics as well as exposure to PM 2.5 and ozone). All statistical analyses were conducted using SAS 9.4 (Cary, North Carolina) PROC LOGISTIC.

Results

After applying the previously stated criteria, we had data on 968,529 singleton, spontaneous preterm deliveries born to US residents residing in 401 US counties from January 1, 2000 through December 31, 2004. Of this total, 545,993 (56.4%) were born during the warm season (May 1 – to October 31) and 277,764 (28.7%) were born during the summer (June 1 – August 31). Because stronger associations were observed for warm season (May through October 31) and summer deliveries (June 1 through August 31) than other seasons, we present the demographic characteristics of the warm season and summer deliveries in Table 2.1.

The preterm births were distributed evenly across the five years of the study period, with each year contributing about 20% of the total warm season deliveries. The deliveries were distributed across the US climactic regions according to the population density of the region with the largest proportions in the Northeast (19.3%), South (17.0%), and Southeast (16.1%). The largest proportion of mothers identified as Non-Hispanic White (46.8%), followed by Hispanic (25.0%), Non-Hispanic Black (21.9%) and Non-Hispanic Other (5.6%). More than half of mothers who delivered in the warm season had a high school degree or less (53.3%). The greatest proportion of mothers were 18 to 25 years old (35.1%), followed by 26 – 30 years old (24.9%). The vast majority of mothers began receiving prenatal care in the first trimester (80.2%). Cigarette smoking is self-reported and data were missing for over 16% of the warm season delivering mothers. Of those with complete data, about 9% reported smoking cigarettes at some point during their pregnancy. This was the first child among 38% of mothers. Over 86% of the preterm deliveries occurred after 32 weeks of completed gestation, categorizing them as moderate to late preterm deliveries. The breakdown of infant sex among warm season deliveries was 46.6% female and 53.4% male.

Table 2.1 Demographics of study population. (N=545,993 warm season preterm deliveries, N=277,764 summer deliveries)

Characteristic	**N (%)[a]**	**N (%)[a]**
	Warm Season	**Summer Season**
Year of Delivery		
2000	102,750 (18.8)	51,840 (18.7)
2001	104,996 (19.2)	53,326 (19.2)
2002	107,048 (19.6)	54,121 (19.5)
2003	118,616 (21.7)	59,842 (21.5)
2004	112,583 (20.6)	58,365 (21.1)
Month of Delivery		
May	93,085 (17.1)	-
June	92,614 (17.0)	92,614 (33.3)
July	96,049 (17.6)	96,049 (34.6)
August	89,101 (16.3)	89,101 (32.1)
September	82,987 (15.2)	-
October	92,157 (16.9)	-
US Climate Region of Maternal Residence		
Northeast	105,498 (19.3)	53,666 (19.3)
Southeast	88,061 (16.1)	44,249 (15.9)
Ohio Valley	80,529 (14.8)	40,557 (14.6)
Upper Midwest	37,705 (6.9)	19,069 (6.9)
Northern Rockies and Plains	4,252 (0.8)	2,162 (0.8)
South	92,588 (17.0)	48,805 (17.6)
Southwest	33,694 (6.2)	16,988 (6.1)
West	87,063 (15.6)	43,915 (15.8)
Northwest	16,603 (3.0)	8,353 (3.0)
Maternal race/ethnicity		
Hispanic	136,654 (25.0)	70,608 (25.4)
Non-Hispanic Black	119,329 (21.9)	60,646 (21.8)
Non-Hispanic White	255,597 (46.8)	129,444 (46.6)
Non-Hispanic Other	30,672 (5.6)	15,235 (5.5)
Unknown or not stated	3,741 (0.7)	1,831 (0.7)
Maternal educational level		
High school graduate or less	290,831 (53.3)	148,890 (53.6)
Some college	113,779 (20.8)	57,760 (20.8)

Bachelor’s degree	80,136 (14.7)	40,485 (14.6)
Masters, Doctorate or Professional	52,932 (9.7)	26,359 (9.5)
Unknown or not stated	8,315 (1.5)	4,270 (1.5)
Maternal age in years		
< 18	23,376 (4.3)	12,169 (4.4)
18 – 25	191,689 (35.1)	98,536 (35.5)
26 – 30	135,998 (24.9)	69,112 (24.9)
31 – 35	121,983 (22.3)	61,413 (22.1)
36 – 40	60,470 (11.1)	30,373 (10.9)
41 – 45	11,575 (2.1)	5,704 (2.1)
> 45	900 (0.2)	455 (0.2)
Missing	2	2
Prenatal care		
No prenatal care	10,162 (1.9)	5,116 (1.8)
Prenatal care began month 7-9	14,761 (2.7)	7,364 (2.7)
Prenatal care began month 4-6	74,601 (13.7)	38,702 (13.9)
Prenatal care began month 1-3	438,070 (80.2)	222,320 (80.0)
Unknown or not stated	8,399 (1.5)	4,262 (1.5)
Cigarette Smoking During Pregnancy		
Yes	50,127 (9.2)	25,556 (9.3)
No	405,266 (74.2)	206,325 (75.4)
Unknown or not stated	90,600 (16.6)	41,882 (15.3)
Parity		
1	208,766 (38.2)	106,429 (38.3)
2	164,799 (30.2)	83,416 (30.0)
3	95,471 (17.5)	48,575 (17.5)
≥ 4	76,455 (14.0)	39,076 (14.1)
Unknown or not stated	502 (0.1)	268 (0.1)
Preterm Delivery Category		
Moderate to late (≥ 32 weeks)	470,648 (86.2)	240,028 (86.4)
Very preterm (≥ 28 to <32)	46,847 (8.6)	23,361 (8.4)
Extremely preterm (< 28)	28,498 (5.2)	14,375 (5.2)
Sex of Infant		
Female	254,632 (46.6)	129,316 (46.6)
Male	291361 (53.4)	148,448 (53.4)

[a] Some percentages not equal to 100% due to rounding.

Table 2.2 describes the distribution of average apparent temperature and maximum apparent temperature across the warm season, broken down by climactic region of the US. The highest average apparent temperatures were observed in the South (Arkansas, Kansas, Louisiana, Mississippi, Oklahoma, and Texas), (Hazard period:

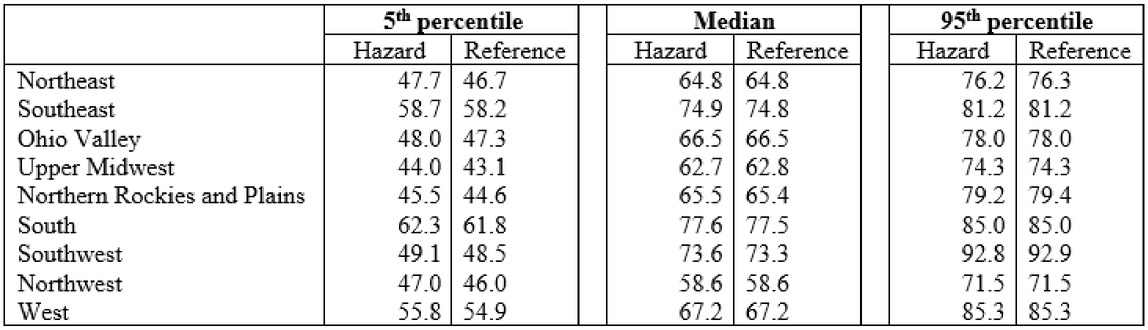
Median 77.6º F, 5th percentile 62.3º F, 95th percentile 85.0º F; Reference period: Median 77.5º F, 5th percentile 61.8º F, 95th percentile 85.0º F). This was followed by the Southwest (Arizona, Colorado, New Mexico, and Utah), (Hazard period: Median 73.6º F, 5th percentile 49.1º F, 95th percentile 92.8º F; Reference period: Median 73.3º F, 5th percentile 48.5º F, 95th percentile 92.9º F). The warm season apparent temperatures were most extreme in the Southwest where the 95th percentile for the 24-hour daily average apparent temperature was 92.8 º F for the hazard period and 92.9 º F for the reference periods. In addition, the 95th percentile for the 24-hour daily maximum apparent temperature in the Southwest was 104.1º F for the hazard period and 104.2º F for the reference periods.

Results for air temperature were consistent with the findings for apparent temperature and we identified a null effect of relative humidity (Supplementary Material Table S2.1).

The median 24-hour average PM 2.5 was highest in the Northeast, (Hazard period: Median 19.5 ug/m^3; Reference period: 19.8 ug/m^3) (Table 2.3). There was very little variability in the distribution of median ozone across the US for the warm season. This is likely because we did not have the geographic resolution to capture localized heterogeneity in ozone levels. Despite the removal of outliers greater than 2.5 standard deviations from the mean, we did observe some very high ozone levels at the 95th percentile in the Upper Midwest, Northern Rockies and Plains, and the Northwest. This could be related to inaccuracies in the data that was downloaded from the EPA AQS Stations or may be the result of high ozone levels nearby some monitors. (Table 2.3)

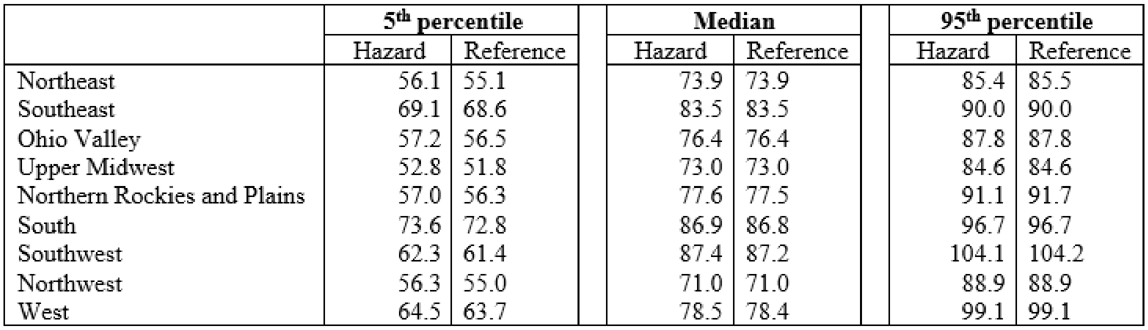
Table 2.2 Distribution of apparent temperature for hazard and reference periods by climate region (May 1 to October 31, 2000-2004).

24-Hour Average Apparent Temperature (F°)



	5th percentile		Median		95th percentile	
	Hazard	Reference	Hazard	Reference	Hazard	Reference
Northeast	47.7	46.7	64.8	64.8	76.2	76.3
Southeast	58.7	58.2	74.9	74.8	81.2	81.2
Ohio Valley	48.0	47.3	66.5	66.5	78.0	78.0
Upper Midwest	44.0	43.1	62.7	62.8	74.3	74.3
Northern Rockies and Plains	45.5	44.6	65.5	65.4	79.2	79.4
South	62.3	61.8	77.6	77.5	85.0	85.0
Southwest	49.1	48.5	73.6	73.3	92.8	92.9
Northwest	47.0	46.0	58.6	58.6	71.5	71.5
West	55.8	54.9	67.2	67.2	85.3	85.3

24-Hour Maximum Apparent Temperature (F°)



	5th percentile		Median		95th percentile	
	Hazard	Reference	Hazard	Reference	Hazard	Reference
Northeast	56.1	55.1	73.9	73.9	85.4	85.5
Southeast	69.1	68.6	83.5	83.5	90.0	90.0
Ohio Valley	57.2	56.5	76.4	76.4	87.8	87.8
Upper Midwest	52.8	51.8	73.0	73.0	84.6	84.6
Northern Rockies and Plains	57.0	56.3	77.6	77.5	91.1	91.7
South	73.6	72.8	86.9	86.8	96.7	96.7
Southwest	62.3	61.4	87.4	87.2	104.1	104.2
Northwest	56.3	55.0	71.0	71.0	88.9	88.9
West	64.5	63.7	78.5	78.4	99.1	99.1

Table 2.3 Distribution of air pollutants (PM 2.5 and ground level ozone) for hazard and reference periods by climate region (May 1 to October 31, 2000-2004).

24-Hour Average Particulate Matter 2.5 (µg/m^3)

	5th percentile		Median		95th percentile	
	Hazard	Reference	Hazard	Reference	Hazard	Reference
Northeast	5.6	5.7	19.5	19.8	82.6	82.7
Southeast	5.4	5.4	16.4	16.6	90.4	90.3
Ohio Valley	6.1	6.2	16.0	16.2	83.4	83.6
Upper Midwest	5.5	5.4	16.1	16.3	80.8	80.9
Northern Rockies and Plains	3.5	3.8	9.8	10.0	88.8	88.8
South	6.5	6.4	15.2	15.2	97.2	97.2
Southwest	4.2	4.2	8.5	8.5	100.5	100.3
Northwest	3.1	3.2	9.1	9.3	83.2	83.4
West	5.8	5.9	15.7	15.9	88.9	89.0

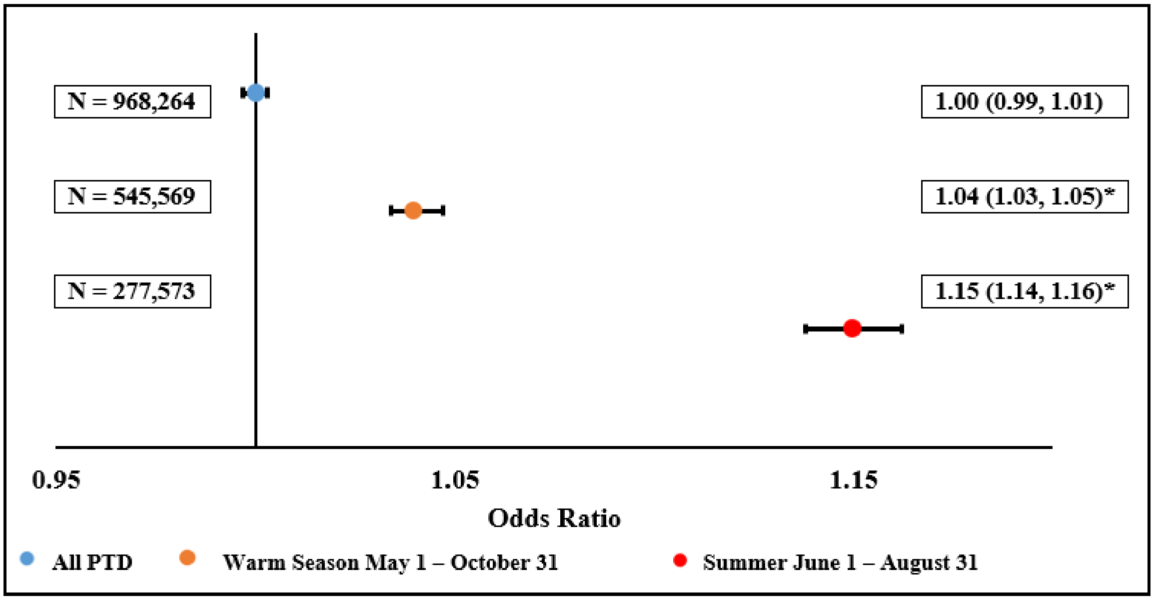
8-Hour Daily Maximum Ozone (ppm)

	5th percentile		Median		95th percentile	
	Hazard	Reference	Hazard	Reference	Hazard	Reference
Northeast	0.02	0.02	0.05	0.05	0.09	0.09
Southeast	0.02	0.02	0.04	0.04	0.07	0.07
Ohio Valley	0.02	0.02	0.04	0.04	0.06	0.07
Upper Midwest	0.03	0.03	0.04	0.04	59.72	60.08
Northern Rockies and Plains	0.03	0.03	0.04	0.04	57.20	58.64
South	0.02	0.02	0.05	0.05	0.07	0.07
Southwest	0.04	0.04	0.05	0.05	0.07	0.07
Northwest	0.02	0.02	0.04	0.04	67.10	66.95
West	0.03	0.03	0.05	0.05	0.08	0.08

Figure 2.3A-F depicts the odds ratios and corresponding 95% confidence intervals for a 10 unit increase in average daily apparent temperature (lag$_{2-6}$ days). We found a null association when examining the impact of average daily apparent temperature on preterm deliveries occurring across the entire calendar year (OR = 1.00, 95% CI 0.99 – 1.01). For preterm deliveries occurring in the warm season we observed a statistically significant increased odds of 4.2% (OR = 1.04, 95% CI 1.04 – 1.05). For preterm deliveries occurring in the summer we observed a statistically significant increased odds of 15.2% (OR = 1.15, 95% CI 1.14 – 1.16). (Plot 2.3A)

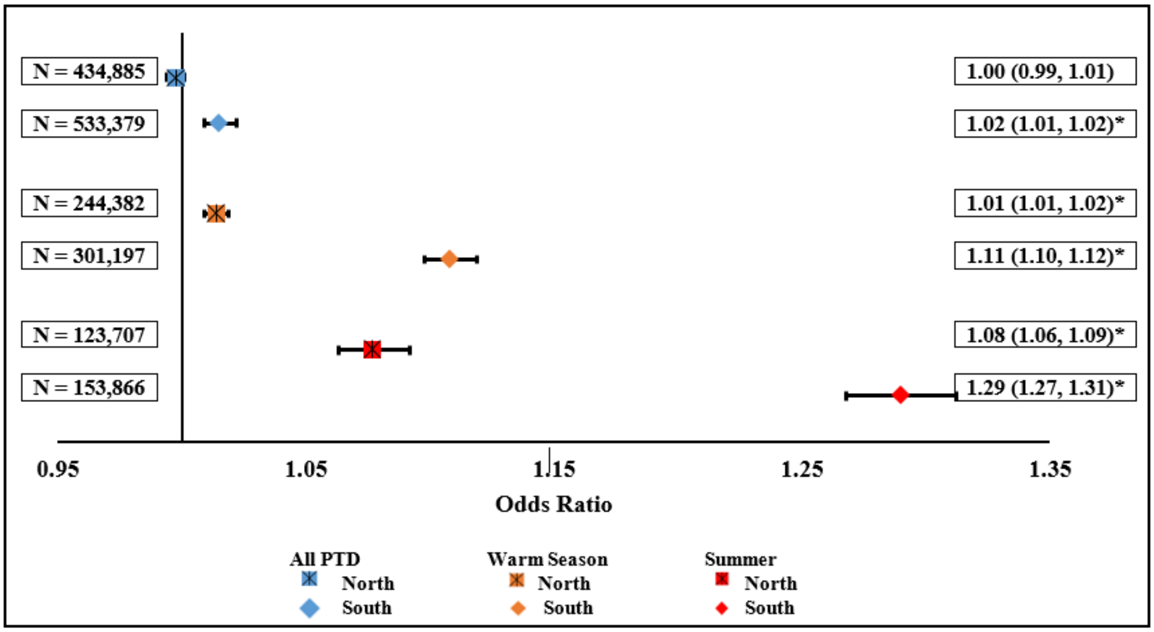
Figure 2.3A–2.3F Odds ratios and 95% confidence intervals for a 10-degree Fahrenheit increase in average daily apparent temperature (lag$_{2-6}$ days), 2000–2004.

2.3A Preterm deliveries occurring across the entire calendar year (blue), the warm season May 1 to October 31 (orange), and the summer season June 1 to August 31 (red).



When stratified by region we observed that the increased odds observed in the warm and summer seasons were largely driven by the association between heat and preterm delivery in the Southern half of the US (which includes NOAA Climate Regions = Southeast, South, Southwest, West) as compared to the Northern half of the US (NOAA Climate Regions = Northeast, Ohio Valley, Upper Midwest, Northern Rockies and Plains, and Northwest). For the warm season we observed an odds ratio of 1.01 for the Northern half of the US (95% CI 1.01 – 1.02) compared to 1.11 for the Southern half of the US (95% CI 1.10 – 1.12) for a 10 unit increase in average apparent temperature. The regional difference was most profound for summer deliveries where women in the Northern half of the US had an 8% increased odds (OR = 1.08, 95% CI 1.06 – 1.09) and women in the Southern half of the US had a 29% increased odds (OR = 1.29, 95% CI 1.27 – 1.31). (Plot2.3B)

2.3B Preterm deliveries occurring across the entire calendar year (blue), the warm season May 1 to October 31 (orange), and the summer season June 1 to August 31 (red), stratified by Northern United States[a] and Southern United States[b].

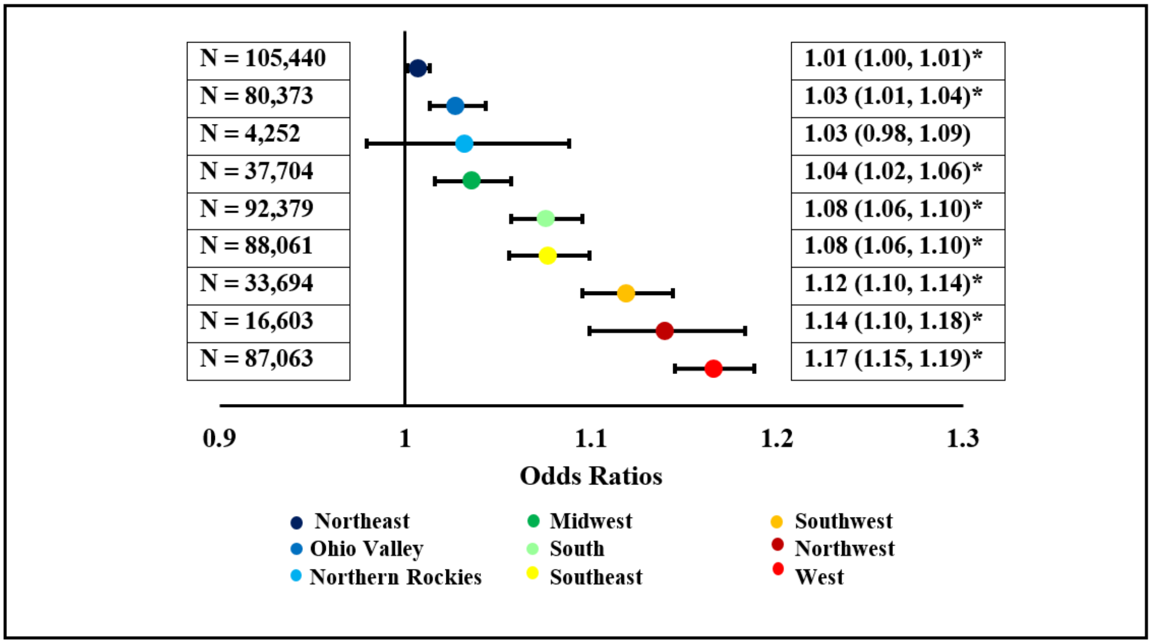


[a] North = Northeast, Ohio Valley, Upper Midwest, Northern Rockies and Plains, Northwest [b]South = Southeast, South, Southwest, West

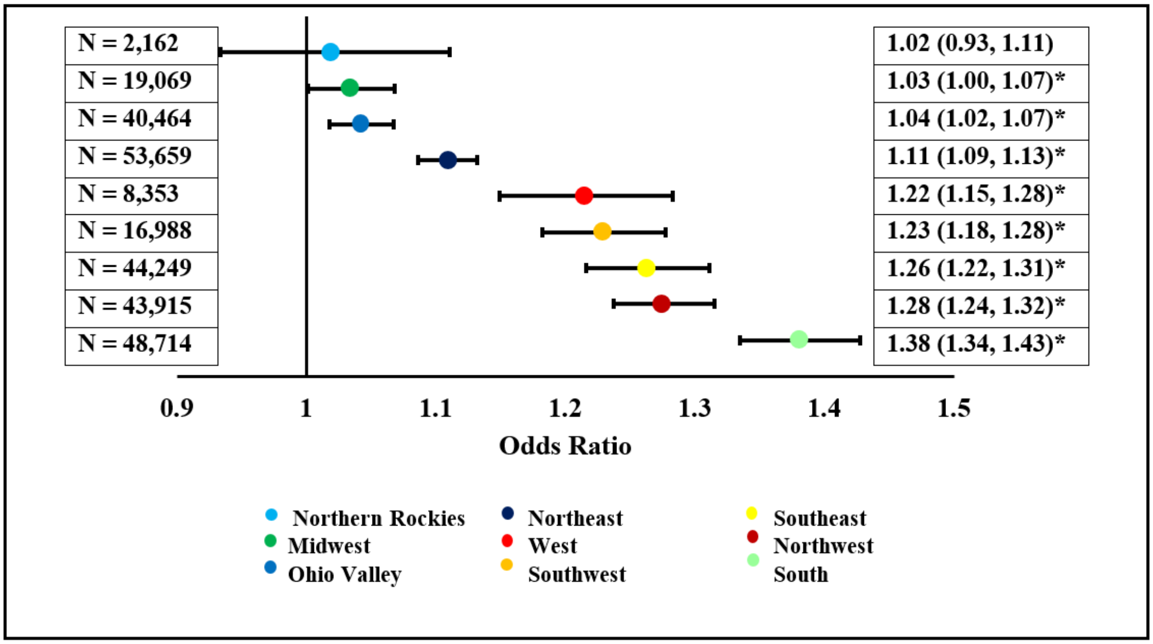
To more precisely examine the regional effects we stratified these data by the nine climactic regions of the US. We observed that the increased odds differed dramatically for the warm season from an odds ratio of 1.01 in the Northeast (95% CI 1.00 – 1.01) to 1.17 in the Northwest (95% CI 1.15 – 1.19). (Plot 2.3C)

For preterm deliveries occurring in the summer we observed the strongest association in the South (climate region) with a 38% increased odds (OR = 1.38, 95% CI 1.34 – 1.43). When examining differences by maternal race/ethnicity we again stratified by the Northern and Southern half of the US and looked separately at deliveries occurring in the warm season and the summer. (Plot 2.3D)

2.3C Preterm deliveries occurring in the warm season May 1 to October 31, stratified by NOAA climate regions of the contiguous United States.

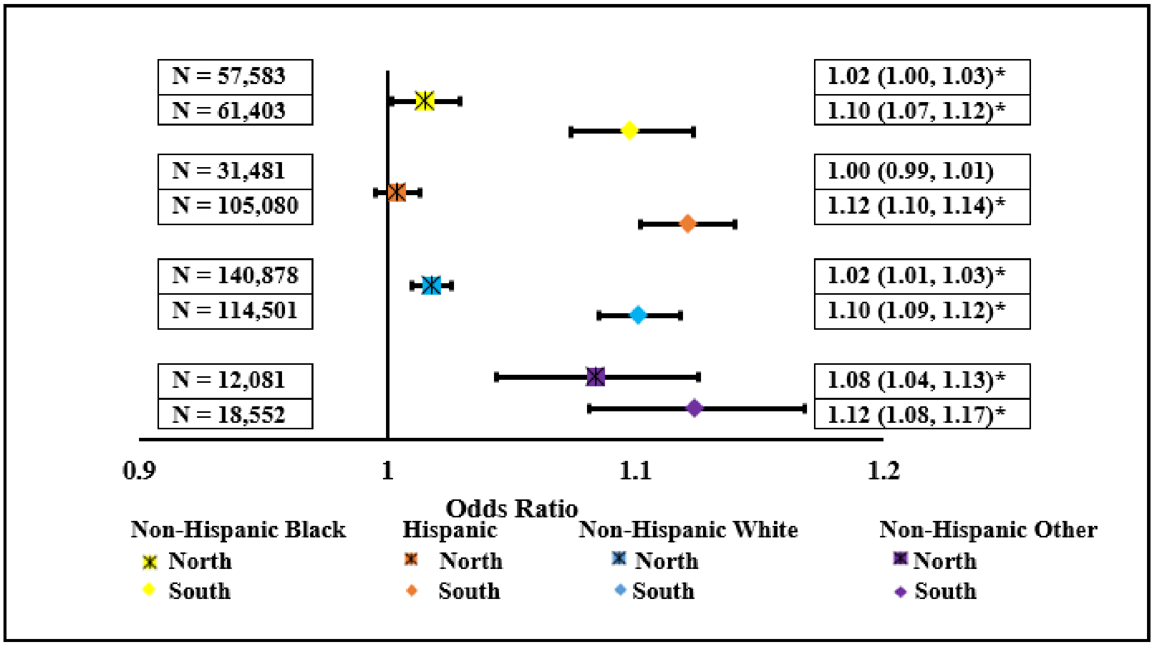


2.3D Preterm deliveries occurring in the Summer June 1 to August 31, stratified by NOAA climate regions of the contiguous United States.



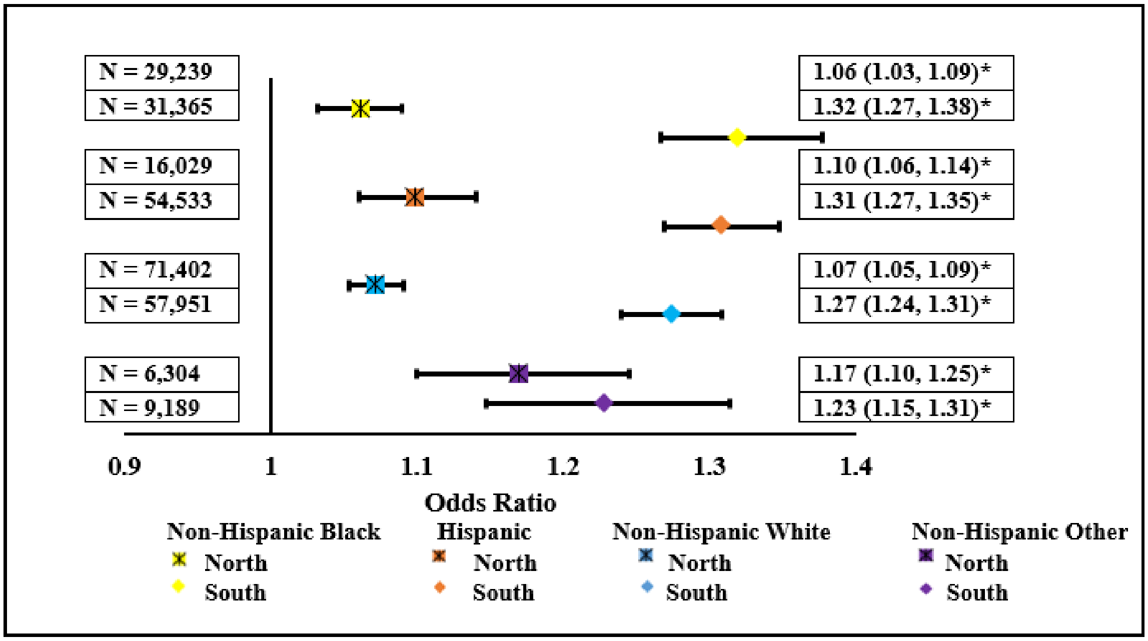
We observed the greatest increased odds among Non-Hispanic Black and Hispanic mothers living in the Southern half of the US who gave birth in the summer months, with 32% and 31% increased odds, respectively. (Southern US, Non-Hispanic Black mothers OR = 1.32, 95% CI 1.27 – 1.38 and Southern US, Hispanic mothers OR = 1.31, 95% CI 1.27 – 1.35). (Plots 2.3E and 2.3F).

2.3E Preterm deliveries occurring in the warm season May 1 to October 31, stratified by region of the United States (North[a], South[b]) and maternal race/ethnicity.



[a]North = Northeast, Ohio Valley, Upper Midwest, Northern Rockies and Plains, Northwest [b]South = Southeast, South, Southwest, West

2.3F Preterm deliveries occurring in the Summer June 1 to July 31, stratified by region of the United States (North[a], South[b]) and maternal race/ethnicity.



[a]North = Northeast, Ohio Valley, Upper Midwest, Northern Rockies and Plains, Northwest [b]South = Southeast, South, Southwest, West

We observed no effect modification by any other maternal characteristics, including pregnancy related conditions known to be associated with adverse pregnancy outcomes such as diabetes, chronic hypertension, pregnancy hypertension, and eclampsia. We also did not observe modification of air pollution on the relationship between daily average apparent temperature and preterm delivery. Analyses of the independent relationships between the air pollutants $PM_{2.5}$ and ozone on preterm delivery also yielded null results (not shown).

The direction and magnitude of the associations were consistent when using apparent temperature or air temperature as the independent predictor. When examining the impact of relative humidity independently we observed null results. This suggests that the impact of heat stress on pregnancy is driven by the air temperature and humidity is less of a factor. Results for air temperature and relative humidity are presented in the supplementary material.

Discussion

Our findings suggest that there is an increase in heat-associated preterm delivery in the warm and summer seasons in the US, primarily driven by stronger associations in the Southern half of the US compared to the Northern half. The increased odds are most elevated in the summer months and differ by maternal race/ethnicity, with Non-Hispanic Black women and Hispanic women emerging as the most vulnerable groups. The magnitude and direction of our findings correspond with the previous literature, especially our findings of an increased risk of preterm delivery in the warm season and the enhanced vulnerability of these racial/ethnic subgroups.

In 2010, Basu et al. published the results of a case-crossover study of 58,681 preterm births across 16 California counties and observed an increased risk of 8.6% for a 10-degree Fahrenheit increase in weekly apparent temperature in the warm season. They observed the highest risks in younger, Black and Asian mothers (Basu et al., 2010). Similar to our study their associations were independent of air pollutant exposure. In 2017, two papers (Avalos and Basu) were published using medical record data from 14,466 California mothers experiencing singleton preterm deliveries (Avalos et al., 2017; Basu et al., 2017). The case-crossover analyses observed an 11.6% overall increase in preterm birth with a 10-degree Fahrenheit increase in weekly average apparent temperature in the week prior to the birth. When the authors limited their analyses to warm season births, the increase in preterm birth increased to 22.1%. With the use of maternal health records, these studies had an enhanced ability to account for maternal factors (compared to birth record studies) and the highest risks emerged for mothers who were younger, Black, Hispanic, underweight, Medicaid recipients, smokers, and had pre-existing conditions (Avalos et al., 2017; Basu et al., 2017).

In contrast, to these three studies which were limited to California residents, a fourth case-crossover study published by Ha in 2017 utilized data from 12 US clinical sites (locations in: CA, DC, DE, FL, IL, IN, OH, MA, MD, NY, TX, UT). This study identified impacts of extreme ambient heat and cold at multiple points during pregnancy on preterm birth. For the week before the delivery, they observed a 5-degree Fahrenheit increase in heat was associated with 1.12 to 1.16 times the odds of early delivery in the warm season (Ha et al., 2017).

Additional studies assessing heat-related preterm delivery utilizing alternative study designs have also found an increased risk or rate of preterm delivery. In 2019, Sun et al. utilized a retrospective cohort study of 32 million US singleton births and identified that days of extreme heat, but not extreme cold, were associated with increased risk of preterm birth in the contiguous US (Sun et al., 2019). In 2015, Kloog et al. utilized a cross-sectional design examining data on 473,977 births in Massachusetts and found a slight decrease (0.26%) in gestational age when looking at temperature exposure across the entire pregnancy (Kloog et al., 2015).

Our study has a number of strengths that build upon the previous literature. The use of a publicly available, national dataset allowed us to examine a large, heterogeneous population of women across the climactically diverse country of the US. This granted us the ability to identify the enhanced vulnerability to heat stress in pregnant women in the Southern US, an observation not previously seen in the literature. Our large sample size allowed us to identify vulnerable racial/ethnic subgroups that had been previously examined only in the state of California. Our large sample size also provided the ability to generate precise point estimates and examine various subcategories within climactic regions with adequate power. Our utilization of the case-crossover design eliminates the threat of confounding from non-time varying maternal factors.

However, the use of a large, publicly available national dataset based on birth certificates also introduced important limitations. Studies utilizing birth records are limited by the variables reported on the birth record and the accuracy of these variables. The reliability and validity of birth record data is known to be inconsistent. A number of studies have identified underreporting of maternal characteristics on the birth record (especially for non-English speaking mothers). (Northam et al., 2006; Reichman et al., 2007). It is possible that under reporting of maternal conditions such as diabetes and preeclampsia biased our results towards the null for these subgroup analyses. Salemi et al., identified that sensitivity for profoundly visible birth defects like gastroschisis and anencephaly was as low as 54–55% on the birth record (Salemi et al., 2015). This would suggest that birth defects under reported on the birth certificate and that some birth defect cases remain in our analytical sample despite our efforts to exclude them. We lacked data on key maternal variables like socioeconomic status, occupation, air conditioning access, and time-activity patterns, all of which might influence the risk of heat-related preterm delivery. We also lacked data on certain risk factors known to be associated with preterm delivery such as maternal nutritional status and family history. Because the NVSS natality data are only available for counties with greater than 100,000 residents our study lacked the ability to assess the heat-preterm relationship in rural areas where mothers may experience heat stress differently and lack access to adequate prenatal care. Lastly, because the publicly available dataset lacked information on the exact date of delivery we had to impute this variable and this likely introduced some exposure misclassification.

Non-differential exposure misclassification also arose from the use of monitoring stations to apply the meteorological data to the maternal residence county — especially in large counties with only one monitor. This exposure misclassification is not likely to differ by the hazard and reference periods and so likely biased our results towards the null. Lastly, because our geographic resolution was at the county level, we are unable to take into account differences in temperature across small geographic areas such as urban heat islands.

Our finding that the increase in heat-related preterm delivery was strongest in the Southern half of the US was surprising because of acclimatization. Because women residing in the Southern US experience high ambient heat more regularly one might expect that they are more resilient to heat stress and are less likely to experience adverse heat-related health outcomes compared to mothers in the more temperate Northern half of the US. Air conditioning and temperature control are also more prevalent in the South, which suggests that high ambient heat poses less of a threat (US EIA, 2020).

The apparent lack of acclimatization in this subgroup and the overall higher temperatures in the southern regions suggests that a threshold exists at which high ambient temperature triggers preterm delivery. Our study lacks the ability to identify this threshold and further study is warranted. Conversely, in the warm season, the Northwest, a more temperate climate region, emerged as the region with the highest odds of preterm delivery with increased apparent temperature. This suggests that women in this region are not acclimatized to heat stress and are sensitive at lower thresholds of apparent temperature.

Our lack of statistically significant findings for preterm delivery and air pollution contrasts with the previous literature which has found associations between exposure to carbon monoxide, nitrous oxides, and particulate matter and decreased gestational length (Bekkar et al., 2020; Mendola et al., 2019; Darrow et al.; 2009; Li et al., 2017). It is possible that our county level, monitor-based exposure assessment lacked the geographic resolution to detect an association between $PM_{2.5}$ and ozone and preterm delivery. It is also possible that seasonal trends in $PM_{2.5}$ and ozone led to a lack of variability in exposure across the hazard and reference periods. While several studies have identified an association between $PM_{2.5}$ and preterm delivery, most have focused on levels across an entire trimester or pregnancy and few have examined an exposure window immediately before the delivery. Future studies of these contaminants in the critical window prior to the birth, utilizing more refined exposure assessment techniques, are warranted.

Spontaneous preterm delivery is a complex and multifactorial process with multiple possible etiologies. As consistent findings emerge about the threat of heat stress to gestational length, a number of potential mechanisms of action have been postulated. These mechanisms primarily operate through two processes: general reduced thermoregulatory capacity and dehydration. When the human body experiences heat stress, it diverts blood away from the vital organs to the surface of the skin in an effort to cool down (Basu et al., 2010; Bouchama et al., 2002). Increased weight gain and the physiological burden of the fetus, combined with increased plasma blood volume, may hinder a women’s thermoregulatory capacity making her more vulnerable to heat stress. This maternal physiologic stress may lead to premature rupture of membranes, triggering preterm delivery (Kuehn et al., 2017). Dehydration from heat stress may trigger the release of labor inducing hormones prostaglandin and oxytocin. Extreme dehydration could restrict uterine blood flow causing fetal distress (Avalos et al., 2017; Stan et al., 2002; Bouchama et al., 2002; Astrand et al., 2003).

The exact mechanism by which heat stress and/or dehydration leads to obstetrical complications likely differs by the exposure period, with heat stress in the first trimester influencing the mother and developing fetus differently than the window prior to birth. Given the design of this study, we are only able to examine the transient effect of heat stress in the window immediately before the delivery. Future studies should examine the vulnerability of women at other time points.

This study adds to the growing literature about the enhanced vulnerability of pregnant women to heat stress. As oppressively hot days continue to increase in frequency and intensity across the US and globally, heat-health recommendations should always specify that warnings about heat-wave and heat-health safety apply to expecting mothers (NASA, 2019). Obstetricians and other maternal health medical providers should also be aware of this vulnerability, and communicate the risk to patients as well as provide increased monitoring to mothers delivering in the summer, especially those at high risk of pregnancy complications. In addition to communicating risk and enhancing monitoring, medical providers should also emphasize ways to reduce heat exposure, by staying hydrated and remaining in a cooler indoor environment if possible.

As municipalities work to increase their heat resiliency through climate change adaptation, they should consider reduction in preterm delivery and other adverse pregnancy outcomes a potential benefit of these adaptations. Heat reducing strategies like cool roofs and increased green space might reduce the occurrence of heat-related preterm birth, especially in areas experiencing urban-heat islands.

Given the findings of this study and others, further examination of heat-related adverse birth outcomes is necessary. Future studies should assess multiple windows of exposure throughout pregnancy and include better monitoring of maternal temperature exposure, perhaps with wearable thermometers and corresponding questionnaires to capture time-activity information. Our findings about the increased vulnerability of women in the Southern US suggest future studies with improved exposure metrics should target this population.

Table 2.S1 Odds ratios and corresponding 95% confidence intervals for 10-unit increase in 6 meteorological variables analyzed, daily average apparent temperature, daily maximum apparent temperature, daily average air temperature, daily maximum air temperature, daily average relative humidity, daily maximum relative humidity.

	Sample N	Average Apparent Temperature (Fahrenheit)	Maximum Apparent Temperature (Fahrenheit)	Average Air Temperature (Fahrenheit)	Maximum Air Temperature (Fahrenheit)	Average Relative Humidity (%)	Maximum Relative Humidity (%)
All PTD	968,529	1.00 (0.99, 1.01)	0.99 (0.99, 1.00)	1.00 (0.99, 1.01)	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season PTD	545,993	1.04 (1.04, 1.05)*	1.07 (1.06, 1.07)*	1.07 (1.06, 1.08)*	1.07 (1.06, 1.07)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Summer Months PTD	277,764	1.15 (1.14, 1.16)*	1.12 (1.10, 1.13)*	1.15 (1.14, 1.17)*	1.12 (1.11, 1.13)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
All PTD							
Northern US	434,485	0.99 (0.99,1.00)	0.99 (0.99, 1.00)	0.99 (0.98, 1.00)*	0.99 (0.99, 1.00)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Southern US	533,379	1.02 (1.01, 1.02)*	1.00 (0.99, 1.01)	1.01 (1.00, 1.02)*	1.00 (0.99, 1.01)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season PTD							
Northern US	244,372	1.01 (1.00, 1.02)*	1.04 (1.03. 1.05)*	1.05 (1.03, 1.05)*	1.04 (1.03, 1.05)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Southern US	301,197	1.11 (1.09, 1.12)*	1.10 (1.09, 1.11)*	1.11 (1.10, 1.12)*	1.10 (1.09, 1.11)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Summer Months PTD							
Northern US	123,707	1.08 (1.06, 1.09)*	1.05 (1.04, 1.07)*	1.08 (1.07, 1.09)*	1.06 (1.04, 1.07)*	0.99 (0.98, 1.00)	1.01 (0.99, 1.02)
Southern US	153,866	1.29 (1.27, 1.31)*	1.22 (1.20, 1.24)*	1.28 (1.27, 1.31)*	1.22 (1.20, 1.24)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season PTD							
Southeast	88,061	1.08 (1.06, 1.10)*	1.07 (1.05, 1.09)*	1.08 (1.06, 1.10)*	1.07 (1.05, 1.09)*	1.00 (0.98, 1.01)	1.01 (0.99, 1.03)
Ohio Valley	80,529	1.03 (1.01, 1.04)*	1.04 (1.03, 1.05)*	1.03 (1.01, 1.04)*	1.04 (1.03, 1.05)*	0.97 (0.96, 0.98)*	0.99 (0.97, 1.01)
Northeast	105,498	1.01 (1.00, 1.01)*	1.04 (1.03, 1.05)*	1.05 (1.04, 1.07)*	1.04 (1.03, 1.05)*	1.00 (1.00, 1.00)	0.99 (0.97, 1.01)
Upper Midwest	37,705	1.04 (1.02, 1.06)*	1.04 (1.03, 1.06)*	1.04 (1.02, 1.06)*	1.05 (1.03, 1.05)*	0.97 (0.95, 0.98)*	1.00 (1.00, 1.00)
Southwest	33,694	1.12 (1.10, 1.14)*	1.11 (1.09, 1.14)*	1.12 (1.10, 1.14)*	1.11 (1.09, 1.14)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
South	92,588	1.08 (1.06, 1.10)*	1.09 (1.07, 1.10)*	1.08 (1.06, 1.10)*	1.09 (1.07, 1.11)*	0.98 (0.97, 0.99)*	0.99 (0.98, 1.00)
Northern Rockies	4,252	1.02 (0.98, 1.09)	1.03 (0.98, 1.08)	1.04 (0.98, 1.09)	1.02 (0.98, 1.08)	0.99 (0.96, 1.04)	1.05 (0.99, 1.11)
West	87,063	1.16 (1.15, 1.19)*	1.12 (1.10, 1.13)*	1.17 (1.14, 1.19)*	1.12 (1.10, 1.13)*	0.99 (0.98, 1.00)	1.00 (1.00, 1.00)
Northwest	16,603	1.14 (1.10, 1.18)*	1.08 (1.05, 1.11)*	1.14 (1.10, 1.18)*	1.08 (1.05, 1.11)*	0.99 (0.96, 1.01)	0.99 (0.96, 1.03)
Summer Months PTD							
Southeast	44,249	1.26 (1.22, 1.31)*	1.22 (1.18, 1.26)*	1.27 (1.22, 1.32)*	1.22 (1.18, 1.26)*	0.98 (0.96, 0.99)*	0.98 (0.96, 1.02)
Ohio Valley	40,464	1.04 (1.02, 1.07)*	1.03 (1.01, 1.05)*	1.05 (1.02, 1.07)*	1.03 (1.01, 1.05)*	0.98 (0.96, 0.99)*	0.99 (0.97, 1.01)
Northeast	53,659	1.11 (1.09, 1.13)*	1.07 (1.05, 1.09)*	1.11 (1.09, 1.13)*	1.07 (1.05, 1.09)*	1.01 (1.00, 1.03)*	1.02 (0.99, 1.03)
Upper Midwest	19,069	1.03 (1.00, 1.07)*	1.02 (0.99, 1.05)	1.04 (1.01, 1.07)*	1.03 (0.99, 1.06)	0.99 (0.97, 1.02)	1.02 (0.99, 1.06)
Southwest	16,988	1.23 (1.18, 1.28)*	1.20 (1.16, 1.24)*	1.23 (1.18, 1.28)*	1.20 (1.16, 1.24)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
South	48,714	1.38 (1.34, 1.43)*	1.32 (1.28, 1.36)*	1.38 (1.33, 1.43)*	1.31 (1.28, 1.35)*	0.96 (0.94, 0.97)*	0.99 (0.98, 1.02)

Northern Rockies	2,162	1.03 (0.93, 1.11)	1.01 (0.93, 1.10)	1.02 (0.93, 1.11)	1.01 (0.93, 1.10)	1.07 (0.99, 1.14)	1.10 (1.01, 1.20)*
West	8,353	1.28 (1.24, 1.32)*	1.17 (1.14, 1.20)*	1.27 (1.23, 1.31)*	1.16 (1.14, 1.19)*	1.01 (0.99, 1.03)	0.98 (0.96, 0.99)
Northwest	43,915	1.22 (1.15, 1.28)*	1.11 (1.07, 1.15)*	1.21 (1.15, 1.28)*	1.11 (1.07, 1.15)*	0.95 (0.91, 0.98)*	0.94 (0.90, 0.98)*
Warm Season PTD							
Hispanic	136,654	1.04 (1.02, 1.05)*	1.09 (1.08, 1.10)*	1.10 (1.08, 1.11)*	1.09 (1.08, 1.10)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic Black	119,329	1.04 (1.03, 1.05)*	1.05 (1.04, 1.07)*	1.06 (1.04, 1.07)*	1.06 (1.04, 1.07)*	1.00 1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic White	255,597	1.04 (1.03, 1.05)*	1.06 (1.05, 1.07)*	1.06 (1.05, 1.07)*	1.06 (1.05, 1.07)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Other	30,672	1.10 (1.07, 1.13)*	1.09 (1.07, 1.12)*	1.10 (1.07, 1.13)*	1.09 1.07, 1.12)*	1.00 1.00, 1.00)	1.00 (1.00, 1.00)
Summer Months PTD							
Hispanic	70,562	1.22 (1.19, 1.25)*	1.16 (1.14, 1.19)*	1.22 (1.19, 1.25)*	1.16 (1.14, 1.19)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic Black	60,604	1.13 (1.11, 1.16)*	1.11 (1.08, 1.13)*	1.14 (1.11, 1.16)*	1.11 (1.08, 1.13)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic White	129,353	1.13 (1.11, 1.15)*	1.10 (1.08, 1.11)*	1.13 (1.12, 1.15)*	1.10 (1.08, 1.11)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Other	15,223	1.20 (1.14, 1.25)*	1.14 (1.10, 1.19)*	1.20 (1.14, 1.25)*	1.14 1.10, 1.19)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season PTD							
Hispanic (North)	57,583	1.00 (0.99, 1.01)	1.05 (1.03, 1.07)*	1.06 (1.03, 1.08)*	1.05 (1.03, 1.07)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Hispanic (South)	61,403	1.12 (1.10, 1.14)*	1.11 (1.09, 1.13)*	1.12 (1.10, 1.14)*	1.11 (1.09, 1.12)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic Black (N)	31,481	1.02 (1.01, 1.03)*	1.02 (1.02, 1.05)*	1.03 (1.01, 1.05)*	1.03 (1.02, 1.05)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic Black (S)	105,080	1.10 (1.07, 1.12)*	1.10 (1.07, 1.12)*	1.10 (1.08, 1.13)*	1.10 (1.07, 1.12)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic White (N)	140,878	1.02 (1.01, 1.03)*	1.04 (1.03, 1.05)*	1.04 (1.03, 1.06)*	1.04 (1.03, 1.05)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic White (S)	114,501	1.12 (1.10, 1.14)*	1.10 (1.07, 1.14)*	1.10 (1.09, 1.12)*	1.09 (1.08, 1.11)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Other (N)	12,081	1.08 (1.04, 1.13)*	1.08 (1.04, 1.11)*	1.09 (1.05, 1.13)*	1.08 (1.05, 1.12)*	0.97 (0.94, 0.99)*	0.99 (0.95, 1.02)
Other (S)	18,552	1.12 (1.08, 1.17)*	1.09 (1.08, 1.11)*	1.12 (1.08, 1.17)*	1.10 1.07, 1.14)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Summer Months PTD							
Hispanic (North)	29,239	1.10 (1.06, 1.14)*	1.07 (1.03, 1.10)*	1.10 (1.06, 1.14)*	1.14 (1.03, 1.10)*	0.98 (0.96, 1.00)	0.98 (0.95, 1.01)
Hispanic (South)	31,365	1.31 (1.27, 1.35)*	1.23 (1.20, 1.26)*	1.31 (1.27, 1.35)*	1.22 (1.19, 1.26)*	1.00 (1.00, 1.00)	1.00 (1.00,1.00)
Non-Hispanic Black (N)	16,029	1.15 (1.03, 1.09)*	1.11 (1.01, 1.07)*	1.12 (1.03, 1.09)*	1.04 (1.01, 1.07)*	1.01 (0.99, 1.03)	1.03 (1.00, 1.06)
Non-Hispanic Black (S)	54,533	1.32 (1.27, 1.38)*	1.27 (1.22, 1.31)*	1.32 (1.27, 1.38)*	1.26 (1.22, 1.31)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic White (N)	71,402	1.07 (1.05, 1.09)*	1.05 (1.03, 1.06)*	1.13 (1.06, 1.09)*	1.06 (1.03, 1.07)*	0.99 (0.98, 1.01)	1.01 (0.99, 1.02)
Non-Hispanic White (S)	57,591	1.27 (1.24, 1.31)*	1.21 (1.18, 1.24)*	1.27 (1.24, 1.31)*	1.21 (1.18, 1.23)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Other (N)	6,304	1.17 (1.10, 1.25)*	1.14 (1.08, 1.21)*	1.18 (1.11, 1.25)*	1.14 (1.08, 1.21)*	0.96 (0.92, 0.99)*	0.96 (0.92, 1.02)
Other (S)	9,189	1.23 (1.15, 1.31)*	1.14 (1.08, 1.21)*	1.22 (1.14, 1.31)*	1.14 (1.08, 1.21)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)

CHAPTER 3. ACUTE IMPACT OF TEMPERATURE ON THE RISK OF STILLBIRTH IN THE US

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Abstract

Several studies have identified pregnant women as a group with an increased vulnerability to adverse health impacts of heat stress through studies of preterm delivery and low birthweight, but fewer studies have examined the role of increased ambient temperature on the risk of stillbirth. As temperatures continue to rise because of anthropogenic climate change, it is important that we fully characterize the increased vulnerability of pregnant women. We utilized a case-crossover design to examine the impact of a 10-degree increase in weekly average apparent temperature in the week preceding delivery among 42,160 stillborn infants delivered in the contiguous United States from January 1, 2000 to December 31, 2004. We observed a statistically significant increase in the risk of stillbirth in the warm season (May 1 to October 31) and the meteorological summer (June 1 to August 31), Odds Ratio = 1.10 (95% Confidence Interval 1.06 – 1.13) and Odds Ratio = 1.19 (95% CI 1.13 – 1.25), respectively. The risk was higher in Southern states compared to Northern states, and among women who were Hispanic, had inadequate prenatal care, or were diagnosed with a hypertensive condition.

Introduction

According to the Intergovernmental Panel on Climate Change and the US National Climate Assessment one of the most threatening impacts of climate change is the continued increase in the frequency and intensity of extreme heat (IPCC, 2018; Ebi et al., 2018). Extreme heat is associated with many adverse impacts to the environment and human health (IPCC, 2018). A robust literature has characterized the impacts of heat stress on humans, including associations between increased ambient temperature and cardiovascular disease, respiratory disease, all-cause mortality, emergency room hospitalizations, mental health problems, allergic responses, and spread of vector-borne infectious diseases (Cui et al., 2014, Anderson et al., 2013; Limaye et al., 2018, Vaidyanathan, et al., 2019; Upperman et al., 2017; Ogen et al., 2017).

Public health officials have consistently identified children under 5 years of age, individuals over 65, the immunocompromised and outdoor workers as vulnerable groups who are at increased risk of experiencing an adverse health event from heat stress (Weir, 2002). Often missing from the vulnerable population designation are pregnant women who are also at increased risk of adverse health and pregnancy outcomes. While numerous studies have identified a link between increased temperatures and preterm delivery and low birth weight, fewer have assessed the impact of heat stress on the risk of stillbirth (Bekker at al., 2020; Kuehn et al., 2017). A recent systematic review of the US literature on heat stress and adverse pregnancy outcomes identified only two studies that examined stillbirth as a primary outcome (Bekkar et al., 2017). A global systematic review of studies on maternal heat stress and adverse pregnancy outcomes identified three additional studies that examined stillbirth (Kuehn et al., 2017). A small number of studies suggest that risk of stillbirth is increased by exposure to maternal air pollution, but the literature is sparse and limited by small sample sizes (Faiz et al., 2012; Faiz et al., 2013; DeFranco et al., 2015). The lack of literature on the impact of environmental risk factors for stillbirth indicates that stillbirth is an often-neglected public health problem.

The lack of research and public health emphasis on stillbirth is exacerbated by the absence of a consistent stillbirth definition. The most commonly used definition is the death of an infant occurring after 20 weeks' gestation either prior to or during delivery (Goldenberg et al., 2011). However, the World Health Organization recognizes a stillbirth as a death after 28 weeks' gestation. Some definitions consider gestational age coupled with birthweight, and a stillbirth designation is given if an infant is lost at 20 weeks' gestation or greater and the birth weight is more than 2500 grams (WHO, 2020). Worldwide, an estimated 3 million stillbirths occur every year and while recent reductions in maternal and early childhood mortality have been promising, the prevalence of stillbirths has not fallen at comparable rate (Lawn et al., 2016). In the United States, about 1 in 160 births result in the tragedy of stillborn child. This rate is 10 times higher than that of infant loss to Sudden Infant Death Syndrome (SIDS) (Lawn et al., 2016; Stillbirth Collaborative Research Network, 2011).

Furthermore, studies have found that women who experience stillbirth report adverse psychological effects including depression, shame, anxiety, guilt, PTSD, and suicidal ideologies (Badenhorst et al., 2007). Healthcare costs of stillbirth include not only those incurred in the affected pregnancy but also in subsequent pregnancies, as women with a history of stillbirth require more careful monitoring (Ogwulu et al., 2015). Causes of stillbirth are undetermined in about 50% of pregnancies and in cases with known etiology causes are diverse and include placental abruption, umbilical cord accidents and abnormalities, asphyxia due to obstructed labor, congenital anomalies, and maternal disease such as hypertension and infection (Stillbirth Collaborative Research Network, 2011). Maternal risk factors for stillbirth are not entirely understood, but research suggests increased risks from smoking, obesity, advanced age, lower education, and inadequate prenatal care (Goldenberg et al. 2011; Lawn et al. 2016; Stillbirth Collaborative Research Network, 2011). Like many maternal-fetal health outcomes in the United States, racial disparities persist and Non-Hispanic Black women are twice as likely to experience a stillbirth compared to Non-Hispanic White women. It is important to note that this racial disparity in health, and those in other maternal-infant health indicators, arise not from differences in innate biological risk but instead are a consequence of historic and present, deeply entrenched, systemic racism. This is further complicated by implicit racial bias in the provision of healthcare to Black women and their babies (Burris et al., 2019; Taylor, 2020; NICHQ, 2020).

In an effort to enhance our understanding of environmental causes of stillbirth and the increased vulnerability of pregnant women to heat stress we undertook the present study to examine ambient temperature in the week leading up to the delivery as a potential trigger for stillbirth in the contiguous United States over a 5-year period from 2000 through 2004. This study combines stillbirth data from the US National Center for Health Statistics (NCHS) with meteorological data from the National Oceanic and

Atmospheric Administration (NOAA) Automated Surface Observing System (ASOS), and air pollutant data from the Environmental Protection Agency (EPA) Air Quality System (AQS), applied in a case-crossover design with over 40,000 stillborn infants.

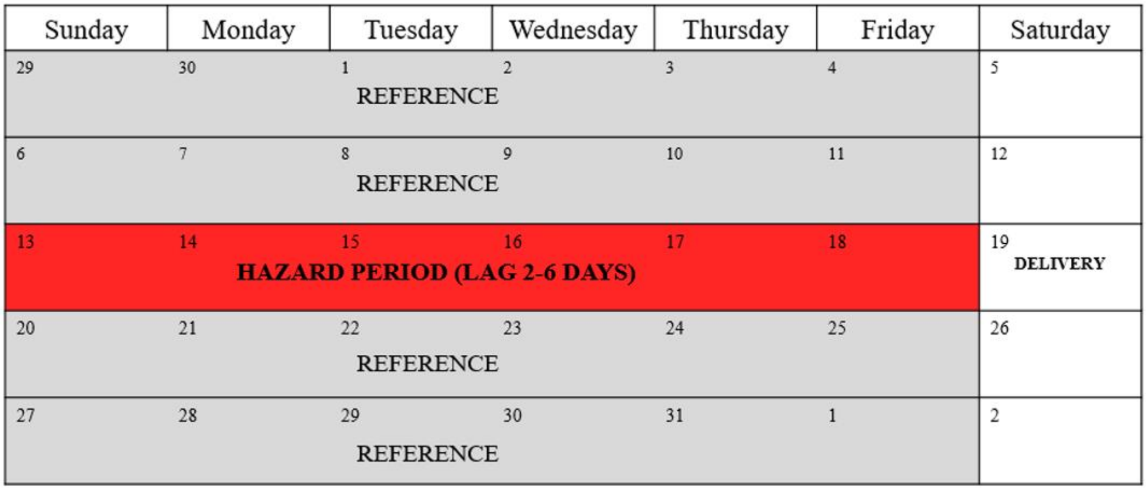
Methods

Study Design

The study utilizes a bi-directional case-crossover design with a hazard lag period of 2-6 days and a 4 to 1 hazard to reference ratio. First introduced by Malcom Maclure and Murray Mittleman in the late 1980s, the case-crossover design is a method for studying transient effects on the risk of acute events (Maclure, 1991). The design resembles a retrospective nonrandomized crossover study and is ideal for the study of time varying factors like weather and air pollution as a trigger of acute events. Since the initial use of the case-crossover design to study behaviors and activities that triggered acute myocardial infarction, it has been used to study environmental exposures during the critical window of time immediately before a woman gives birth (Mittleman et al., 1995; Avalos et al., 2017; Basu et al., 2010; Basu et al., 2017; Rammah et al., 2019). The case-crossover approach has been used by Avalos, Basu, Rammah, and others, to study weather related triggers of preterm birth, stillbirth, and placental abruption (Avalos et al., 2017; Basu et al., 2010; Basu et al., 2016; Basu et al., 2017; Rammah et al., 2019).

In this case-only design, the mother serves as her own control, eliminating the threat of confounding by non-time dependent maternal factors. The comparison occurs between the hazard period before the acute event and selected reference periods. We assigned the hazard period as one week prior to the delivery based on previous findings and the biologically relevant window for stillbirth resulting from an acute exposure (Basu et al., 2016; Ha et al.; 2017). Considering the delivery date as day 1, the hazard lag period includes days 2 to 6. We assigned four reference periods for comparison, which occur within 30 days of the delivery date. Each reference period is the same length as the hazard period (one week) and consists of the same days of the week as the hazard period to avoid potential confounding by day of the week. We balanced the design with two reference periods before the hazard period and two reference periods after the hazard period. Figure 3.1 depicts an example of the assignment of the hazard and reference periods for a delivery occurring on July 19, 2003.

Figure 3.1 Depiction of hazard and reference period assignment for example delivery date July 19, 2003.

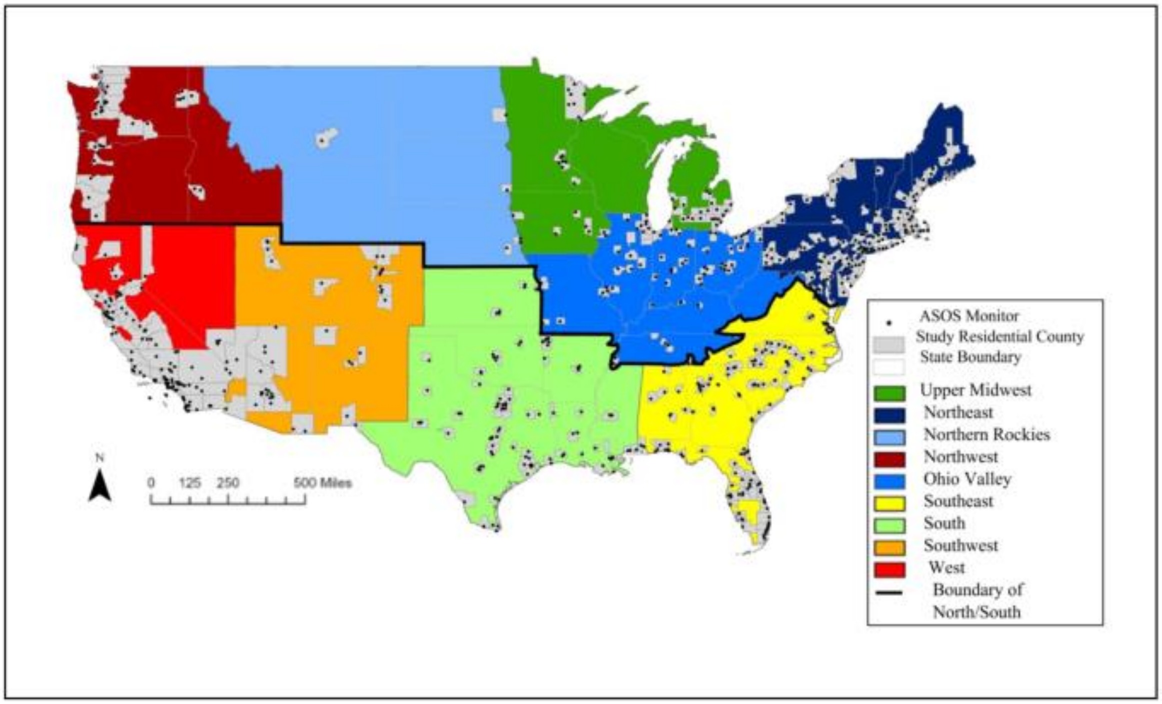


Sunday	Monday	Tuesday	Wednesday	Thursday	Friday	Saturday
29	30	1 REFERENCE	2	3	4	5
6	7	8 REFERENCE	9	10	11	12
13	14	15 HAZARD PERIOD (LAG 2-6 DAYS)	16	17	18	19 DELIVERY
20	21	22 REFERENCE	23	24	25	26
27	28	29 REFERENCE	30	31	1	2

Study Population

We utilized data on fetal deaths occurring from January 1, 2000 through December 31, 2004 to United States residents through fetal death records from the National Center for Health Statistics (NCHS), Vital Statistics System (NVSS) Fetal Death files. NCHS NVSS fetal death and natality data are limited to births occurring to U.S. resident women living in a county with a population greater than 100,000 people. We restricted the analysis to women residing in the contiguous United States, excluding counties in Alaska, Hawaii, and Puerto Rico. The publicly available data from NCHS NVSS does not contain the exact date of birth so we imputed the date of delivery using data on birth year and month, gestational age, date of the mother's last menstrual period, and the day of the week of the delivery. This methodology was previously used by Sun et al. to utilize public birth records for the study of preterm delivery and markers of fetal growth (Sun et al., 2019a; Sun et al., 2019b). Because of this limitation, we limited the analysis to women with complete data on these three variables. Additional exclusion criteria included women with missing data for maternal residence state and county, fetal deaths occurring before 20 weeks' gestation, multiple pregnancies, and presence of birth defects and chromosomal anomalies. The final inclusion criteria was the presence of at least one ASOS weather monitoring station within the maternal residence county boundary. The final analytical sample contains data on 42,160 stillborn infants across 401 US counties. Figure 3.2 depicts a map of the geographic distribution of the study population.

Figure 3.2 Distribution of study population across the United States, NOAA US Climate Regions, and location of ASOS Weather monitors relevant to the geographic area of the study population.



Outcome assessment

Stillborn cases included in the present analysis were ascertained from NCHS NVSS fetal death records. We did not consider birthweight in our case definition. In addition to gestational age, other maternal characteristics were extracted from fetal death records including race/ethnicity, education, age in years, access to prenatal care, cigarette smoking in pregnancy, parity, and the sex of the fetus. Because we utilized de-identified, publicly available data, the study was determined to be exempt from formal review by the Institutional Review Board at the Boston University Medical Campus.

Exposure assessment

Meteorological variables were ascertained from the NOAA Automated Surface Observing System (ASOS). This automated observing network is located at airports across the United States and provides essential observations for the National Weather Service (NWS), the Federal Aviation Administration (FAA), and the Department of Defense (DOD). ASOS stations take minute-by-minute observations and are monitored for quality control 24-hours a day. We downloaded raw observations for air temperature, dew point, and relative humidity from weather stations across the United States from January 1, 2000 to December 31, 2004. We then calculated 24-hour daily averages, 24-hour daily minimums, and 24-hour daily maximums for each of these three meteorological factors: air temperature, dew point, and relative humidity. In addition, we also assessed apparent temperature, which is a combination of humidity and air temperature that better assesses how a person feels when experiencing heat stress. Multiple techniques exist for calculating apparent temperature (Anderson et al., 2013). We utilized the following formula to be consistent with other environmental health studies of heat stress: apparent temperature = (-2.653 + (0.994 * Air Temperature Celsius) + (0.0153 * Dew Point Celsius^2)). Apparent temperature was also assessed as 24-hour average daily, 24-hour daily minimum, and 24-hour daily maximum measures.

Data on the maternal residence county was then linked to the appropriate weather station(s). If a maternal residence county had a single weather station within the county boundary, the values from that station were assigned. If a maternal residence county had multiple stations within the county, data were averaged across stations.

To assess effect modification by air pollution, data for particulate matter size 2.5 microns in diameter ($PM_{2.5}$) and ozone were ascertained from the US EPA Air Quality System (AQS) monitoring stations. In the case of $PM_{2.5}$, the 24-hour daily average was downloaded from AQS. In the case of ozone, we use the average 8-hour daily maximum.

We used ArcGIS Pro (ESRI, Redlands, CA) to map the study population and all monitoring stations and link the maternal residence county to the appropriate station(s) for all exposure variables.

Statistical analysis

We calculated odds ratios (ORs) and corresponding 95% confidence intervals (CIs) using univariate conditional logistic regression with the exposure of interest (e.g., daily average apparent temperature) as a linear term and stillbirth as a binary variable (Y/N) applied to each study period (hazard period = Y, reference period = N). To assess effect measure modification, we stratified by potential modifiers in separate models; these included all maternal characteristics in Table 1 as well as exposure to PM 2.5 and ozone). All statistical analyses were conducted using SAS 9.4 (Cary, North Carolina) PROC LOGISTIC.

Results

After applying the inclusion criteria, the final analytical sample contained data on 42,160 stillborn infants born to US residents residing in 401 US counties from January 1, 2000 through December 31, 2004. Of this total, 23,958 (56.8%) were born in the warm season (May 1 to October 31) and 12,204 (28.9%) were born in the meteorological summer (June 1 to August 31). Because stronger associations were observed for warm season and summer deliveries, we presented the demographic characteristics of the warm season and summer deliveries in Table 3.1.

The stillborn deliveries were distributed evenly across the five years of the study period with a slight decrease over time. Of the warm season deliveries 5,119 (21.4%) occurred in 2000 compared to 4,498 (18.8%) in 2004. Looking across the climactic regions of the United States during the warm season, the largest proportion of stillbirths (24.1%) occurred in the West (California and Nevada). This was followed by the Northeast with 21.1% of stillbirths and the Southeast with 17.0%. The largest proportion of women identified as Non-Hispanic White (36.5%), followed by Non-Hispanic Black (27.4%) and Hispanic (26.2%) and Non-Hispanic Other (5.7%). Half of the women had a high school diploma or lower as their highest level of education (50.2%) and the greatest proportion of women fell into the 18-to-25-year old category (27.7%) followed by the 31 – 35 year category (21.7%). Most women began receiving their prenatal care in the first trimester (74.2%) and only 3.5% received no prenatal care. Cigarette smoking data were missing for 32.7% of the warm season delivering women. Of those with complete data, about 8% reported smoking cigarettes at some point during their pregnancy. There was also a large proportion of subjects (27.2%) with missing data on parity. Of those with complete data, 32.5% were having their first child. Most of the stillborn deliveries occurred between 20 and 27 weeks' gestation (49.5%), followed by 37-40 weeks' (16.4%). There were more male infants in the stillbirth population (52.9%) compared to females (47.1%).

Table 3.1. Demographics of study population (N=23,958 warm season stillbirths).

Characteristic	N(%)[a]
Year of Delivery	
2000	5,119 (21.4)
2001	4,805 (20.1)
2002	4,926 (20.6)
2003	4,610 (19.2)
2004	4,498 (18.8)
Month of Delivery	
May	3,964 (16.6)
June	4,008 (16.7)
July	4,245 (17.7)
August	3,951 (16.5)
September	3,792 (15.8)
October	3,998 (16.7)
US Climate Region (Maternal Residence)	
Northeast	5,043 (21.1)
Southeast	4,066 (17.0)
Ohio Valley	2,876 (12.0)
Upper Midwest	1,251 (5.2)
Northern Rockies and Plains	111 (0.5)
South	2,910 (12.2)
Southwest	1,401 (5.9)
West	5,766 (24.1)
Northwest	534 (2.2)
Maternal race/ethnicity	
Hispanic	6,277 (26.2)
Non-Hispanic Black	6,561 (27.4)
Non-Hispanic White	8,736 (36.5)
Non-Hispanic Other	1,353 (5.7)
Unknown or not stated	1,031 (4.3)
Maternal education	
High school graduate or less	12,024 (50.2)
Some college	4,329 (18.1)
Bachelor’s degree	3,075 (12.8)
Master’s, Doctorate or Professional	1,620 (6.8)
Unknown or not stated	2,910 (12.2)
Maternal age in years	
< 18	860 (3.6)
18 – 25	6,644 (27.7)
26 – 30	4,740 (19.8)
31 – 35	5,199 (21.7)

36 – 40	3,464 (14.5)
41 – 45	1,686 (7.0)
> 45	1,365 (5.7)
Prenatal care	
No prenatal care	827 (3.5)
Prenatal care began month 7 – 9	474 (2.0)
Prenatal care began month 4 – 6	2,697 (11.3)
Prenatal care began month 1 – 3	17,779 (74.2)
Unknown or not stated	2,181 (9.1)
Cigarette smoking during pregnancy	
Yes	1,881 (7.9)
No	14,248 (59.5)
Unknown or not stated	7,829 (32.7)
Parity	
1	7,786 (32.5)
2	4,718 (19.7)
3	2,651 (11.1)
>/= 4	2,279 (9.5)
Unknown or not stated	6,524 (27.2)
Gestational age category	
20 – 27 weeks	11,867 (49.5)
28 – 32 weeks	3,707 (15.5)
33 – 36 weeks	3,601 (15.0)
37 – 40 weeks	3,921 (16.4)
> 40 weeks	862 (3.6)
Sex of infant	
Female	11,276 (47.1)
Male	12,682 (52.9)

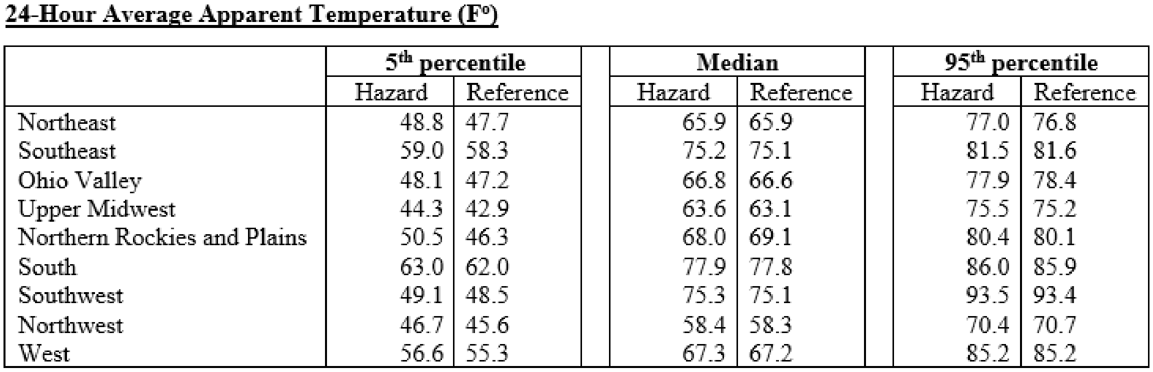
[a] Some percentages not equal to 100% due to rounding.

Table 3.2 describes the distribution of average apparent temperature and maximum apparent temperature across the warm season, broken down by climactic region of the United States. The highest average apparent temperatures were observed in the South (Arkansas, Kansas, Louisiana, Mississippi, Oklahoma, and Texas) (Hazard period: Median 77.9° F, 5th percentile 63.0° F, 95th percentile 86.0° F; Reference period: Median 77.8° F, 5th percentile 62.0° F, 95th percentile 85.9° F). This was followed by the

Southwest (Arizona, Colorado, New Mexico, and Utah) (Hazard period: Median 75.3º F, 5th percentile 49.1º F, 95th percentile 93.5º F; Reference period: Median 75.1º F, 5th percentile 48.5º F, 95th percentile 93.4º F).

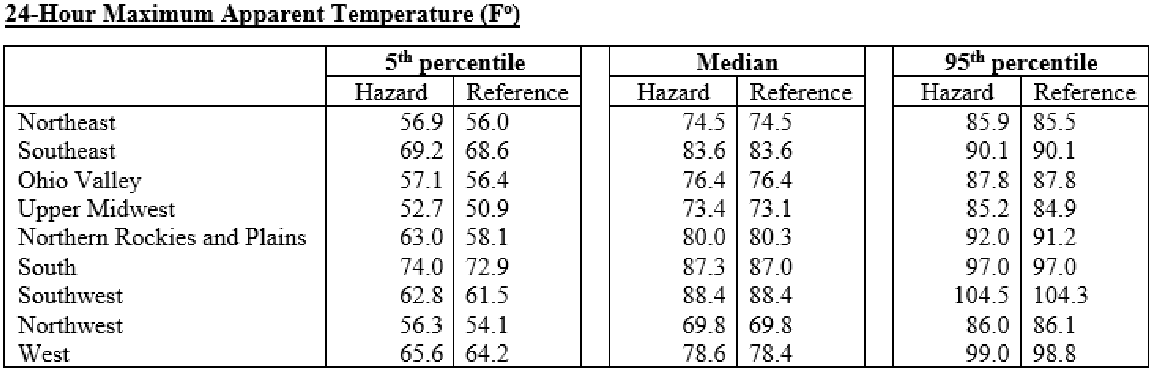
The warm season apparent temperatures were most extreme in the Southwest where the 95th percentile for the 24-hour daily average apparent temperature was 93.5º F for the hazard period and 93.4º F for the reference period. The 95th percentile for the 24-hour daily maximum apparent temperature in the Southwest was 104.5º F for the hazard period and 104.3º F for the reference period.

Table 3.2. Distribution of apparent temperature for hazard and reference periods by climate region (May 1 to October 31, 2000–2004).



24-Hour Average Apparent Temperature (F°)

	5th percentile		Median		95th percentile	
	Hazard	Reference	Hazard	Reference	Hazard	Reference
Northeast	48.8	47.7	65.9	65.9	77.0	76.8
Southeast	59.0	58.3	75.2	75.1	81.5	81.6
Ohio Valley	48.1	47.2	66.8	66.6	77.9	78.4
Upper Midwest	44.3	42.9	63.6	63.1	75.5	75.2
Northern Rockies and Plains	50.5	46.3	68.0	69.1	80.4	80.1
South	63.0	62.0	77.9	77.8	86.0	85.9
Southwest	49.1	48.5	75.3	75.1	93.5	93.4
Northwest	46.7	45.6	58.4	58.3	70.4	70.7
West	56.6	55.3	67.3	67.2	85.2	85.2

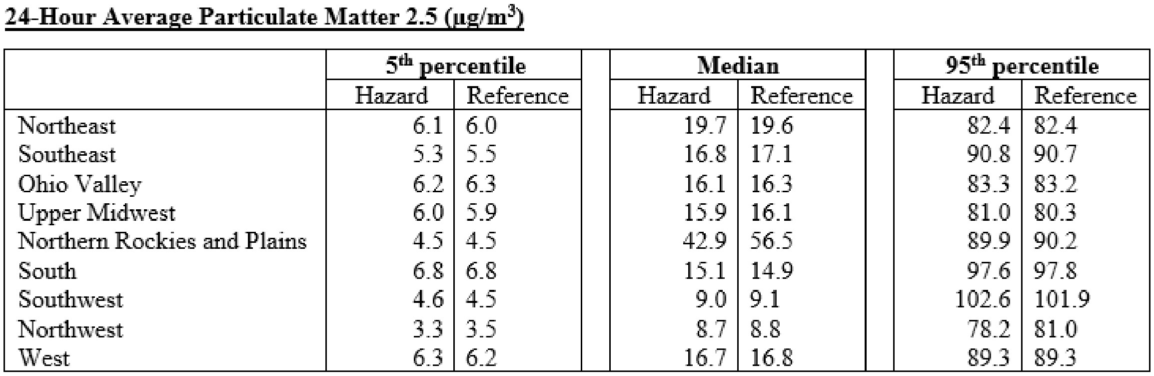


24-Hour Maximum Apparent Temperature (F°)

	5th percentile		Median		95th percentile	
	Hazard	Reference	Hazard	Reference	Hazard	Reference
Northeast	56.9	56.0	74.5	74.5	85.9	85.5
Southeast	69.2	68.6	83.6	83.6	90.1	90.1
Ohio Valley	57.1	56.4	76.4	76.4	87.8	87.8
Upper Midwest	52.7	50.9	73.4	73.1	85.2	84.9
Northern Rockies and Plains	63.0	58.1	80.0	80.3	92.0	91.2
South	74.0	72.9	87.3	87.0	97.0	97.0
Southwest	62.8	61.5	88.4	88.4	104.5	104.3
Northwest	56.3	54.1	69.8	69.8	86.0	86.1
West	65.6	64.2	78.6	78.4	99.0	98.8

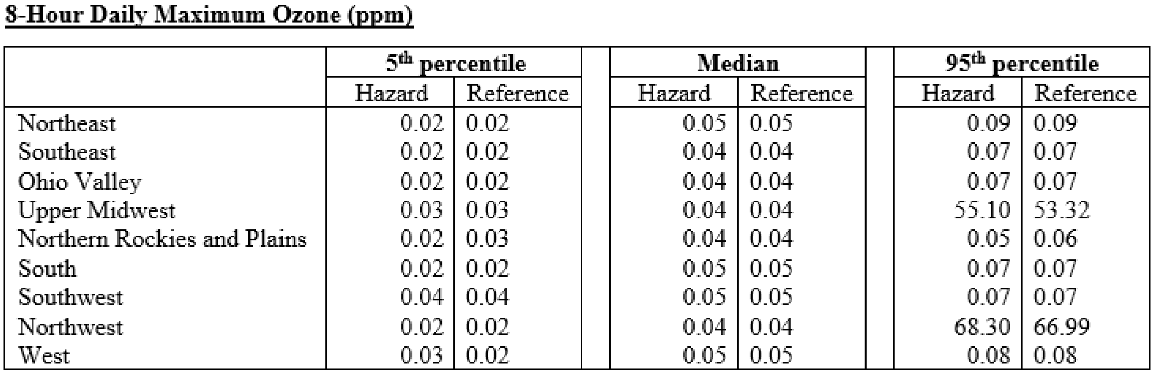
The median 24-hour average $PM_{2.5}$ was highest in the Northern Rockies and Plains (Dakotas, Montana, Nebraska, Wyoming) (Hazard period: Median 42.9 ug/m^3; Reference period: 56.5 ug/m^3). There was very little variability in the distribution of median ozone across the United States for the warm season. This is likely because we did not have the geographic resolution to capture localized heterogeneity in ozone levels. Despite the removal of outliers greater than 2.5 standard deviations from the mean, we did observe some high ozone levels at the 95th percentile in the Upper Midwest and the Northwest. This could be related to inaccuracies in the data that was downloaded from the EPA AQS Stations or may be the result of very high ozone levels nearby some monitors. (Table 3.3)

Table 3.3. Distribution of air pollutants (PM 2.5 and ground level ozone) for hazard and reference periods by climate region (May 1 to October 31, 2000–2004).



24-Hour Average Particulate Matter 2.5 ($\mu g/m^3$)

	5th percentile		Median		95th percentile	
	Hazard	Reference	Hazard	Reference	Hazard	Reference
Northeast	6.1	6.0	19.7	19.6	82.4	82.4
Southeast	5.3	5.5	16.8	17.1	90.8	90.7
Ohio Valley	6.2	6.3	16.1	16.3	83.3	83.2
Upper Midwest	6.0	5.9	15.9	16.1	81.0	80.3
Northern Rockies and Plains	4.5	4.5	42.9	56.5	89.9	90.2
South	6.8	6.8	15.1	14.9	97.6	97.8
Southwest	4.6	4.5	9.0	9.1	102.6	101.9
Northwest	3.3	3.5	8.7	8.8	78.2	81.0
West	6.3	6.2	16.7	16.8	89.3	89.3



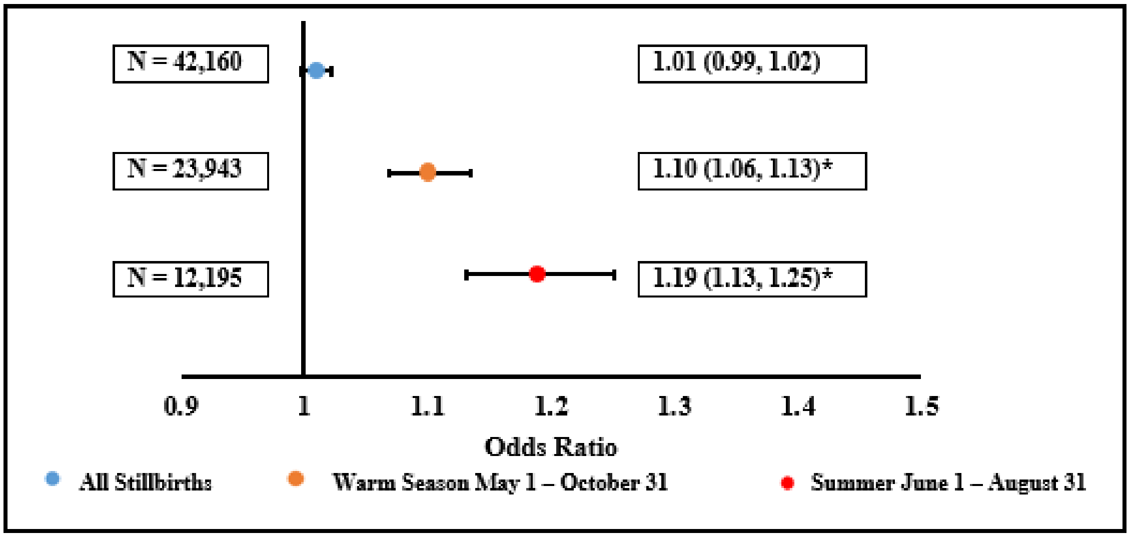
8-Hour Daily Maximum Ozone (ppm)

	5th percentile		Median		95th percentile	
	Hazard	Reference	Hazard	Reference	Hazard	Reference
Northeast	0.02	0.02	0.05	0.05	0.09	0.09
Southeast	0.02	0.02	0.04	0.04	0.07	0.07
Ohio Valley	0.02	0.02	0.04	0.04	0.07	0.07
Upper Midwest	0.03	0.03	0.04	0.04	55.10	53.32
Northern Rockies and Plains	0.02	0.03	0.04	0.04	0.05	0.06
South	0.02	0.02	0.05	0.05	0.07	0.07
Southwest	0.04	0.04	0.05	0.05	0.07	0.07
Northwest	0.02	0.02	0.04	0.04	68.30	66.99
West	0.03	0.02	0.05	0.05	0.08	0.08

Figure 3.3A–F depicts the ORs and corresponding 95% CIs for a 10 unit increase in average daily apparent temperature (lag$_{2\text{-}6}$ days). We found a null association when examining the impact of average daily apparent temperature on stillbirths occurring across the entire calendar year (OR = 1.01, 95% CI 0.99 – 1.02). For stillbirths occurring in the warm season we observed a 9.5% statistically significant increased odds (OR = 1.10, 95% CI 1.06 – 1.13). For stillbirths occurring in the summer we observed a 19% statistically significant increased odds (OR = 1.19, 95% CI 1.13 – 1.25). (Plot 3.3A)

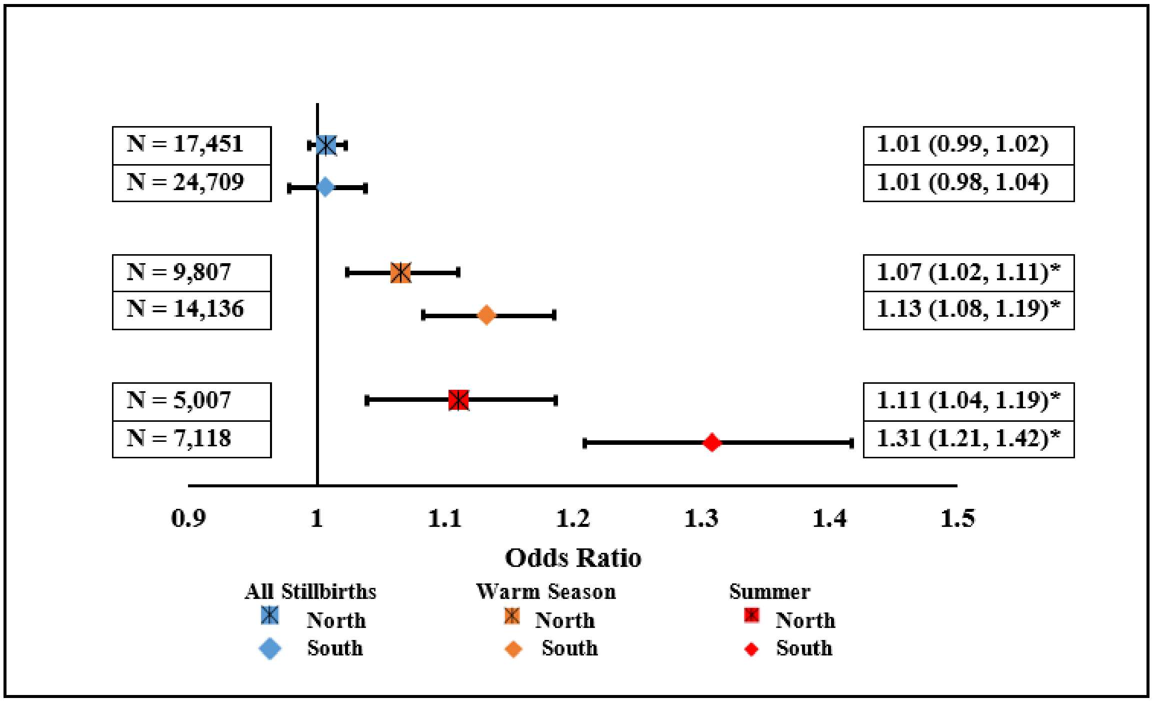
Figure 3.3A–3.3F Odds ratios and 95% confidence intervals for a 10-degree Fahrenheit increase in average daily apparent temperature (lag$_{2\text{-}6}$ days), 2000–2004.

3.3A Stillbirths occurring across the entire calendar year (blue), the warm season May to October 31 (orange), and the summer season June 1 to August 31 (red).



When stratifying by region we observed that the increased odds observed in the warm and summer seasons were largely driven by the association between heat and stillbirth in the Southern half of United States (NOAA Climate Regions = Southeast, South, Southwest, West) compared to the Northern half of the United States (NOAA Climate Regions = Northeast, Ohio Valley, Upper Midwest, Northern Rockies and Plains, and Northwest). For the warm season we observed an odds ratio of 1.07 for the Northern half (95% CI 1.02 – 1.11) compared to 1.13 for the Southern half (95% CI 1.08 – 1.19). The regional difference was most pronounced in the summer month deliveries where women residing in the Northern half of the US had an 11% increased odds (95% CI 1.04 – 1.19) while those in the Southern half had a 31% increased odds (95% CI 1.21 – 1.42). (Plot 3.3B)

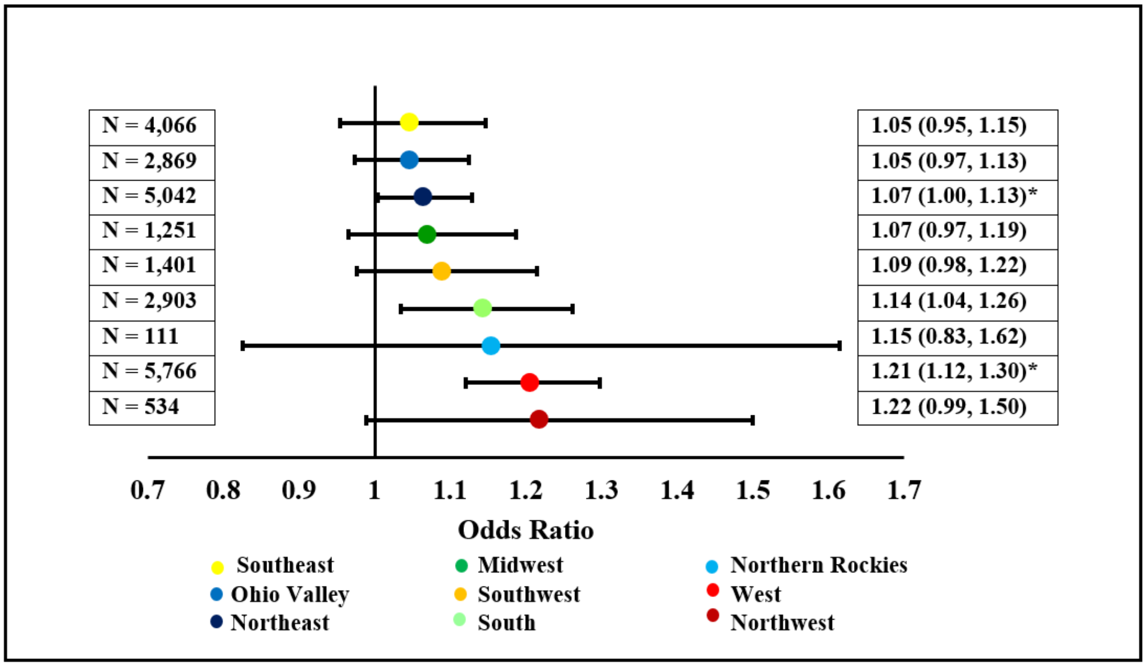
3.3B Stillbirths occurring across the entire calendar year (blue), the warm season May 1 to October 31 (orange), and the summer season June 1 to August 31 (red), stratified by Northern United States[a] and Southern United States[b].



[a] North = Northeast, Ohio Valley, Upper Midwest, Northern Rockies and Plains, Northwest [b]South = Southeast, South, Southwest, West

To more precisely examine the regional effects, we stratified the results by the nine climactic regions of the United States and observed that for women delivering in the warm season the increased odds differed dramatically from 5% increased odds (95% CI 0.954 – 1.147) in the Southeast to a 22% increased odds in the Northwest (95% CI 0.99 – 1.50). (Plot 3.3C)

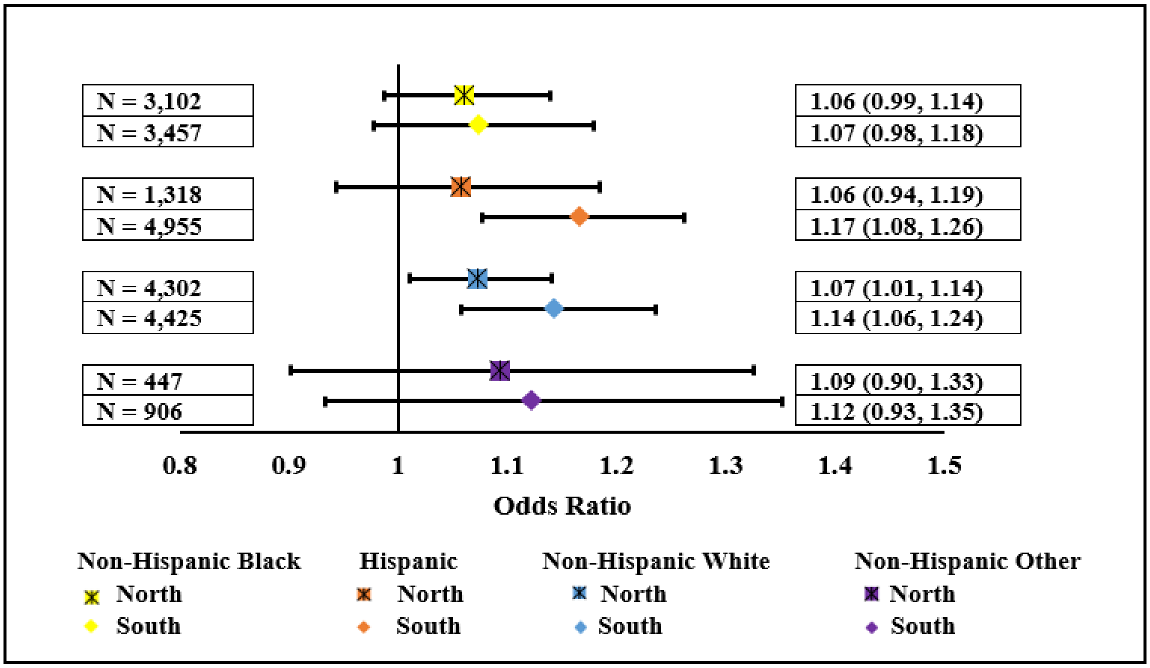
3.3C Stillbirths occurring in the warm season May 1 to October 31, stratified by NOAA climate regions of the contiguous United States.



Looking across the entire US there was a slight increase in odds for Hispanic women delivering in the warm season (13%), compared to Non-Hispanic white women (10%). The racial/ethnic differences were much more profound when we stratified by the Northern and Southern half of the US. Consistently, we observed the greatest odds of warm season heat-related stillbirth in the Southern half of the US. The greatest odds of stillbirth was observed in Hispanic women residing in the Southern half of the United

States (OR = 1.17 95% CI 1.08 – 1.26). These odds were much greater than that observed for Hispanic women residing in the Northern half of the US (OR = 1.06, 95% CI 0.94 – 1.19). (Plot 3.3D)

3.3D Stillbirths occurring in the warm season May 1 to October 31, stratified by region of the United States (North[a], South[b]) and maternal race/ethnicity.

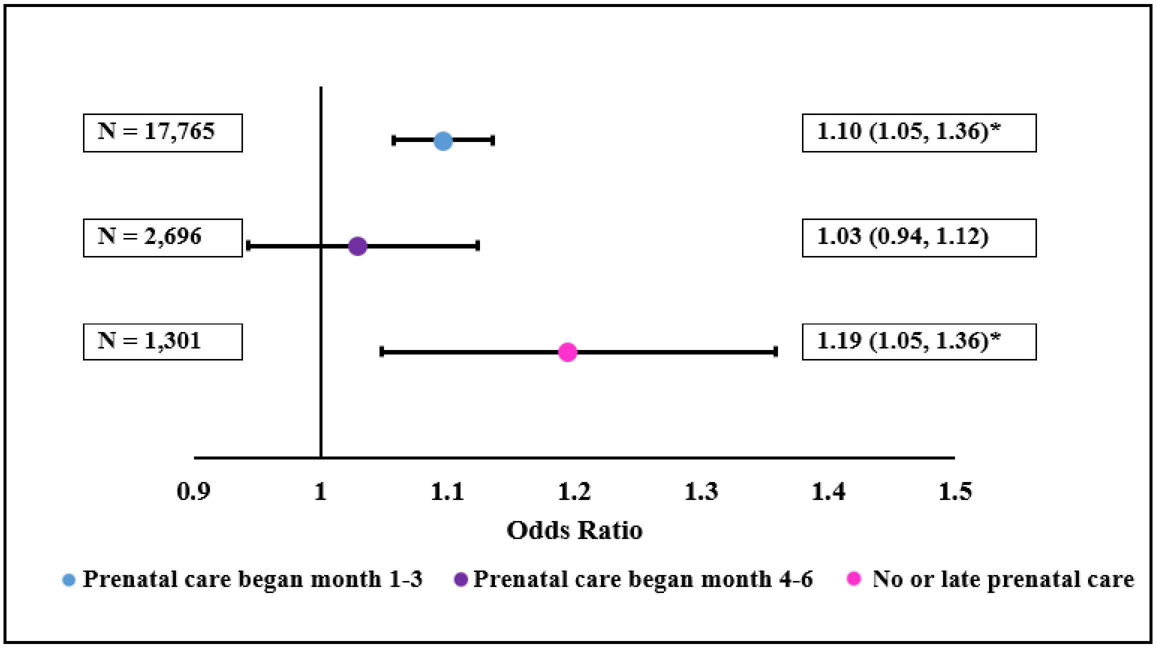


[a]North = Northeast, Ohio Valley, Upper Midwest, Northern Rockies and Plains, Northwest [b]South = Southeast, South, Southwest, West

When we examined effect modification by the other maternal factors available in the fetal death record (Table 1), two factors emerged as a modifier of the relationship between apparent temperature and odds of stillbirth, access to prenatal care and diagnosis of a maternal hypertensive condition. While women who began prenatal care in the first trimester had an increased odds of 1.10 (95% CI 1.06 – 1.14), the increased odds nearly doubled in women who had no or late prenatal care access. For women who had no prenatal care access or began their prenatal care after their 7th month of pregnancy, the

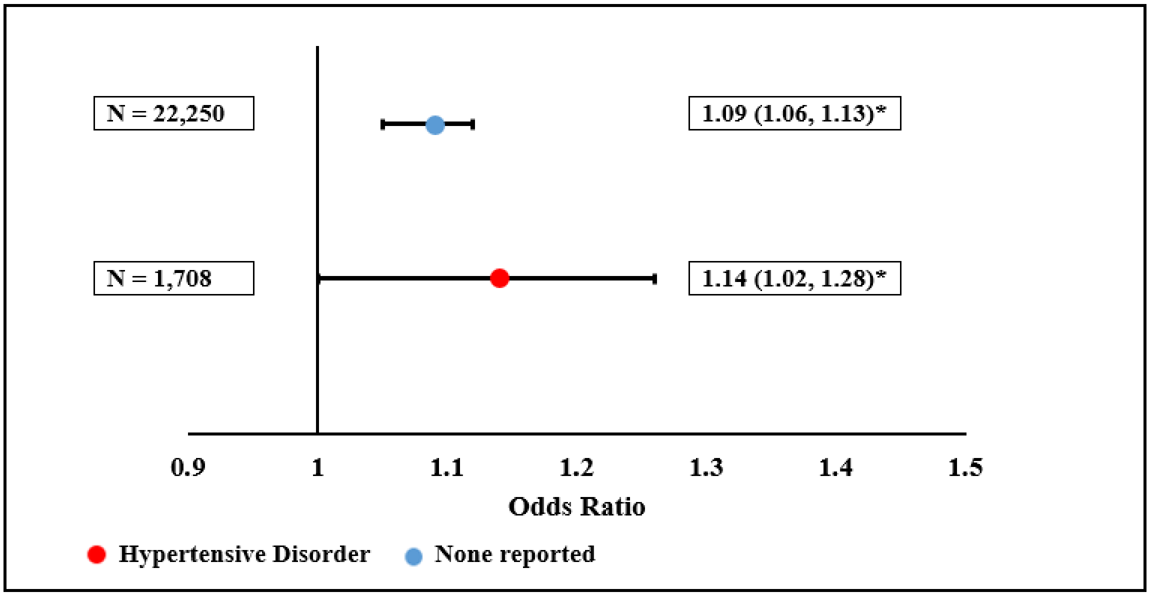
10-degree increase in average apparent temperature resulted in an odds ratio of 1.19 (95% CI 1.05 – 1.36). (Plot 3.3E)

3.3E Stillbirths occurring in the warm season May 1 to October 31, stratified by prenatal care access.



When we examined the association separately in women who were suffering chronic or pregnancy related conditions known to be associated with adverse pregnancy outcomes, we observed no impact of maternal diabetes. However, women suffering from a hypertensive condition (chronic hypertension, pregnancy-induced hypertension, or eclampsia) had an increased odds of 1.14 (95% CI 1.02 – 1.28) compared to women without any of these conditions who had an odds of 1.09 (1.06 – 1.13). Notably, these comparisons had a relatively low sample size (Table 1). (Plot 3.3F)

3.3F Stillbirths occurring in the warm season May 1 to October 31, comparing warm season delivering mothers experiencing a hypertensive condition (eclampsia, pregnancy-induced hypertension, chronic hypertension) to those without.



Results for air temperature were consistent with the findings for apparent temperature and we identified a null effect of relative humidity, with the exception of one analysis. For Non-Hispanic Black women residing in the Northern half of the United States a 10-unit increase in average relative humidity in the week preceding the birth was associated with a 6% increased odds of stillbirth (95% CI 1.05 – 1.12) and a 10-unit increase in maximum daily relative humidity was associated with a 10% increased odds (95% CI 1.03 – 1.19) (Supplementary Material Table S3.1).

We did not have data on the cause of the stillbirth. However, we did have a variable indicating that the woman suffered a placental abruption as a complication of the pregnancy. These women did not have a greater odds than those without placental abruption (OR for placental abruption in the warm season = 1.08 (95% CI 0.97 – 1.20)).

We did not observe any modification of air pollution on the relationship between daily average apparent temperature and stillbirth. Analyses of the independent relationships between the air pollutants $PM_{2.5}$ and ozone on stillbirth also yielded null results (not shown).

Discussion

Our findings suggest that there is an increase in heat-associated stillbirth in the warm and summer seasons in the United States, primarily driven by stronger associations in the Southern half of the US compared to the Northern half. The odds are most elevated in the summer months and differ by maternal race/ethnicity, with Hispanic women residing in the Southern US emerging as the most vulnerable.

While the literature on maternal heat exposure and stillbirth (and stillbirth in general) is quite sparse, our findings are in agreement with three earlier studies from the US. The first case-crossover study, published by Basu et al. in 2016, observed that a 10-degree increase in average apparent temperature in the week prior to the delivery was associated with a 10.4% increased risk of stillbirth in the warm season in California. Similar to our findings, they observed the association to be independent of air pollution exposure and greatest among Hispanic women (Basu et al., 2016).

In 2017 Ha et al. published data on 987 stillbirths from 12 clinical sites across the US (locations in: CA, DC, DE, FL, IL, IN, OH, MA, MD, NY, TX, UT) and observed a 6% increase in risk was associated with every 1-degree Celsius increase in apparent temperature in the week prior to the delivery. Notably, this study also looked at cumulative exposure to maternal heat stress across the entire pregnancy and observed a statistically significant 3-fold increase in stillbirth for chronic heat exposure compared to mild temperatures (aOR = 3.07 (95% CI 3.07 – 4.47) (Ha et al., 2017).

In 2019, Rammah et al. reported a 45% increased risk of stillbirth with a 10-degree Fahrenheit increase in apparent temperature in the week preceding the delivery for deliveries occurring from May to September in Harris County, Texas. They also found these associations to be independent of air pollution exposure and identified the greatest risks among Hispanic and Non-Hispanic Black women. Rammah et al. also evaluated stillbirths caused by placental abruption and found that this group had a 93% increased odds associated with a 10-degree increase in apparent temperature in the week leading up to the delivery (OR = 1.93, CI 1.15 – 3.23) (Rammah et al., 2019). We also assessed stillbirths related to placental abruption (as indicated on the fetal death record) but did not observe increased risk in this group compared to all warm season stillbirths without placental abruption indicated.

A few studies of maternal heat stress and stillbirth have also been undertaken outside of the United States. In 2012 Strand et al. found an increased risk of stillbirth with higher ambient temperatures in the last four weeks of pregnancy among women from Brisbane, Australia (Strand et al., 2012). Also in Brisbane, Li et al. identified an increased risk of stillbirth associated with heat in the second trimester (Li et al., 2018). Lastly, in a multi-decade study of seasonal and temperature patterns in adverse birth outcomes in Japan, Fakuda et al. observed an increase in fetal deaths in September 2010 following an unusually hot summer (Fukuda et al., 2014).

Examining our findings in the context of earlier studies, highlights both the strengths and limitations of our present work. The use of this publicly available, national dataset allowed us to examine a large, heterogeneous population of women across our entire climactically diverse country. This granted us the ability to identify the enhanced vulnerability to heat stress in pregnant women in the Southern half of the United States, an observation not previously reported in the literature. Our large sample size also allowed us to identify vulnerable racial and ethnic subgroups with precise point estimates and adequate power. Lastly, our utilization of the case-crossover design eliminated the threat of confounding from non-time varying maternal factors.

While the national dataset of fetal death records provided many strengths, it also introduced important limitations. Studies utilizing these records are limited by the variables reported on the record and the accuracy of these reported variables. Thus, we lacked data on key maternal variables such as socioeconomic status, occupation, air conditioning access, and time-activity patterns, all of which might influence the risk of heat-related stillbirths. Because the NVSS fetal death record data are only available for counties with greater than 100,000 residents, our study was also unable to assess the relationship between heat stress and stillbirth in rural areas where women may experience heat stress differently and may lack access to adequate prenatal care. Because the publicly available dataset lacked information on the exact day of delivery our imputed variable likely introduced some exposure misclassification, biasing the results towards the null.

Non-differential exposure misclassification also arose from the use of monitoring stations to apply the meteorological data to the maternal residence county — especially in large counties with only one weather or air monitor. We do not believe that this exposure misclassification differed by the hazard and reference periods and so likely biased our results towards the null. Our study also lacked the ability to account for differences in temperature due to factors such as the urban heat island because our geographic resolution was limited to the county level.

Like the majority of the earlier studies, our study examined all-cause stillbirth and lacked the ability to differentiate between the diverse causes of stillbirth. Because some stillbirths may be the result of an accident or illness prior to or during delivery, the use of all-cause stillbirth is not the best-case definition for a study of heat exposure or air pollution as a trigger of stillbirth. Unfortunately, we lacked data on the specific causes of the stillbirths, which likely biased the results towards the null.

Our analysis of climactic, region-specific associations yielded interesting results. The highest risk of maternal heat-related stillbirth occurred in the Northwest and the lowest risk occurred in the Southeast. These results are in an opposite direction compared to our observation that the association was stronger in the Southern half of the US as compared to the Northern half. It is possible that this finding is attributable to acclimatization and women in the Southeastern US are more acclimated to heat than women in the Northwestern US, reducing their risk of a heat-related adverse pregnancy event.

Our study was designed to assess the acute impact of heat in the week preceding the birth but other studies have identified other susceptible windows including the four weeks prior to delivery, the second trimester, and the entire pregnancy. It is possible that heat stress acts on maternal fetal health in different ways at different points in the pregnancy. Possible mechanisms by which heat may increase risk of stillbirth include through the triggering of a preterm delivery at a point that is incompatible with extrauterine life, lowering amniotic fluid volume, damaging or degrading the placenta, or causing a placental abruption (Bakkar et al., 2020; Stan et al., 2002; Ha et al., 2018; Prada et al., 1998; Browne et al., 2015; Li et al., 2003; He et al., 2018).

This study adds to the growing consensus about the enhanced vulnerability of pregnant women to heat stress. As oppressively hot days continue to increase in frequency and intensity across the US and globally, heat-health recommendations should always specify that warnings about heat-wave and heat-health safety also apply to expectant women. Obstetricians and other maternal health medical providers should also be aware of this vulnerability, and communicate this risk to patients as well as provide increased monitoring to expectant women delivering in the summer, especially those at high risk of pregnancy complications.

As municipalities work to increase their heat resiliency through climate change adaptation, they should consider reduction in stillbirth and other adverse pregnancy outcomes a potential benefit of their adaptations. Heat reducing strategies like cool roofs and increased green space might reduce the occurrence of heat-related adverse pregnancy outcomes, especially in areas experiencing urban-heat islands.

To the best of our knowledge, this is one of the largest etiological studies of stillbirth in the United States. Our case-only design and sample size of over 42,000 stillborn infants allowed us to examine seasonal differences in risk as well as subpopulations at increased risk. Given the findings of this study and others, further examination of heat-related adverse birth outcomes is necessary. Future studies should assess multiple windows of exposure throughout the pregnancy and improve upon the present work with precise monitoring of maternal temperature exposure, perhaps with wearable thermometers and corresponding questionnaires to capture time-activity information. Our findings about the increased vulnerability of women in the Southern half of the US suggest future studies with improved exposure metrics should include this population.

Table 3.S1. Odds ratios and corresponding 95% confidence intervals for 10-unit increase in 6 meteorological variables analyzed, daily average apparent temperature, daily maximum apparent temperature, daily average air temperature, daily maximum air temperature, daily average relative humidity, daily maximum relative humidity.

	Sample N	Average Apparent Temperature (Fahrenheit)	Maximum Apparent Temperature (Fahrenheit)	Average Air Temperature (Fahrenheit)	Maximum Air Temperature (Fahrenheit)	Average Relative Humidity (%)	Maximum Relative Humidity (%)
All Stillbirths	42,160	1.01 (0.99, 1.02)	0.99 (0.97, 1.01)	0.99 (0.97, 1.01)	0.99 (0.98, 1.01)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season Stillbirths	23,958	1.09 (1.06, 1.13)*	1.09 (1.06, 1.12)*	1.10 (1.07, 1.13)*	1.09 (1.06, 1.12)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Summer Month Stillbirths	12,204	1.19 (1.13, 1.25)*	1.15 (1.10, 1.20)*	1.19 (1.13, 1.25)*	1.15 (1.10, 1.20)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
All Stillbirths							
Northern US	17,451	1.01 (0.99, 1.02)	0.99 (0.96, 1.01)	0.99 (0.96, 1.01)	0.99 (0.96, 1.01)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Southern US	24,709	1.01 (0.98, 1.04)	1.00 (0.98, 1.03)	1.01 (0.98, 1.04)	1.0 0.98, 1.03)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season Stillbirths							
Northern US	9,807	1.07 (1.02, 1.11)*	1.06 (1.02, 1.10)*	1.07 (1.03, 1.11)*	1.06 (1.02, 1.10)*	1.01 (0.98, 1.04)	1.02 (0.99, 1.08)
Southern US	14,136	1.13 (1.08, 1.19)*	1.12 (1.08, 1.17)*	1.13 (1.08, 1.19)*	1.12 (1.07, 1.16)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Summer Month Stillbirths							
Northern US	5,007	1.11 (1.04, 1.19)*	1.08 (1.02, 1.14)*	1.11 (1.04, 1.19)*	1.08 (1.01, 1.14)*	0.99 (0.95, 1.03)	0.99 (0.94, 1.06)
Southern US	7,188	1.31 (1.21, 1.42)*	1.25 (1.17, 1.34)*	1.30 (1.21, 1.41)*	1.24 (1.17, 1.33)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season Stillbirths							
Southeast	4,066	1.05 (0.95, 1.15)	1.06 (0.97, 1.16)	1.05 (0.95, 1.15)	1.06 (0.97, 1.16)	1.02 (0.96, 1.07)	1.00 (0.93, 1.08)
Ohio Valley	2,876	1.05 (0.97, 1.13)	1.04 (0.98, 1.12)	1.05 (0.98, 1.13)	1.04 (0.98, 1.12)	1.02 (0.96, 1.08)	1.02 (0.93, 1.10)
Northeast	5,043	1.07 (1.00, 1.13)*	1.05 (1.00, 1.11)	1.07 (1.01, 1.13)*	1.05 (1.00, 1.11)	1.04 (1.00, 1.08)*	1.08 (1.02, 1.14)*
Upper Midwest	1,251	1.07 (0.97, 1.19)	1.07 (0.97, 1.17)	1.07 (0.97, 1.19)	1.08 (0.98, 1.19)	0.91 (0.84, 0.99)*	0.92 (0.82, 1.04)
Southwest	1,401	1.09 (0.98, 1.22)	1.08 (0.98, 1.19)	1.09 (0.98, 1.22)	1.07 (0.97, 1.17)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
South	2,910	1.14 (1.04, 1.26)*	1.14 (1.04, 1.25)*	1.15 (1.04, 1.27)*	1.14 (1.04, 1.26)*	0.95 (0.90 1.01)	0.93 (0.86, 0.99)*
Northern Rockies	111	1.15 (0.83, 1.62)	1.12 (0.83, 1.52)	1.16 (0.83, 1.63)	1.13 (0.83, 1.53)	0.85 (0.64, 1.14)	0.81 (0.56, 1.17)
West	5,766	1.21 (1.12, 1.30)*	1.15 (1.09, 1.22)*	1.20 (1.12, 1.30)*	1.15 (1.09, 1.22)*	0.95 (0.91, 0.99)*	0.94 (0.89, 0.98)
Northwest	534	1.22 (0.99, 1.50)	1.17 (1.01, 1.35)*	1.22 (0.99, 1.51)	1.17 (1.01, 1.35)*	0.90 (0.79, 1.02)	0.94 (0.77, 1.14)
Warm Season Stillbirths							
Hispanic	6,277	1.13 (1.06, 1.21)*	1.11 (1.05, 1.18)*	1.13 (1.06, 1.20)*	1.12 (1.05, 1.18)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic Black	6,561	1.07 (1.01, 1.13)*	1.06 (1.01, 1.12)*	1.07 (1.00, 1.13)*	1.06 (1.01, 1.12)*	1.03 (0.99, 1.07)	1.03 (0.98, 1.08)
Non-Hispanic White	8,736	1.10 (1.05, 1.15)*	1.09 (1.05, 1.14)*	1.10 (1.05, 1.16)*	1.09 (1.04, 1.14)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic Other	1,353	1.11 (0.97, 1.27)	1.07 (0.96, 1.20)	1.11 (0.96, 1.27)	1.07 (0.96, 1.19)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season Stillbirths							
Hispanic (North)	3,102	1.06 (0.94, 1.19)	1.04 (0.94, 1.15)	1.06 (0.94, 1.19)	1.04 (0.94, 1.15)	1.02 (0.95, 1.10)	1.06 (0.96, 1.18)

Hispanic (South)	3,457	1.17 (1.07, 1.26)*	1.14 (1.07, 1.22)*	1.17 (1.08, 1.26)*	1.15 (1.07, 1.22)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic Black (N)	1,318	1.06 (0.99, 1.14)	1.06 (0.99, 1.13)	1.06 (0.99, 1.14)	1.05 (0.99, 1.13)	1.06 (1.05, 1.12)*	1.10 (1.03, 1.19)*
Non-Hispanic Black (S)	4,955	1.07 (0.98, 1.18)	1.08 (0.99, 1.17)	1.08 (0.98, 1.18)	1.08 (0.99, 1.17)	1.00 (0.95, 1.06)	0.97 (1.91, 1.04)
Non-Hispanic White (N)	4,302	1.07 (1.01, 1.14)	1.07 (1.02, 1.13)*	1.08 (1.01, 1.15)*	1.07 (1.02, 1.13)*	0.97 (0.93, 1.01)	0.98 (0.92, 1.04)
Non-Hispanic White (S)	4,425	1.14 (1.06, 1.24)*	1.12 (1.05, 1.20)*	1.14 (1.06, 1.24)*	1.12 (1.05, 1.20)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Non-Hispanic Other (N)	447	1.09 (0.90, 1.32)	1.06 (0.89, 1.25)	1.09 (0.90, 1.33)	1.05 (0.89, 1.25)	1.12 (0.98, 1.27)	1.13 (0.93, 1.38)
Non-Hispanic Other (S)	906	1.12 (0.93, 1.35)	1.09 (0.94, 1.26)	1.12 (0.93, 1.34)	1.09 (0.94, 1.26)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season Stillbirths							
No or late prenatal care	1,301	1.19 (1.05, 1.36)*	1.15 (1.02, 1.29)*	1.20 (1.05, 1.36)*	1.15 (1.02, 1.29)*	0.99 (0.92, 1.08)	0.99 (0.91, 1.10)
Prenatal began 4-6 month	2,696	1.03 (0.94, 1.12)	1.05 (0.97, 1.13)	1.04 (0.95, 1.13)	1.05 (0.97, 1.13)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Prenatal began 1-3 month	17,765	1.10 (1.06, 1.14)*	1.09 (1.06, 1.12)*	1.10 (1.06, 1.14)*	1.09 (1.06, 1.12)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season Stillbirths							
Hypertensive Disorder	1,708	1.14 (1.02, 1.28)*	1.14 (1.03, 1.26)*	1.15 (1.02, 1.29)*	1.14 (1.03, 1.27)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
None reported	22,250	1.09 (1.06, 1.13)*	1.08 (1.05, 1.11)*	1.09 (1.06, 1.13)*	1.08 (1.05, 1.12)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
Warm Season Stillbirths							
20 – 27 weeks gestation	11,687	1.10 (1.05, 1.15)*	1.09 (1.05, 1.13)*	1.10 (1.05, 1.15)*	1.09 (1.05, 1.13)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
28 – 32 weeks gestation	3,707	1.09 (1.01, 1.18)*	1.09 (1.02, 1.16)*	1.09 (1.01, 1.18)*	1.09 (1.02, 1.16)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
33 – 36 weeks gestation	3,601	1.09 (1.01, 1.18)*	1.07 (0.99, 1.14)	1.09 (1.01, 1.18)*	1.07 (1.00, 1.14)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
37 – 40 weeks gestation	3,921	1.12 (1.04, 1.21)*	1.12 (1.05, 1.20)*	1.13 (1.05, 1.22)*	1.12 (1.05, 1.20)*	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)
> 40 weeks gestation	862	0.99 (0.85, 1.17)	0.99 (0.87, 1.15)	1.00 (0.85, 1.17)	1.00 (0.87, 1.15)	1.01 (0.92, 1.12)	1.03 (0.91, 1.17)

CHAPTER 4. RESIDENTIAL PROXIMITY TO ROADWAYS AND PLACENTAL-ASSOCIATED STILLBIRTHS: A CASE-CONTROL STUDY

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Abstract

We conducted a retrospective case-control study of 1,097 women in Massachusetts and Rhode Island, USA to examine the association between stillbirth related to placental abruption or placental insufficiency and maternal exposure to traffic-related air pollution. We utilized distance to nearest roadway proximity metrics as a proxy for traffic-related air pollution exposure. No meaningful increase in the overall odds of placental-associated stillbirths was observed (adjusted OR: 1.1, 95% CI: 0.5–2.8). However, mothers living within 50 meters of a roadway had a 60% increased odds of experiencing a stillbirth related to placental abruption compared to mothers living greater than 200 meters away. This suggestive finding was imprecise due to the small case number in the highest exposure category (95% CI: 0.6–4.0). Future studies of placental abruption with more precise exposure assessments are warranted.

Introduction

Globally an estimated 3 million stillbirths occur each year, and while promising reductions have been achieved in maternal and early childhood mortality, the rate of stillbirth has remained constant in recent years (Goldenberg et al., 2011; Lawn et al., 2016; WHO, 2018). In the United States 1 of every 160 births is stillborn (Siddika et al., 2016; Cousens et al., 2011). Healthcare costs of stillbirth include those incurred during delivery and in subsequent pregnancies, as pregnant women with a history of stillbirth require careful prenatal monitoring (Ogwulu et al., 2015). Studies have found that mothers who experience a stillbirth have adverse psychosocial consequences including depression, anxiety, shame, guilt, post-traumatic stress disorder, and suicidal ideation (Ogwulu et al., 2015; Barr et al., 2008; Hughes et al., 2003; Turton et al., 2001).

There is no universal definition of stillbirth but the most commonly used definition is “the death of an infant occurring after 20 weeks of gestation either prior to or during the delivery (CDC, 2016). Causes of stillbirth are unknown in about half of all pregnancies, and in cases with known etiology, the causes are diverse and include placental abruption, placental insufficiency, congenital anomalies, umbilical cord anomalies and accidents, asphyxia due to obstructed labor, maternal accidents, and maternal diseases such as diabetes, hypertension, and infection (Goldenberg et al., 2011; Yakoob et al., 2010). The diverse reasons for the occurrence of a stillbirth make “all cause stillbirth” a problematic definition for epidemiologic research since this broad categorization introduces substantial outcome misclassification.

Few risk factors for stillbirth have been identified, including maternal smoking, advanced age, obesity, inadequate prenatal care, and low education (Goldenberg et al., 2011; Yakoob et al., 2010; Fretts et al., 2005). Like many other health outcomes in the United States, racial disparities exist as Non-Hispanic black women are two times more likely to experience a stillbirth compared to Non-Hispanic white women (Gregory et al., 2014).

Because the placenta is responsible for the exchange of oxygen and nutrients from mother to baby optimal placental vascularization is critically important for the maintenance of a healthy pregnancy. Potential mechanisms by which air pollution might impact placental function and thereby lead to placental abruption or insufficiency include systemic inflammation and oxidative stress, endothelial dysfunction, decrease in DNA methylation, systemic changes in hematocrit and blood viscosity, and disturbances to hemodynamic responses (Wesselink et al., 2017; Hettfleish et al., 2017; Kannan et al., 2006; de Melo et al., 2014; Slama et al., 2008; Veras et al., 2008).

While research suggests that risk of stillbirth is increased by maternal exposure to air pollution, this literature is limited because of its failure to differentiate among the diverse causes of stillbirth. In the present study we aimed to address this limitation by restricting our analyses to placental-associated stillbirths, that is, a stillbirth in which the physician-diagnosed cause was placental abruption or placental insufficiency (Siddika et al., 2016; Glinianaia et al., 2004; Faiz et al., 2012; Faiz et al., 2013; Zhu et al., 2015). Traffic-related air pollution is comprised of a number of air pollutants including carbon monoxide, carbon dioxide, hydrocarbons, nitrogen oxides, particulate matter, mobile-source air toxics (such as benzene, formaldehyde, acetaldehyde, 1,3,-butadiene, and lead), and secondary-by-products such as ozone and nitrates (HEI, 2010). Other health studies using residential proximity to roadway metrics as a proxy for air pollution exposure have found roadway proximity to be associated with increased risk of cardiovascular disease mortality, myocardial infarction, and ischemic stroke (Rodrigues et al., 2017; Hart et al., 2013; Kulick et al., 2018). While technological advancements in cleaner motor vehicle fuels have reduced some contaminants, traffic-related air pollution remains a problem in the United States and around the world as projections estimate that the motor vehicle fleet will continue to grow (Brookings Institution, 2017). This, coupled with increases in global urbanization, means that more people will live in close proximity to major roadways in the years to come and so the possible impact of prenatal exposure on stillbirth is an important research topic.

The present retrospective case-control study examined the association between maternal exposure to traffic-related air pollution and placental-associated stillbirths in Massachusetts and Rhode Island from 1968–1995 using residential proximity to major roadways as a proxy air pollution exposure measure.

Materials and Methods

Selection of study population

The current analysis utilized data collected as part of the Boston University Children's Health Study, a retrospective case-control study of birth defects and stillbirths and prenatal exposure to tetrachloroethylene (PCE)-contaminated drinking water. The study includes births (n=1,097) to women who resided in 24 Massachusetts and Rhode Island towns with a history of PCE contaminated drinking water from the use of vinyl-lined drinking water pipes in public water systems. The study population has been previously described in detail (Aschengrau et al., 2008; Aschengrau et al., 2009; Aschengrau et al., 2011). The study towns were predominantly suburban communities.

Cases were ascertained by manual review of all fetal death records from the 24 study towns from January 1, 1968 - December 31, 1995. Stillbirth cases were restricted to those whose physician-diagnosed cause of death was "placental abruption" or "placental insufficiency." Requirements for fetal death certificates differ slightly in Massachusetts and Rhode Island. In Massachusetts a fetal death certificate is issued for a stillbirth at least 20 weeks' gestation and/or weighing at least 350 grams. In Rhode Island a fetal death certificate is issued for a stillbirth at least 20 weeks' with no consideration of fetal weight. We do not believe that these different definitions impacted the results because birth weight and gestation are closely correlated. A total of 305 placenta-related stillbirths were identified during the ascertainment period; 301 remained after excluding four duplicates.

Live-born controls were randomly selected from the birth records of infants whose mothers resided in the same 24 study towns and gave birth during the same time period as the case mothers. The random selection process utilized frequency matching by state and delivery year to ensure that the number of controls from each state was proportional to the number of births that occurred each year in that state during the case ascertainment period. Thus, 55% of controls were drawn from Massachusetts and 45% of controls were drawn from Rhode Island. A total of 800 controls were targeted for selection; 794 remained after excluding duplicates.

Data collection from vital records and self-administered questionnaire

We abstracted the fetal death records and live birth certificates and obtained computerized vital records data from the Massachusetts Department of Public Health (MADPH) and the Rhode Island Department of Health (RIDOH) to obtain the following variables for cases and controls: infant's name (if one was given), date of birth and gestational age; maternal and paternal names; maternal residential address at time of delivery; maternal and paternal age; and maternal race, education level, pregnancy history, date of last menstrual period, and prenatal care information. The study was approved by the Institutional Review Boards of Boston University Medical Center, the Massachusetts Department of Public Health and the Rhode Island Department of Health (IRB #: H-31740, approved on December 20, 2012).

The identifying information from the vital records was used to trace the case and control mothers using internet-based sources and public records. During this process, we found that 18% of case mothers and 7% of control mothers were deceased. We successfully located 72% of the living case mothers and 88% of the living control mothers and mailed them a self-administered questionnaire to ascertain information on potential confounding variables unavailable in vital records. Thirty-five percent of case mothers and 32% of control mothers returned their self-administered questionnaire after multiple reminders (Aschengrau et al., 2018).

Geocoding maternal residential address at delivery

Maternal residential address at delivery as indicated on the fetal death record or live birth certificate was geocoded to latitude and longitude using ArcGIS 10.0 (ESRI, Redlands, CA). The geocoding process assigned each address to a land parcel. If an address could not be assigned to a land parcel then it was geocoded to the nearest parcel by street number. If a street number was not available (N = 6) then the address was geocoded to the middle of the street (if the street was less than or equal to 0.5 miles) or to the intersection of the address with the nearest cross-street (if the street was greater than 0.5 miles). We were able to successfully geocode 98.5% of maternal residential addresses. Study staff conducting the geocoding were blinded to both the exposure status and case/control status of the mother (Aschengrau et al., 2018).

Assessing traffic-related air pollution exposure

As previously mentioned, exposure to traffic-related air pollution was defined by the proxy measure distance to nearest roadway. We obtained road data for the entire study region from the 1990 US Census Topologically Integrated Geographic Encoding and Referencing System (TIGER) files, classified as: A1 (primary highways with limited access i.e. interstate highways), A2 (primary roads without limited access i.e. highways connecting cities and towns), and A3 (smaller secondary roads connecting cities and towns). We corrected road locations in the Massachusetts and Rhode Island towns by comparing to assessor's land parcel maps for the study towns. After comparing the changes in TIGER line files over the study period and finding insignificant changes for these cities and towns we proceeded to use the 1990 US TIGER line files. We account for changes in population density throughout the study period by adjusting for year of delivery in our final adjusted model.

Using ArcGIS 10.0 (ESRI, Redlands, CA) we calculated the following exposure metrics based on our previously published work [14]. First, we calculated the shortest Euclidean distance from the maternal residence parcel centroid to the nearest roadway (A1–A3 roads). Second, we calculated the shortest Euclidean distance from the maternal residence to the nearest highway (A1–A2 roads), and the total sum of roadways (A1–A3) that fell within various sized buffers around the residence as a continuous variable in an effort to characterize traffic density in the area around the residence. Buffers included 50 meters, 100 meters, 200 meters, 250 meters, 300 meters, 400 meters, and 500 meters. We also assessed the total sum of highway (A1–A2) that fell within the 100-meter buffer. For our analyses distance to road estimates were categorized as: < 50 meters, 50-199 meters, and >= 200 meters. These categories were based on the distribution of roadway distances in our data as well as cutoffs used in prior studies that are based on the known decrease in deposition of contaminants as distance from roadway increases (Wesselink et al., 2017; Karner et al., 2010).

Statistical Analysis

Descriptive characteristics of cases and controls were compared (Table 4.1). The primary analyses compared odds of stillbirth in the distance to road exposure categories <50 meters and 50–199 meters using ≥ 200 meters as the reference category. Additional analyses included continuous shortest Euclidean distance to roadway, continuous shortest Euclidean distance to highway, quartiles of exposure based on the distribution of shortest Euclidean distance to roadway in our study population, below or above the median for roadway distance, below or above the median for highway distance, and continuous sum of roadway distance in the buffers 100 meters and 500 meters.

The strength of the association between residential proximity to roadway and stillbirth was measured using odds ratios and statistical precision was assessed using corresponding 95% confidence intervals. We examined all placental-associated stillbirths combined and then stillbirths related to placental abruption and stillbirths related to placental insufficiency separately. Multivariable logistic regression was used to estimate odds ratios while controlling for confounding factors. We examined confounders individually and included the confounder in the final adjusted models if it changed the crude odds ratio by greater than 5%. We also controlled for PCE exposure in our adjusted models in three ways: as a binary yes/no exposure variable, an exposure percentile, and an exposure level above 40 ppb, the 1980 remediation level for PCE when the contamination was discovered in 1980. None of these variables had an effect on our point estimates so PCE exposure status was not included in our final adjusted models. The final models included year of delivery (as a continuous measure), maternal residence state at delivery, maternal educational level, and receipt of prenatal care in the first trimester. All of the covariates remaining in the final adjusted model were covariates ascertained from the vital records, with the exception of receipt of prenatal care in the first trimester — ascertained via the maternal questionnaire and imputed for missing data.

For confounders with missing data we utilized multiple imputation methods (PROC MI). Information on missing data is available in Table 4.1. We generated 20 imputed data sets using fully conditional specification (FCS) multiple imputation methods based on 28 variables, including distance to nearest roadway and case/control status. Estimates from the 20 imputed data sets were combined for use in the adjusted analyses. Multiple imputation has been shown to be a valid method for use when covariate data is missing. Conducting analyses with the imputed variables has been shown to be less biased than restricting your analyses to cases and controls with complete data (Stern et al., 2009). All statistical analyses were conducted using SAS 9.4 (SAS Institute, Cary, North Carolina).

Results

After excluding 5 cases and 11 controls with insufficient residential information, 1,097 women were included in the final analysis, including 296 placental-associated stillborn cases (placental abruption n = 195, placental insufficiency n = 98) and 783 live born controls. Mothers of stillborn cases were more likely than mothers of liveborn controls to deliver during the early years (1968-1978) of the ascertainment period (Table 1). There were also some differences among demographic characteristics of case and control mothers (Table 4.1). Case mothers and their male partners were more likely to have completed college compared with controls. Case mothers were also more likely to have had a prior livebirth and to have smoked during their pregnancies compared to control mothers. A higher proportion of case mothers did not receive prenatal care during their first trimester and control mothers were more likely to have consumed alcoholic beverages than case mothers. Missing data on the demographic characteristics may have influenced these comparisons if subjects with missing data had different distributions than those without missing data. However, as described above, multiple imputation methods were used to fill in missing covariate data in the adjusted analyses.

Table 4.1. Selected characteristics of cases (N = 296) and controls (N = 783).

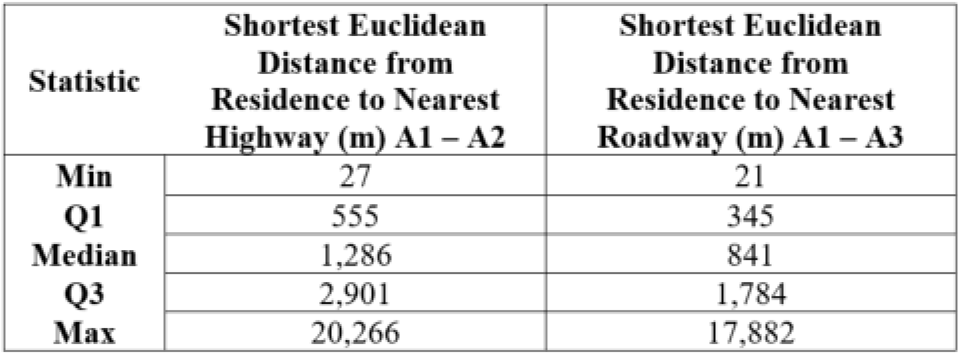
Characteristic	**Cases**	**Controls**
	(N = 296)	**(N = 783)**
	N (%)^a	**N (%)^a**
Year of Delivery		
1968-1978	165 (55.7)	278 (35.5)
1979-1988	79 (26.7)	293 (37.4)
1989-1995	52 (17.6)	212 (27.1)
Mother's residence state at delivery		
Massachusetts	155 (52.4)	442 (56.4)
Rhode Island	141 (47.6)	341 (43.6)
Maternal age at delivery		
Mean (SD)	27.0 (5.9)	27.0 (5.5)
Missing	1	0
Maternal race/ethnicity		
White	153 (91.6)	623 (90.0)
Non-White	14 (8.4)	69 (10.0)
Missing	129	91
Maternal educational level		
< High school	19 (12.8)	96 (14.1)
High school graduate	57 (38.3)	247 (36.2)
Some college	28 (18.8)	175 (25.7)
College graduate	45 (30.2)	164 (24.0)
Missing	147	101
Paternal age at delivery		
Mean (SD)	30.1 (6.8)	29.8 (6.1)
Missing	77	34
Paternal education level		
< High school	23 (16.3)	90 (13.8)
High school graduate	48 (34.0)	221 (33.9)
Some college	19 (13.5)	139 (21.3)
College graduate	51 (36.2)	202 (31.0)
Missing	155	131
Prenatal care in first trimester		
Yes	94 (81.7)	485 (88.2)
No	21 (18.3)	65 (11.8)
Missing	181	233
Maternal prenatal smoking		
Yes	18 (31.0)	70 (23.3)
No	40 (69.0)	230 (76.7)
Missing	238	483

Maternal prenatal alcohol consumption		
Yes	17 (29.8)	72 (35.0)
No	40 (70.2)	134 (65.0)
Missing	239	577
Prior pregnancy loss		
Yes	19 (24.4)	70 (23.3)
No	59 (75.6)	230 (76.7)
Missing	218	483
Prior livebirth		
Yes	105 (62.5)	388 (56.4)
No	63 (37.5)	300 (43.6)
Missing	128	95

[a] Missing data not included in percentages.

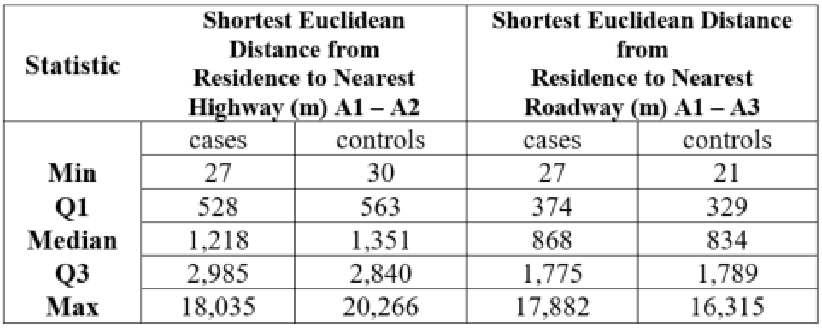
The median distance from residence to major roadway in the study population was 841 meters with a range of 21 meters to over 17,882 meters (Table 4.2). The median distance was similar for cases (868 meters) and controls (834 meters). The median distance from residence to major highway in the study population was 1,286 meters with a range of 27 meters to over 20,000 meters. The median distance to highway was shorter for cases (1,218 meters) compared with controls (1,351 meters) (Table 4.3).

Table 4.2. Distance to road exposure distribution in the study population (N = 1,079)



Statistic	Shortest Euclidean Distance from Residence to Nearest Highway (m) A1 – A2	Shortest Euclidean Distance from Residence to Nearest Roadway (m) A1 – A3
Min	27	21
Q1	555	345
Median	1,286	841
Q3	2,901	1,784
Max	20,266	17,882

Table 4.3. Distance to road exposure distribution by case (N = 296) and control (N = 783) status.



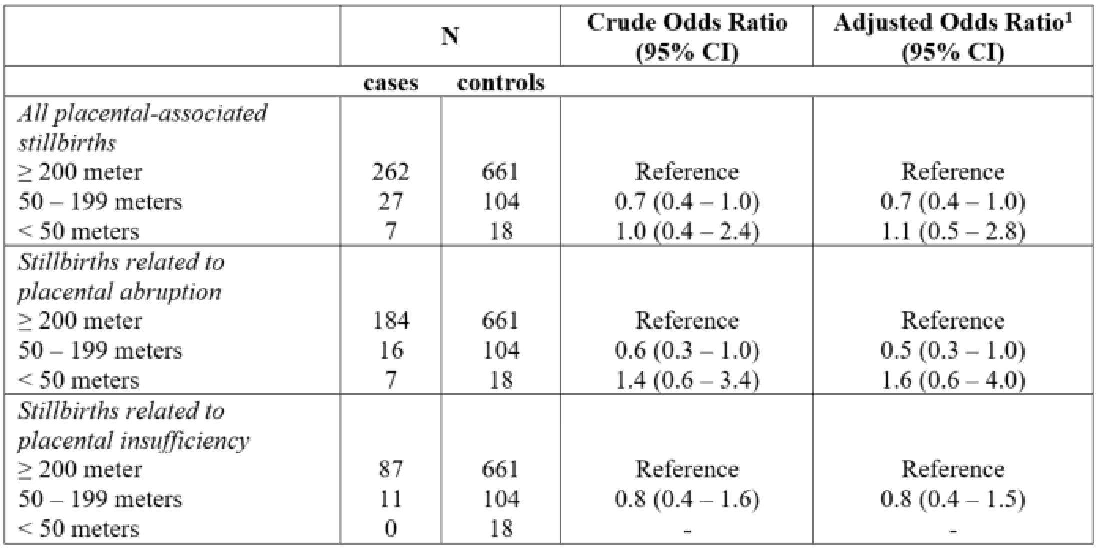
Statistic	Shortest Euclidean Distance from Residence to Nearest Highway (m) A1 – A2		Shortest Euclidean Distance from Residence to Nearest Roadway (m) A1 – A3	
	cases	controls	cases	controls
Min	27	30	27	21
Q1	528	563	374	329
Median	1,218	1,351	868	834
Q3	2,985	2,840	1,775	1,789
Max	18,035	20,266	17,882	16,315

We did not find any meaningful associations when we examined the relationship between roadway distance and the occurrence odds of stillbirth (Table 4.4). When compared to proximity greater than 200 meters away, close proximity to roadways (<50 meters) was not associated with placental-associated stillbirths overall both when we examined distance to roadways (A1-A3) (adjusted OR 1.1, 95% CI: 0.5-2.8) and distance to highways (A1-A2) (adjusted OR: 0.8, 95% CI: 0.2-4.1). In fact, unexpected inverse associations were observed for living 50-199 meters away from A1-A3 roadways and A1-A2 highways (adjusted ORs: 0.7, 95% CI: 0.4-1.0 and 0.7, 95% CI:0.4-1.0, respectively).

When the analysis was limited to stillbirth cases related to placental abruption, the crude and adjusted ORs for distance to nearest roadway <50 meters (A1–A3) were 1.4 (95% CI: 0.6-3.4) and 1.6 (95% CI: 0.6-4.0), respectively. The confidence intervals indicate low statistical precision due to the small case numbers in this exposure category. Inverse associations were again observed for the intermediate distance category (50-199 meters). No cases of stillbirth related to placental insufficiency were observed among mothers who lived <50 meters from a major roadway. All of the analyses examining the association between sum of roadways within various sized buffers around the maternal residence and stillbirth yielded null results (results not shown).

Table 4.4. Frequencies, odds ratios, and corresponding 95% confidence intervals for stillbirth, stillbirth related to placental abruption, and stillbirth related to placental insufficiency.

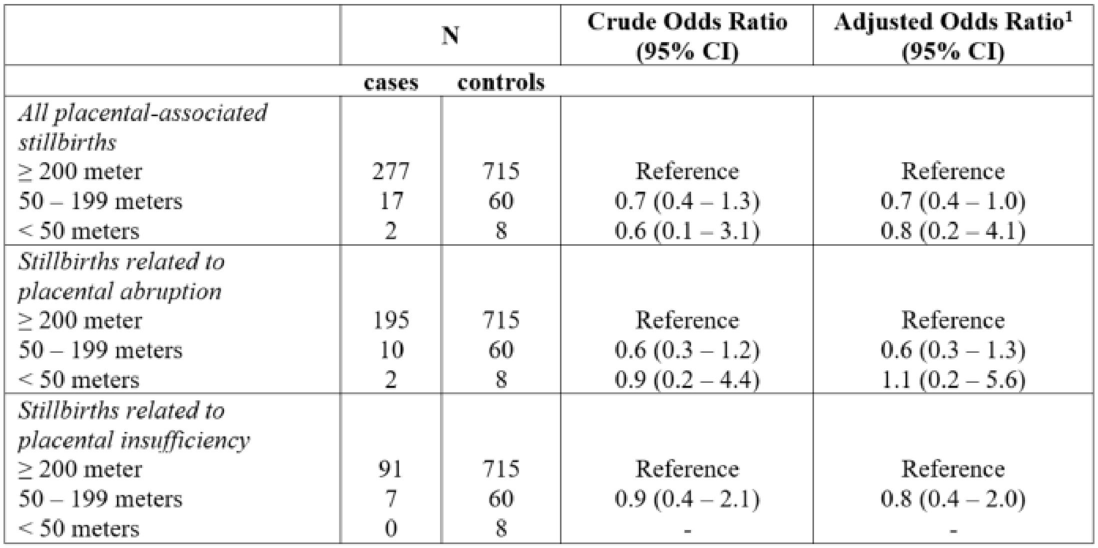
4a. Distance to roadways (A1 – A3)



	N		Crude Odds Ratio (95% CI)	Adjusted Odds Ratio[1] (95% CI)
	cases	**controls**		
All placental-associated stillbirths				
≥ 200 meter	262	661	Reference	Reference
50 – 199 meters	27	104	0.7 (0.4 – 1.0)	0.7 (0.4 – 1.0)
< 50 meters	7	18	1.0 (0.4 – 2.4)	1.1 (0.5 – 2.8)
Stillbirths related to placental abruption				
≥ 200 meter	184	661	Reference	Reference
50 – 199 meters	16	104	0.6 (0.3 – 1.0)	0.5 (0.3 – 1.0)
< 50 meters	7	18	1.4 (0.6 – 3.4)	1.6 (0.6 – 4.0)
Stillbirths related to placental insufficiency				
≥ 200 meter	87	661	Reference	Reference
50 – 199 meters	11	104	0.8 (0.4 – 1.6)	0.8 (0.4 – 1.5)
< 50 meters	0	18	-	-

[1] Adjusted for year of delivery, maternal residence state at delivery, maternal educational level, and receipt of prenatal care in the first trimester.

4b. Distance to highways (A1 – A2)



	N		Crude Odds Ratio (95% CI)	Adjusted Odds Ratio[1] (95% CI)
	cases	**controls**		
All placental-associated stillbirths				
≥ 200 meter	277	715	Reference	Reference
50 – 199 meters	17	60	0.7 (0.4 – 1.3)	0.7 (0.4 – 1.0)
< 50 meters	2	8	0.6 (0.1 – 3.1)	0.8 (0.2 – 4.1)
Stillbirths related to placental abruption				
≥ 200 meter	195	715	Reference	Reference
50 – 199 meters	10	60	0.6 (0.3 – 1.2)	0.6 (0.3 – 1.3)
< 50 meters	2	8	0.9 (0.2 – 4.4)	1.1 (0.2 – 5.6)
Stillbirths related to placental insufficiency				
≥ 200 meter	91	715	Reference	Reference
50 – 199 meters	7	60	0.9 (0.4 – 2.1)	0.8 (0.4 – 2.0)
< 50 meters	0	8	-	-

[1] Adjusted for year of delivery, maternal residence state at delivery, maternal educational level, and receipt of prenatal care in the first trimester.

Discussion

We observed no meaningful associations between residential proximity to major roadways and the overall risk of placental-associated stillbirth. Previous studies of near roadway air pollution have found that concentrations of most traffic-related air pollutants significantly decrease beyond 50 meters from the roadway (Karner et al., 2010). Informed by these findings, we set scientifically-based exposure categories. However, despite our large sample of 1,097 women the distribution of roadway distances in our study was such that few mothers lived within 50 meters of a highway. In fact, the median distance to major highway was 1,283 meters. Exposure to traffic related air pollution would be better estimated by 24-hour monitoring of the constituent contaminants throughout the study region, or by using multivariable modeling techniques such as land use regression. However, due to the historical nature of our study and the lack of data availability we relied on simple road proximity metrics. Road proximity metrics as a proxy for traffic-related air pollution have been utilized in studies of other adverse pregnancy outcomes in which positive associations have been observed. In a Japanese study, Yorifuji et al. observed an increased placenta-birth weight ratio (a biomarker for poorer placental transport function) was associated with proximity to major roads. They also found that proximity to roadway was associated with lower placental weight and lower birth weight (Yorifuji et al., 2012). Utilizing maternal residential history from Vancouver, British Columbia, Brauer et al. found that maternal residence within 50 meters of a highway was associated with a 22% increase in low birth weight (Brauer et al., 2008). Conversely, a large study looking at road networks in North West England found null associations between road proximity and preterm birth, low birth weight, and small for gestational age. However, this study used an exposure cutoff of greater than or less than 200 meters distance from roadway (Hannam et al., 2013).

As previously mentioned, we conducted this analysis in a study whose main purpose was to assess the relationship between prenatal exposure to PCE-contaminated drinking water and birth defects and stillbirths in Massachusetts and Rhode Island. However, when we examined the mother's PCE exposure status in adjusted models, we found it had no effect on the associations under study and so it was not included in the final models.

We observed a moderate increase in the odds of stillbirth related to placental abruption among women who lived within 50 meters of a major roadway compared with women who lived greater than 200 meters away. While this finding was imprecise, the magnitude of the association suggests that further research with a larger number of exposed subjects is warranted. We also observed unexpected inverse associations of living 50-199 meters from roadways and highways (Table 4a and 4b). These associations could result from the small sample size or unmeasured residual confounding.

This finding is in agreement with our earlier published retrospective cohort study that observed increased risks of stillbirth and placental abruption in women living nearby major roadways (risk ratios comparing <100 meters vs >200 meters = 1.75 (95% CI: 0.82–3.76) and 1.71 (95% CI: 0.56–5.23), respectively).[14] Other retrospective cohort studies of stillbirth and air pollution have produced inconsistent results (Faiz et al., 2012;

Faiz et al., 2013; Hwang et al., 2011). This could result from substantial heterogeneity in air pollution exposure metrics. In particular, some studies captured regional air pollutant exposures as a result of industrial activity, while others captured occupational exposures, or localized air pollution from automobile sources. Inconsistencies in the prior literature may also have arisen from the broad stillbirth classification previously discussed.

Our study strengths included a large number of stillbirth cases, our ability to successfully geocode over 98.5% of mothers' addresses and improve our exposure classification by using US Census TIGER codes to categorize road segments and our enhanced outcome classification achieved by restricting our analyses to placental-related stillbirths. Because we reviewed the cause of stillbirth on several thousand fetal death records for a 27-year period across two states, we identified stillbirths due to many diverse causes, including those attributed to a maternal fall or vehicular accident. We did not include such cases in the current study because their inclusion would have likely biased the results towards the null since these cases were unlikely to be related to air pollution exposure.

The study also had several limitations, including non-differential exposure misclassification. This could have arisen from five main sources. First, the historical nature of our study prevented us from utilizing more precise exposure assessment techniques such as 24-hour regional monitoring or land use regression. Second, we assigned mother's exposures based on her residential address and did not include other locations where she may have spent substantial time during her pregnancy such as during commuting or at her workplace. Third, our exposure assessment did not take into account other factors that impact near roadway air quality including traffic congestion, weather, temporal patterns, and season, although we did adjust for year of birth which would account for annual increases in traffic congestion over time. Fourth, there were few women in our study population from Massachusetts and Rhode Island who lived near major roadways. Fifth, non-differential exposure misclassification could have arisen from geocoding the maternal residence at the land parcel level which might introduce inaccuracies depending on where the residence sits on the parcel or even which rooms of the home the mother spends the most of her time. Lastly, there were some differences in the characteristics of cases and controls (Table 1). However, adjusted analyses that accounted for missing data determined that they did not have a meaningful impact on the association. Based on these and our previous findings, further study of the association between placental abruption and air pollution is warranted, preferably in urban areas where more women live in close proximity to roadways.

In conclusion, we did not observe a meaningful increase in the overall odds of placental-associated stillbirth among women living in close proximity to major roadways. However, mothers living within 50 meters of a roadway had a modest increased odds of experiencing a stillbirth related to placental abruption. This suggestive finding was imprecise and likely affected by exposure misclassification. Future studies of air pollution exposure and stillbirth should focus on urban areas, use advanced exposure assessment techniques, and consider the underlying causes of stillbirth in their analysis.

CHAPTER 5. CONCLUSION

The overall objective of the dissertation was to investigate the role of two important environmental factors impacting pregnancy outcomes — maternal heat stress and air pollution. *Chapter 2* identified a 10-degree Fahrenheit increase in average daily apparent temperature in the week preceding delivery was associated with 4% increased odds of preterm delivery in the warm season and a 15% increased odds in the meteorological summer. *Chapter 3* identified a 10-degree Fahrenheit increase in average daily apparent temperature in the week preceding delivery was associated with a 10% increased odds of stillbirth in the warm season and a 19% increased odds in the summer. *Chapter 4* identified an overall null effect of traffic-related air pollution exposure measured by maternal residential proximity to major roadways and placental-associated stillbirth, but suggestive findings of an increase in placental abruption stillbirths for women living within 50 meters of the roadway calls for further study.

Chapter Summaries

Chapter 2. Acute impact of ambient temperature on preterm delivery in the US

The aim of *Chapter 2* was to examine maternal exposure to increased ambient temperature as a potential trigger of spontaneous preterm delivery. We utilized a case-crossover design to examine the impact of a 10-degree increase in average apparent temperature in the week preceding delivery among 968,529 women with preterm deliveries occurring across the contiguous US from January 1, 2000 through December 31, 2004. We observed a statistically significant increased risk of preterm deliveries occurring in the warm season (May 1 to Oct 31) and the meteorological summer (June 1 to August 31), Odds Ratio = 1.04 (95% Confidence Interval 1.03 – 1.05) and Odds Ratio = 1.15 (95% CI 1.14 – 1.16), respectively. The odds were higher in the Southern half of the US compared to Northern half of the US. For the warm season the increased odds was only 1% in the North, compared to 11% in the Southern half of the country. For deliveries occurring in the summer, there was an 8% increased odds of preterm delivery in the Northern half, compared to a 29% increased odds in the Southern half. Looking at summer month deliveries across the entire contiguous US by race/ethnicity Hispanic women emerged most vulnerable with a 22% increased odds associated with a 10-degree increase in average apparent temperature. We also conducted stratified race/ethnicity analyses by region of the country and Non-Hispanic Black women in the Southern states had a 32% increased odds, Hispanic women a 31% increased odds, and Non-Hispanic White women a 27% increased odds.

Chapter 3. Acute impact of ambient temperate on stillbirth in the US

The aim of *Chapter 3* was to examine maternal exposure to increased ambient temperature as a potential trigger of stillbirth. We utilized a case-crossover design to examine the impact of a 10-degree increase in average apparent temperature in the week preceding delivery among 42,160 pregnancies resulting in stillborn loss across the contiguous US from January 1, 2000 through December 31, 2004. We observed a statistically significant increase in the risk of stillbirth in the warm season (May 1 to October 31) and the meteorological summer (June 1 to August 31) Odds Ratio = 1.10 (95% Confidence Interval 1.06 – 1.13) and Odds Ratio = 1.19 (95% CI 1.13 – 1.25), respectively. The risk was higher in Southern states compared to Northern states, and among women who were Hispanic, had inadequate prenatal care, or were diagnosed with a hypertensive condition. The highest odds were observed in the summer deliveries that occurred in the Southern half of the United States (Odds Ratio = 1.31 (95% CI 1.2 – 1.42)). Hispanic women consistently emerged as the most vulnerable, with the highest odds of all racial/ethnic groups for analyses of the warm season across the country (13% increased odds) and in regional stratifications (17% increased odds for Hispanic women residing in the Southern half of the country). The effect of increased heat on women with late or no access to prenatal care (19% increased odds) was almost double that of women who began their prenatal care in the first trimester (9% increased odds). Consistent with observations in previous literature, women with a hypertensive condition were more vulnerable (14% increased odds w/ hypertensive condition compared to 9% increased odds without).

Chapter 4. Residential Proximity to Roadways and Placental-Associated Stillbirth: A Case-Control Study

The aim of *Chapter 4* was to examine the association between maternal residential proximity to major roadways and placental-associated stillbirth. We conducted a retrospective case-control study of 1,097 women in Massachusetts and Rhode Island, USA to examine the association between stillbirth related to placental abruption or placental insufficiency and maternal exposure to traffic-related air pollution, utilizing distance to nearest roadway proximity metrics as a proxy for traffic-related air pollution exposure. We observed no meaningful increase in the overall odds of placental-associated stillbirths (adjusted OR = 1.1 (95% CI 0.5 – 2.8). However, mothers living within 50 meters of a roadway had a 60% increased odds of experiencing a stillbirth related to placental abruption compared to mothers living greater than 200 meters away. This suggestive finding was imprecise due to the small case number in the highest exposure category (95% CI: 0.6-4.0). We believe this was the first study examining the association between maternal residential proximity to major roadways and stillbirth and that further study of air pollution and stillbirth is warranted.

Limitations

The following section examines the overall limitations of this work. More detailed limitations can be found in the discussion sections of the individual chapters. Because of their methodological similarities *Chapters 2* and *3* share a lot of strengths and limitations. Our utilization of US birth records and fetal death records gave us substantial sample size. This allowed us to look at the relationship between heat and adverse pregnancy outcomes across the climactically diverse region of the United States and also granted us adequate statistical power to stratify the data and examine the vulnerability of subgroups of the population, like racial/ethnic groups, and women with preexisting conditions.

However, the use of birth record data and fetal death record data also introduces significant limitations to these studies. We were limited by the variables reported on the birth record and fetal death record and the completeness and accuracy of these records. Because we utilized publicly-available de-identified datasets we were forced to impute the exact date of delivery for both the preterm deliveries and the stillbirths. This meant that we had to exclude women with missing data on last menstrual period date from the study. Any incorrectness in the estimating of the date of delivery introduced exposure misclassification.

As we previously discussed in *Chapters 2 and 3*, the reliability and validity of the data reported on the birth record and the use of these data in epidemiologic studies has been called into question (Northam et al., 2006; Reichman et al., 2007). Studies have identified that congenital defects are often under reported on the birth record which would suggest that some babies with congenital defects remained in our analytical sample despite our efforts to exclude them (Salemi et al., 2018). In *Chapters 2 and 3,* we lacked key data on maternal factors that are known to be related to adverse pregnancy outcomes including socioeconomic status, maternal nutritional status, and family history of adverse pregnancy events. We also lacked data on maternal variables that could modify the impact of heat stress on pregnancy including socioeconomic status, occupation, air conditioning access and other housing characteristics, daily activities, and sleeping patterns.

In *Chapters 2 and 3,* exposure misclassification arose from the use of monitoring stations to apply meteorological data to the maternal residence county — especially in large counties with only one monitor. This exposure misclassification is not likely to differ by the hazard and reference periods and so likely biased our results towards the null. Lastly, because our geographic resolution was at the county level, we are unable to take into account differences in temperature across small geographic areas such as urban heat islands. Additionally, our geographic resolution at the county level may have prevented us from identifying the true impacts of PM2.5 and ozone, especially for larger counties.

In *Chapter 3*, our case definition was all-cause stillbirth, which meant we lacked the ability to differentiate between the diverse causes of stillbirth. Because some stillbirths may be the result of an accident or illness prior to or during delivery, the use of all-cause stillbirth is not the best-case definition for a study of heat exposure or air pollution as a trigger of stillbirth. Unfortunately, we lacked data on the specific causes of the stillbirths, which likely biased the results towards the null.

In contrast, we did know more about the cause of the stillbirths in *Chapter 4* and thus were able to limit the analysis to placental-associated stillbirth, which was a strength of this study. Unlike the earlier two studies, we were not reliant on publicly available data. We ascertained the cases from fetal death records in two states but the records were reviewed by research staff and the primary cause was extracted. Additionally, the mothers in this study were traced and received questionnaires to obtain relevant information. While the questionnaires were only returned for a small number of mothers we then used that data to conduct multiple imputation for missing data.

Chapter 4 had several additional limitations. The historical nature of the study prevented us from using more advanced exposure assessment techniques such as 24-hour regional monitoring or land use regression, the mother's exposures were based on the residential address with no consideration of time-activity patterns, and the exposure assessment did not take into account traffic congestion and other modifiers of traffic-related air pollution. Most importantly, we utilized a previously existing cohort of women and the creation of the cohort was not to assess traffic-related air pollution. The study population was predominantly suburban and only a small number of cases and controls lived close enough to the roadway to experience exposure levels that have been shown to impact health outcomes. Additionally, the region the study population was selected from was predominantly White and consequently the study population lacked the racial/ethnic heterogeneity of the broader US population, limiting the generalizability.

Public Health Impact

This dissertation has significant public health impact. It contributes to the growing consensus that pregnant women are especially vulnerable to heat stress and should be designated as such when extreme heat is forecasted. As oppressively hot days continue to increase in frequency and intensity across the US and globally, heat-health recommendations should always specify that warnings about heat-wave and heat-health safety apply to expecting mothers. Obstetricians and other maternal health medical providers should also be aware of this vulnerability, and communicate the risk to patients as well as provide increased monitoring to mothers delivering in the summer, especially those at high risk of pregnancy complications. In addition to communicating risk and enhancing monitoring, medical providers should also emphasize ways to reduce heat exposure, by staying hydrated and remaining in a cooler indoor environment if possible.

The work of *Chapters 2 and 3* contributed new information on trends in vulnerability to heat stress in pregnant women across the US, highlighting that women in southern states were more vulnerable to the impacts of ambient heat exposure. While this finding is somewhat intuitive because this region is generally hotter, it had not been previously described in the literature.

As municipalities work to increase their heat resiliency through climate change adaptation, they should consider reduction in adverse pregnancy outcomes a potential benefit of these adaptations. Heat reducing strategies like cool roofs and increased green space might reduce the occurrence of heat-related pregnancy complications, especially in areas experiencing urban-heat islands.

The work of *Chapters 3 and 4* explores environmental risk factors of stillbirth. Stillbirth is a chronically understudied problem deserving of public health prioritization that it does not receive. The findings that heat stress could increase the odds of stillbirth by as much as 30% in some areas, underscores the need for further examination of environmental risks and maternal stressors leading to stillbirth.

Chapters 2 and 3 identified racial/ethnic differences in vulnerability to the exposure. Consistently, women who identified as Hispanic and Non-Hispanic Black had higher odds of the adverse event than Non-Hispanic White women. These differences are consistent with the previous literature. It is also notable that *Chapters 2 and 3* were case-only studies so comparison of the maternal characteristics of the women who were selected into the study compared to the general population of expectant mothers is informative. In *Chapter 2,* 25% of preterm delivery mothers were Hispanic and 22% were Non-Hispanic Black. In *Chapter 3*, 26% of the women suffering a stillborn child identified as Hispanic, and 27% as Non-Hispanic Black. The population these women were selected from included birth records on over 20 million births. We examined the racial/ethnic breakdown for comparison and found that only 20% of women identified as Hispanic and 15% as Non-Hispanic Black. These comparisons are reflective of the racial/ethnic disparities in maternal fetal health in the United States (CDC, 2020).

As previously noted in *Chapters 2 and 3*, racial disparities in maternal fetal health indicators, arise not from differences in innate biological risk but instead are a consequence of historic and present, deeply entrenched, systemic racism. This is further complicated by implicit racial bias in the provision of healthcare to Black women and their babies (Burris et al., 2019; Taylor, 2020; NICHQ, 2020).

It would be remiss to not consider the findings of this dissertation in the context of the ongoing COVID-19 crisis. According to the CDC, pregnant women are at 70% increased risk of death from COVID-19 (MMWR, CDC, 2020). Additionally, women suffering from COVID-19 have been found to have a slightly increased risk of preterm delivery compared to healthy mothers (MMWR, CDC, 2020). The same racial/ethnic groups most vulnerable to heat stress in our study are also the groups with the highest rates of COVID-19 (CDC, 2020b). As we approach the second warm season of the COVID-19 pandemic this Spring, and with the substantial delays in vaccine rollout, we should, as a society, make every effort to prioritize the safety and comfort of pregnant mothers.

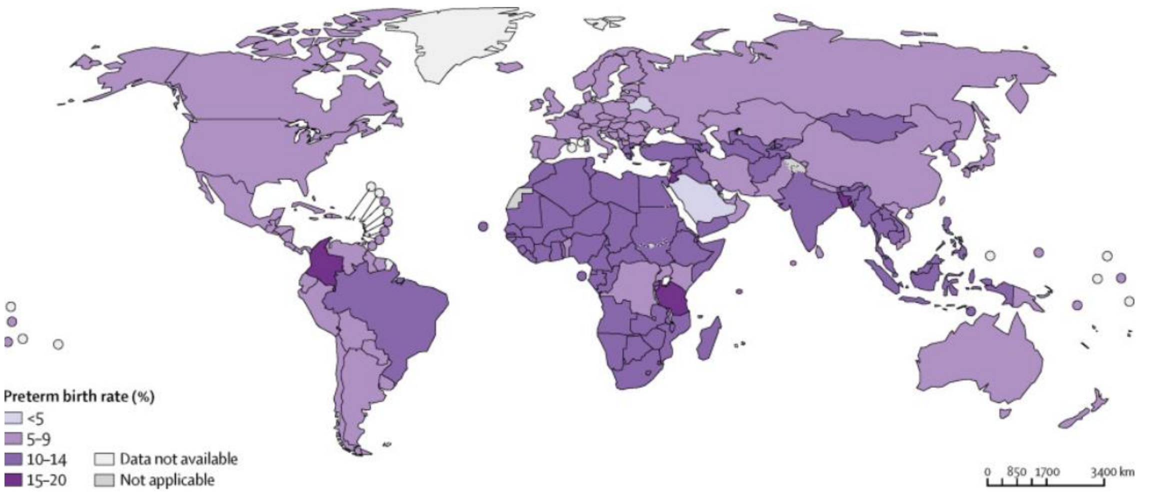
Directions for future research

There are many ways to expand upon the findings of this dissertation, both to address the limitations of this work, and further explore these relationships. In *Chapters 2* and *3,* we examined heat exposure in the week preceding delivery. It is possible that other susceptible windows exist around the time of conception and throughout the course of the pregnancy. Future studies should examine other windows. Many of the limitations of the dissertation could be addressed by enrolling a prospective cohort of pregnant women and better monitoring their ambient temperature exposure, air pollution exposure and activities throughout pregnancy, followed by a detailed assessment of maternal infant health outcomes upon delivery and even in the weeks following the delivery. Detailed information on maternal risk factors and behaviors should be collected, beyond what is available on the birth record. Enhanced exposure assessment might include wearable thermometers, wearable air pollution monitors, or advanced modeling techniques like land use regression or satellite derived measurements.

Chapters 2 and 3 identified regional differences that should be further explored. There are differences in the magnitude of heat exposure in these regions but also in housing characteristics, social and economic demographics, occupations, and other lifestyle factors. Future studies in the US should consider focusing in the South, Southwest, and West where we observed consistently strong associations between heat and adverse pregnancy events.

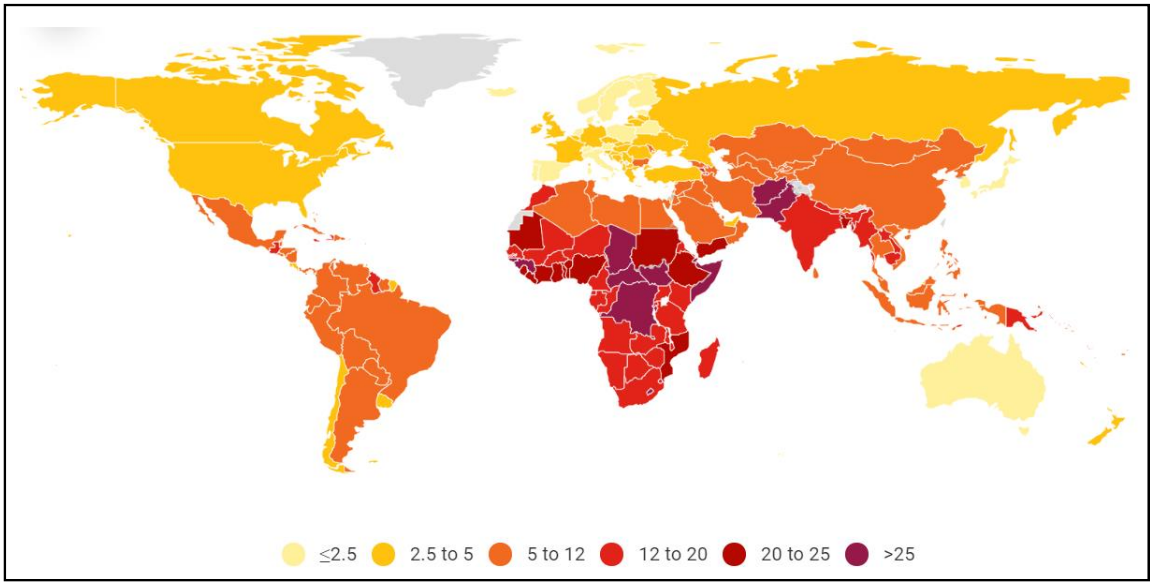
Overall, more studies of environmental risk factors of these pregnancy outcomes are warranted, as the etiologic cause is unknown in 50% of cases. Given the growing burden of climate change related exposures, these should be prioritized. It is essential that future work be conducted through an equity lens, both in and outside of the United States. The maps below show the estimated distribution of preterm delivery and stillbirth worldwide. In the worst impacted countries, almost 1 in 5 babies is born before 37 weeks completed gestation (Chawanpaiboon et al., 2018). For stillbirth, the numbers have been increasingly concentrated in sub-Saharan Africa. The incidence in this region is as high as 28 per 1,000 total births and the global share of stillbirth burden has increased from 25% in 2000 to 40% in 2019 (WHO, 2020). This is particularly concerning given our findings and recent climate projections estimating that the number of people exposed to extreme heat in African cities will increase 20-fold by the end of the century (Guillaume et al., 2019).

Figure 5.1 Global estimates of preterm birth rates by country in 2014
(Chawanpaiboon et al., 2018).



Source: Lancet Glob Health 2019; 7: e37–46 Published Online October 29, 2018
http://dx.doi.org/10.1016/ S2214-109X(18)30451-0

Figure 5.2 Global estimates in stillbirth rate per 1000 births, by country in 2019, (UN/WHO, 2020)



Source: United Nations Inter-agency Group for Child Mortality Estimation (UN IGME) 2020.

Lastly, because consistent associations have been observed between maternal heat Centexposure and adverse pregnancy events, future studies should examine the efficacy of interventions aimed at reducing this exposure. Potential interventions can be applied at both the individual and community level. Interventions aimed at individuals might include energy subsidies to increase access to air conditioning, modified occupational tasks, public-transportation subsidies to ensure pregnant women have access to transportation, and access to mobile technology applications that teach women about the risks of heat and other pregnancy stressors and the importance of maintaining adequate hydration and other healthful behaviors that can benefit themselves and the health of their growing fetus. Community-level interventions should be centered around risk communication to health care providers and first responders, heat resilient strategies and infrastructure like enhanced heat wave warnings, access to community cooling centers, and increased urban green space, cooling roofs, and other climate adaptive infrastructure.

The individual and societal burdens of adverse pregnancy outcomes are profound and public health research and services should continue to address the needs of this sensitive population, especially in the face of climate change.

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