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EXPOSURE TO AMBIENT AIR POLLUTION AND FETAL DEATH IN HARRIS COUNTY, TEXAS

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EXPOSURE TO AMBIENT AIR POLLUTION AND FETAL DEATH IN HARRIS
COUNTY, TEXAS

by

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2018

EXPOSURE TO AMBIENT AIR POLLUTION AND FETAL DEATH
IN HARRIS COUNTY, TEXAS

by

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BS, American University of Beirut, 2006
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Presented to the Faculty of The University of Texas

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for the Degree of

DOCTOR OF PHILOSOPHY

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PREFACE

This doctoral dissertation is presented as three separate manuscripts for publication, formatted according to guidelines of each respective journal and with a distinct bibliography accompanying each manuscript. Chapter I provides an introduction to the project as well as background information. Chapter II is currently under review at the *American Journal of Epidemiology*, Chapter III will be submitted to *Environmental Health Perspectives* and Chapter IV is currently under review at *Environmental Research*. Chapter V provides the conclusions of this investigation. References for the introduction and conclusion to the dissertation are listed following Chapter V.

While completing my doctoral program, I was funded in part as a National Institute for Occupational Safety and Health (NIOSH) Industrial Hygiene trainee at the Southwest Center for Occupational Health (SWCOEH) (#5T42OH008421).

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EXPOSURE TO AMBIENT AIR POLLUTION AND FETAL DEATH
IN HARRIS COUNTY, TEXAS

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The University of Texas
School of Public Health, 2018

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The evidence from studies of maternal ambient air pollutant exposure (including O₃, fine particulate matter (PM_{2.5}) and PM_{2.5} metal constituents) and stillbirth is limited and equivocal. There is also limited evidence of the acute effect of temperature increases in the week preceding delivery and stillbirth. In the first investigation of ambient air pollution, temperature and stillbirth among a large cohort of women in Harris County, Texas, we obtained birth and fetal death records from 2008-2013 and estimated weekly residential levels of apparent temperature and ozone (O₃), fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂) and PM_{2.5} metals from the local monitoring network.

In one study, we used Cox survival models to examine associations between time-varying O₃ exposure and stillbirth with adjustment for PM_{2.5} and NO₂ and further evaluated effect measure modification by race/ethnicity and length of gestation. In another study, we used a case-control design and applied conditional logistic regression to examine associations between PM_{2.5} mass and PM_{2.5} metals by assigning controls (live births) the same truncated exposure period as the gestational length of their matched case. Finally, we used a case-crossover design with symmetric bidirectional sampling of control periods to investigate the association of temperature (lag days 1 through 6) and all-cause stillbirths, as well as

stillbirths caused by placental abruptions, in conditional logistic regression models that adjusted for air pollutant exposure.

We found a 9% (95% confidence interval (CI): 1%, 18%) increased stillbirth risk associated with a 3.61 parts per billion increase in O₃ exposure. The risk was higher among women with pregnancies <37 gestational weeks (hazard ratio (HR) =1.13, 95% CI: 1.04, 1.23) as compared to women with pregnancies of longer gestation (HR=1.05, 95% CI: 0.87, 1.27) and among Hispanic women (HR=1.14, 95% CI: 1.02, 1.27).

We observed null associations between PM_{2.5} metal exposure (modeled as a continuous variable) and stillbirth and slightly increased risks for mothers with exposure to high ($\geq 95^{\text{th}}$ percentile) levels of PM_{2.5} mass. There were also elevated risks (21% to 36%) associated with high exposures ($\geq 95^{\text{th}}$ percentile) to metal constituents of PM_{2.5} (Al, Cr, Cu, Fe, Pb, Mn, Ni, Se, Ti and Zn), with the strongest association observed for Ni (OR = 1.36, 95% confidence interval (CI): 1.03, 1.79).

We found that a 10°F increase in apparent temperature was positively associated with stillbirths caused by placental abruption on lag days 1, 2 and 3. The risk was highest (OR= 1.29, 95% confidence interval (CI): 1.02, 1.63, per 10°F increase) when exposure was examined as a moving average over lag days 1-3. We observed a slightly elevated risk (OR= 1.06, 95% CI: 0.99, 1.13, per 10°F increase) for all-cause stillbirth on lag day 1 and no evidence of an association on subsequent lag days. Our findings contribute to the literature on air pollution and temperature exposures during pregnancy and stillbirth, particularly concerning methods of comparing different risk periods based on gestational length.

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CHAPTER I: AMBIENT AIR POLLUTION AND FETAL DEATH

Introduction and Specific Aims

Exposure to ambient air pollution during pregnancy has been linked to adverse birth outcomes such as low birth weight (LBW), intra-uterine growth restriction (IUGR) and preterm birth (PTB) and these outcomes have been studied extensively (Glinianaia et al. 2004, Maisonet et al. 2004, Stillerman et al. 2008, Vrijheid et al. 2011, Sapkota 2012, Stieb et al. 2012, Zhu et al. 2015, Li et al. 2017, Klepac et al. 2018). In contrast, far fewer studies have examined the association between stillbirth, defined as an intrauterine death that occurs at or after 20 weeks of gestation, and maternal exposure to ambient air pollutants. Such investigations have examined effects due to particulate matter of ≤ 2.5 and ≤ 10 micrometers in aerodynamic diameter (PM_{2.5} and PM₁₀, respectively) (Pereira et al. 1998, Kim et al. 2007, Hwang et al. 2011, Faiz et al. 2012, Faiz et al. 2013, DeFranco et al. 2015, Green et al. 2015, Yang et al. 2018), PM_{2.5} constituents (Ebisu et al. 2018), nitrogen oxides (NO_x) (Landgren 1996, Pereira et al. 1998, Bobak and Leon 1999, Hwang et al. 2011, Faiz et al. 2012, Faiz et al. 2013) sulfur dioxide (SO₂) (Landgren 1996, Bobak and Leon 1999, Faiz et al. 2012, Faiz et al. 2013, Green et al. 2015), carbon monoxide (Pereira et al. 1998, Hwang et al. 2011, Faiz et al. 2012, Faiz et al. 2013, Green et al. 2015) and ozone (O₃) (Pereira et al. 1998, Hwang et al. 2011, Green et al. 2015, Mendola et al. 2017, Yang et al. 2018).

Findings from these studies have been inconsistent, which may be due to differences in study design (that have ranged across a broad spectrum including ecologic studies, case-control studies and cohort studies) and in populations studied, including women in the U.S. (New Jersey, California and Ohio) and elsewhere (Saõ Paulo, Brazil, Czech Republic,

Taiwan and China). Apart from variation in racial and ethnic make-up, these differences in geographic location are important because air quality is influenced by geography and the mixing of local and regional sources of air pollution. Additionally, equivocal findings may have been the result of differences in the geographic scales to assign exposures as well as differences in which periods of pregnancy are of interest (e.g., the entire gestational period, trimesters or month of pregnancy, or much shorter windows at or around the time of the event).

Recent studies also provide evidence of an increased risk of stillbirth with increases in ambient temperature during pregnancy. Investigations of the temperature-stillbirth association have varied in design and have mostly relied on chronic or trimester-specific exposures to temperature fluctuations or extremes (Strand et al. 2012, Arroyo et al. 2016, Li et al. 2018) and the evidence for short-term exposures is also limited (Basu et al. 2016, Ha et al. 2017).

No studies have examined the association between maternal exposure to ambient air pollutants or temperature and stillbirth in Texas. This investigation was conducted in Harris County, Texas, a large urban center characterized by heavy traffic pollution and emissions from industrial complexes (Kleinman et al. 2002, Ryerson et al. 2003). We evaluated the association between maternal exposure to O₃, mass and speciated PM_{2.5} and temperature during gestation and stillbirth. The hypothesis underlining this research question was that pregnant women are more likely to experience a stillbirth event with increased exposure to these pollutants and high temperatures at different windows of exposure. Further, maternal race/ethnicity has been examined as an effect measure modifier in previous studies of air

pollution and adverse birth outcomes. Hence, a secondary objective of the proposed investigation was to examine whether these maternal race/ethnicity modifies the association between exposure to ambient air pollution and stillbirth. The three aims of the study were:

Specific Aim 1. Examine the association between long-term exposures to O₃ and time to a stillbirth event. We estimated weekly maternal residential O₃ concentrations from conception until delivery and used Cox survival models to examine associations between time-varying O₃ exposure and stillbirth. We further evaluated the effect measure modifying potential of maternal race/ethnicity on the association between O₃ exposure and stillbirth and examined whether the risk for stillbirth varied by length of gestation.

Specific Aim 2. Examine the association between short-term exposures to increases in temperature and fetal deaths or stillbirths. We used a case-crossover design and symmetric bidirectional sampling of controls. We applied conditional logistic regression to examine associations between increases of apparent temperature and stillbirth caused by placental abruption, as well as all-cause stillbirth.

Specific Aim 3. Examine the association between exposure to mass and speciated PM_{2.5} and stillbirth. We used a case-control design with truncated exposure periods for controls, as defined by the gestational length of each case, and applied conditional logistic regression to examine associations between exposure to mass PM_{2.5} and 10 PM_{2.5} metal constituents and stillbirth.

Background and Significance

Stillbirth

Stillbirths, defined as spontaneous intrauterine death at 20 weeks of gestation or more, are a significant public health problem in the United States (U.S.). In 2013, a total of 230,595 fetal

deaths at 20 weeks of gestation or more were reported in the U.S. (MacDorman and Gregory 2015). The U.S. fetal mortality rate was at a plateau of 6.05 per 1000 live births and fetal deaths from 2006 until 2012 (Gregory et al. 2014), but has since decreased to 5.96 per 1000 in 2013 (MacDorman and Gregory 2015). Significant disparities in the fetal mortality rate remain among non-Hispanic whites (4.81 per 1000 in 2006 to 4.88 per 1000 in 2013), non-Hispanic blacks (10.73 per 1000 in 2006 to 10.53 per 1000 in 2013) and Hispanic women (5.29 per 1000 in 2006 to 5.22 per 1000 in 2013) (Gregory et al. 2014, MacDorman and Gregory 2015). The overall fetal mortality rate in the state of Texas has been on a similar decline, from 5.52 per 1000 in 2006 to 4.80 per 1000 in 2012 (Texas Department of State Health Services 2015a, 2015c) and slightly increasing to 4.97 per 1000 in 2013 (Texas Department of State Health Services 2015d). However, fetal death rates in Harris County have been relatively higher than the state fetal death rate and closer to the national fetal death rate, ranging from 5.60 per 1000 in 2006 to 5.24 per 1000 in 2012 and 5.84 per 1000 in 2013 (Texas Department of State Health Services 2015a, 2015b, 2015c, 2015d).

Ozone, fine particulate matter and stillbirths

While the literature generally reports suggestive evidence of an association between prenatal exposures to ambient air pollution and stillbirth (Siddika et al. 2016), findings vary by air pollutant and exposure window. In focusing on exposures experienced over the entire pregnancy for ozone (O₃) where results are equivocal, a case-control study of stillbirths conducted in Taiwan reported an odds ratio (OR) of 0.97 (95% CI: 0.91, 1.04) per 10 ppb increase in O₃ exposure (Hwang et al. 2011). Two later cohort studies of women living in

Wuhan, China and California produced similar results (Green et al. 2015, Yang et al. 2018). However, in a recent U.S.-wide study, Mendola *et al.* (2017) reported an elevated risk of stillbirth (relative risk (RR) = 1.39, 95% CI: 1.05, 1.84) with a 7.8 ppb increase in O₃ exposure. Further, results from a multi-pollutant model suggested little evidence of confounding due to other routinely monitored air pollutants (i.e., PM_{2.5}, PM₁₀, SO₂, and NO_x).

The evidence for fine particulate matter (particulate matter of ≤ 2.5 micrometers in aerodynamic diameter; PM_{2.5}) is also equivocal. Five previous studies reported modest associations between gestational exposure to PM_{2.5} and stillbirth (Faiz et al. 2012, DeFranco et al. 2015, Green et al. 2015, Mendola et al. 2017, Ebisu et al. 2018). More recently, Yang et al. (2018) reported a relatively strong association (OR = 1.60, 95% CI: 1.34, 1.91 per a 10 $\mu\text{g}/\text{m}^3$ increase in entire pregnancy PM_{2.5} exposures). Further, the chemical variation of PM_{2.5} constituents varies by study region, which is due to differences in the mix of air pollutant sources across locations (Symanski et al. 2014). In turn, this may explain the inconsistency of findings that have examined associations between PM_{2.5} and adverse birth outcomes (Sun et al. 2016). While several studies have examined associations between chemical constituents of PM_{2.5} and low birth weight and preterm birth (Darrow et al. 2009, Bell et al. 2010, Ebisu and Bell 2012, Basu et al. 2014, Laurent et al. 2014), only one recently published investigation has examined the impact of PM_{2.5} chemical constituents on stillbirth (Ebisu et al. 2018), reporting elevated estimate for exposures to some constituents of PM_{2.5}, including metals such as aluminum (Al), iron (Fe), titanium (Ti) and zinc (Zn).

Several biological mechanisms through which ambient air pollutants may affect fetal survival have been proposed. These include: the trans-placental movement of DNA-damaging pollutants, such as polycyclic aromatic hydrocarbons (PAHs) and PM_{2.5}; oxidative stress on and reduced detoxification capabilities of the fetus; or immune-mediated injuries leading to fetal death (Sram 1999, Faiz et al. 2012, Erickson and Arbour 2014). Further, animal studies report evidence of reduced birth weight (Dell'Omo et al. 1995) and reduced post-natal weight gain (Bignami et al. 1994) in offspring following gestational O₃ exposures. The O₃-stillbirth association is likely mediated by maternal inflammatory responses, which affect fetal growth, and pregnant women are more likely to be exposed than non-pregnant women due to their high alveolar ventilation (Salam et al. 2005).

Finally, evidence from toxicological studies suggests that metal constituents of PM_{2.5} can cause oxidative stress leading to DNA damage and placental inflammation (Wei et al. 2009, Møller et al. 2014). Further, pulmonary inflammation in the mother from PM_{2.5} exposures could lead to reduced oxygen level for the fetus (Sun et al. 2016). These mechanisms have been linked to outcomes such as preterm birth and low birth weight (Ferguson and Chin 2017, Klepac et al. 2018) and could possibly explain the association between PM_{2.5} and stillbirth.

Studies that have examined long-term exposure to air pollutants and stillbirth suffer from shortcomings that include possible misclassification of stillbirth (by combining early and late fetal deaths) (Pedersen 2016). Other limitations relate to assessing exposure periods for the duration of pregnancy that can vary in length from 20 to 37 weeks or longer. Further, the use of survival analysis has been recommended as a means to account for a changing risk

profile for stillbirth across pregnancy, as the highest risks are present in the first trimester and decline thereafter (Strand et al. 2012, Pedersen 2016).

Temperature and stillbirths

Pregnant women are particularly vulnerable to environmental stressors associated with climate change, such as heat exposures (Rylander et al. 2013, Poursafa et al. 2015, Kuehn and McCormick 2017). A growing number of studies have examined the association between ambient temperature and adverse pregnancy outcomes including preterm birth and low birth weight (Strand et al. 2011, Zhang et al. 2017). Recent studies provide evidence of an increased risk of stillbirth associated with increased ambient temperature during pregnancy. These investigations have varied in design and have mostly relied on trimester-specific temperature fluctuations or extremes to characterize exposure (Strand et al. 2012, Arroyo et al. 2016, Li et al. 2018).

There is some evidence suggesting that shorter time periods, for example, up to a week preceding an event, might be more relevant for estimating the effect of temperature exposures on adverse birth outcomes (Basu et al. 2010). Yet, studies investigating the acute effect of elevated ambient temperature on stillbirth are limited; a 2016 case-crossover study in California by Basu et al. (2016) reported a 10.4% (95% confidence interval (CI): 4.4%, 16.8%) increase in stillbirth risk associated with a 10 degrees Fahrenheit (°F) increase in apparent temperature averaged over lag days 2 to 6. Ha et al (2017) temperature also reported a 6% (3%, 9%) increase in risk associated with a 1 degree Celsius (°C) (i.e., 1.8 degrees Fahrenheit; °F) increase in temperature during the week preceding delivery in a case-

crossover analysis among a U.S.-wide cohort. Finally, a case-crossover study in Quebec, Canada, examined daily maximum temperatures and reported a 16% (2%, 33%) increase in risk associated with a 28°C daily maximum temperature relative to 20°C (or 54°F relative to 30°F) on the day before fetal death (Auger et al. 2017).

While causes of stillbirth are varied and may include placental, fetal or umbilical cord abnormalities, maternal medical conditions and obstetric complications (Smith and Fretts 2007, Stillbirth Collaborative Research Network Writing Group 2011), pathologic studies have examined causal or contributory links between placental abruptions and stillbirth (Ptacek et al. 2014). A recent systematic review found that abruption was the most frequently reported risk factor for stillbirth, among other neonatal and perinatal outcomes (Downes et al. 2017). Placental abruption may occur if the integrity of the placenta is compromised by, for example, heat and dehydration, since pregnant women's ability to regulate their body temperature may be compromised given their unique physiological characteristics (Strand et al. 2011). Interestingly, in the single study investigating the association between elevated ambient temperatures and placental abruption to date, He et al. (2018) reported a 7% (0.99%, 1.16%) increase in risk of abruption associated with a weekly maximum of 30 degrees Celsius (°C) compared to 15°C during the week before an abruption event, and the risk was independent of exposures to ambient air pollutants. Further, heat stress may also lead to placental inflammation (Schifano et al. 2013), which is associated with placental abruption and could lead to preterm labor and premature rupture of membranes, which some fetuses might not be able to tolerate (Pinar et al. 2014).

CHAPTER II: TIME-VARYING EXPOSURE TO OZONE AND RISK OF STILLBIRTH IN A NON-ATTAINMENT URBAN REGION

American Journal of Epidemiology

ABSTRACT

This study is the first to use time-to-event analyses to examine stillbirth risk associated with prenatal ozone (O₃) exposure. The study was conducted in a racially and ethnically diverse urban area (Harris County, Texas) with historic non-attainment O₃ levels. We obtained birth and fetal death records from 2008-2013 and estimated weekly maternal residential O₃ concentrations from conception until delivery using inverse distance interpolation from the local monitoring network. We used Cox survival models to examine associations between time-varying O₃ exposure and stillbirth. We examined multi-pollutant models (with particulate matter ≤ 2.5 micrometers in aerodynamic diameter and nitrogen dioxide) and effect measure modification by race/ethnicity and length of gestation. We found a 9% (95% confidence interval (CI): 1%, 18%) increased stillbirth risk associated with a 3.61 parts per billion increase in O₃ exposure. The risk was higher among women with pregnancies <37 gestational weeks (hazard ratio (HR) =1.13, 95% CI: 1.04, 1.23) as compared to women with pregnancies of longer gestation (HR=1.05, 95% CI: 0.87, 1.27) and among Hispanic women (HR=1.14, 95% CI: 1.02, 1.27). Our findings indicate that maternal O₃ exposure is associated with stillbirth risk, and that Hispanic women and women with shorter pregnancies may be at particular risk.

INTRODUCTION

Associations between maternal exposure to ambient air pollution during pregnancy and adverse birth outcomes such as low birth weight (LBW), intra-uterine growth restriction (IUGR) and preterm birth (PTB) have been studied extensively and several systematic reviews report evidence of positive associations (1-9). In contrast, fewer studies have examined the impact of maternal exposure to ambient air pollutants and increased risk of stillbirth, defined as an intrauterine fetal death that occurs at or after 20 weeks of gestation (10-12). Investigations of the associations between poor air quality and stillbirth have examined particulate matter of ≤ 2.5 and ≤ 10 micrometers in aerodynamic diameter ($PM_{2.5}$ and PM_{10} , respectively) (13-19), nitrogen oxides (NO_x) (14, 15, 17, 19-21), sulfur dioxide (SO_2) (14-16, 20, 21), carbon monoxide (CO) (14-17, 19) and ozone (O_3) (16, 17, 19, 22, 23).

Several biological mechanisms through which ambient air pollutants may affect fetal survival have been proposed. These include: the trans-placental movement of DNA-damaging pollutants, such as polycyclic aromatic hydrocarbons (PAHs) and $PM_{2.5}$; oxidative stress on and reduced detoxification capabilities of the fetus; or immune-mediated injuries leading to fetal death (14, 24, 25). While the literature generally reports suggestive evidence of an association between prenatal exposures to ambient air pollution and stillbirth (12), findings vary by air pollutant and exposure window. In focusing on exposures experienced over the entire pregnancy for ozone where results are equivocal, a case-control study of stillbirths conducted in Taiwan reported an odds ratio (OR) of 0.97 (95% CI: 0.91–1.04) per

10 ppb increase in O₃ exposure. Two later cohort studies of women living in Wuhan, China and California produced similar results (16, 23). However, in a recent U.S.-wide study, Mendola et al. reported an elevated risk of stillbirth (relative risk (RR) = 1.39, 95% CI: 1.05-1.84) with a 7.8 ppb increase in O₃ exposure (22). Further, results from a multi-pollutant model suggested little evidence of confounding due to other routinely monitored air pollutants (i.e., PM_{2.5}, PM₁₀, SO₂, and NO_x).

Studies that have examined longer-term exposure to ozone and stillbirth suffer from shortcomings that include possible misclassification of stillbirth (by combining early and late fetal deaths) (26). Other limitations relate to assessing exposure periods for the duration of pregnancy that can vary in length from 20 to 37 weeks or longer. Further, the use of survival analysis has been recommended as a means to account for a changing risk profile for stillbirth across pregnancy, as the highest risks are present in the first trimester and decline thereafter (26, 27).

Given the relatively sparse number of studies and equivocal findings from the investigations that have been carried out, we conducted a retrospective cohort study (26) using time-to-event analyses to examine the risk of stillbirth associated with maternal O₃ exposure in Harris County, Texas, a large urban center. Characterized by heavy traffic pollution and emissions from a large petrochemical complex (28, 29), the county has been designated as a non-attainment area for O₃ since 1992 because it has failed to meet subsequent National Ambient Air Quality Standards (NAAQS) (30), which stipulate that an

area will meet the standard for O₃ if the three-year average of the annual fourth-highest daily maximum 8-hour average at every O₃ monitor is less than or equal to the level of the standard (31). The area has been designated as being in moderate non-attainment for O₃ based on the 2008 8-hour O₃ standard of 0.075 parts per million (ppm) (32) and in marginal non-attainment based on the 2015 8-hour O₃ standard of 0.070 ppm (33). Further, with an ethnically diverse population, a secondary objective was to examine differences in this association among Hispanics, non-Hispanic blacks and non-Hispanic whites. Finally, our third objective was to examine potential differences in susceptibility to O₃ exposure based on the gestational age of the fetus.

METHODS

Study Population

We obtained 394,393 records for singleton live births and fetal deaths occurring between January 1, 2008 and December 31, 2013 for all mothers residing in Harris County, Texas, from the Texas Department of State Health Services (DSHS). The state of Texas defines a stillbirth as an unintended intrauterine fetal death after no less than 20 completed weeks of gestation (34). A fetal death certificate is required if the death involves a fetus weighing 350 grams or more, or with unknown weight, of gestational age of 20 weeks or more (35). This study was approved by University of Texas Health Science Center at Houston (UTHealth) Committee for the Protection of Human Subjects and the Texas DSHS Institutional Review Board.

We abstracted the following maternal and fetal characteristics from birth and fetal death records: maternal age (<20, 20-24, 25-29, 30-34, 35-39 and ≥ 40 years), maternal nativity status and race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other/unknown), maternal education (high school or less, some college, college or beyond), number of prenatal care visits, self-reported smoking (no smoking before or during pregnancy, smoking three months before pregnancy and during pregnancy), pre-pregnancy weight and height from which we computed body mass index (BMI)(weight (kg)/height (m²); classified as <18.5, 18.5 to 24.9, 25.0 to 29.9, 30.0 to 34.9 and ≥ 35), fetal sex, birth weight (grams), and previous poor pregnancy outcomes.

Additionally, gestational age (completed weeks) was estimated by subtracting the date of the last menstrual period (LMP) from the date of birth (or death). Where the LMP date was missing (n=18,373), we used the clinical estimate of gestational age. In total, there were 1,874 stillbirths and 392,512 livebirths in Harris County over the six-year period. We excluded records with missing gestational age and weight (<1%) as well as those with gestational ages outside the range of 20 to 44 weeks (1.1%). In addition, we excluded birth records with implausible birth weight-gestational age data (<1%) (36) as well as those with conception dates more than 20 weeks before the study period began and less than 44 weeks before the study period ended to avoid fixed cohort bias (7.68%) (37). Following these exclusions, there were 1,599 stillbirths and 356,767 live births remaining for analysis (Figure 1).

Air pollution and temperature data

We obtained validated hourly data for O₃ (reported in parts per billion; ppb), PM_{2.5} (µg/m³), and NO₂ (ppb) from all active Texas Commission on Environmental Quality (TCEQ) monitors in the greater Houston area, comprised of eight counties (i.e., Brazoria, Chambers, Fort Bend, Galveston, Harris, Liberty, Montgomery, and Waller counties). During the study period, from January 2007 to December 2013, there were 49 monitoring stations for O₃, 15 stations for PM_{2.5} and 22 stations for NO₂. All monitors measured pollutants continuously and year round. We excluded one O₃ monitor, two PM_{2.5} monitors and one NO₂ monitor that each had more than 25% missing observations over the study period. We calculated the maximum average eight-hour O₃ concentration within a 24-hour period, and the daily average PM_{2.5} and NO₂ concentrations from each monitoring station. We also obtained data from seven weather stations in the study area on apparent temperature (reported in degrees Fahrenheit), a measure that incorporates overall temperature discomfort and accounts for temperature and humidity, from the National Climactic Data Center (38). We computed daily average apparent temperature for each weather station from January 1, 2007 to December 31, 2013. Because there were little differences (0.15% to 5%) in the mean daily temperatures and standard deviations among the weather stations in the study area, we used data from a single monitoring site to develop exposure metrics for temperature.

We used inverse distance weighting (IDW; $p=2$) (39) of the maximum average eight-hour O₃ concentration or the daily average PM_{2.5} or NO₂ concentrations for the three monitoring stations nearest to the mother's geocoded residential address to assign maternal

exposures for every day of pregnancy from conception until date of delivery or death. We constructed exposure estimates for each pollutant by computing weekly averages until the week of a delivery (or death, for stillbirths). This means that for every woman, we computed an exposure measure of average intensity from conception to the 20th week, from conception to the 21st week, from conception to the 22nd week, and so on, through the last week of her gestation when there was a delivery that resulted in a live birth or stillbirth. We used the same method for apparent temperature.

Statistical Analysis

We considered gestational age when the stillbirth occurred as time-to-event data and examined O₃ exposure as a time-varying covariate in a single-pollutant survival model. Live births were censored at their week of delivery. We computed hazard ratios (HR) and 95% CIs to estimate the risk of stillbirth associated with both a unit increase and an interquartile range (IQR) increase in exposure to O₃. We identified the following variables as risk factors for stillbirth and included them in all adjusted models *a priori*: apparent temperature, maternal age, race/ethnicity, education, smoking, pre-pregnancy BMI and prenatal care utilization. All but apparent temperature were included as fixed covariates. We examined temporal trends as indexed by conception date (natural spline of days in the 6-year study period) but the results did not differ from the main analysis. We further evaluated season of conception, maternal nativity status, fetal sex and previous poor pregnancy outcomes as potential confounders singly by examining whether their inclusion in the *a priori* model resulted in a change in the estimated hazard ratio of more than 10% (40). Finally, we evaluated potential confounding

due to exposure to other ambient air pollutants (i.e., PM_{2.5} and NO₂) in multi-pollutant models. Observations with missing covariate data (n=8125) were excluded in the main models and a complete case analysis was performed.

We explored the potential for effect measure modification due to race/ethnicity using stratified analyses of the fully adjusted models. We also stratified by gestational age groups (gestational age <37 completed weeks versus gestational age > 37 completed weeks). Additionally, we conducted two sensitivity analyses. First, we examined the robustness of the exposure assessment by restricting the study population to women who lived within 10 kilometers (km) of the nearest O₃ monitoring station. Second, because of the different proportions of stillbirths and livebirths missing dates of LMP (25.7% versus 4.6%, respectively), we restricted our analysis to those with available dates of LMP. All statistical analyses were conducted using SAS software (Version 9.4, SAS Institute, Cary, North Carolina) and ArcGIS Desktop (Release 10.4.1., Environmental Systems Research Institute (ESRI), Redlands, California).

RESULTS

The mean length of gestation was 29 ± 6.64 weeks for stillbirths and 39 ± 2.23 weeks for live births. Mean birth weight (SD) was 1,291 grams (g) (1083) for stillbirths and 3,253 g (550) for live births; 82.5% of stillbirths and 9.1% of live births were preterm. Table 1 presents a breakdown of other fetal and maternal characteristics among stillbirths and live births. Approximately half of women who delivered a live or stillborn infant were between

the ages of 20-29 (47% of stillbirths, 52% of live births) and had a less than high school education (62% of stillbirths and 54% of live births).

Table 2 represents selected percentiles of the distribution of estimated mean concentrations of air pollutant exposures during pregnancy. The median (IQR) exposure among stillbirths and live births, respectively, was 37.71 ppb (4.31) and 37.88 ppb (3.61) for O₃, 11.50 µg/m³ (1.44) and 11.55 µg/m³ (0.91) for PM_{2.5} and 9.88 ppb (4.44) and 9.92 ppb (3.25) for NO₂. O₃ exposure was negatively correlated with NO₂ (r= -0.50) and PM_{2.5} was weakly correlated with NO₂ (r= 0.26); there was no correlation between O₃ and PM_{2.5} (r= 0.06). Apparent temperature was weakly correlated with O₃ (r= 0.36) and PM_{2.5} (r= 0.33) and negatively correlated with NO₂ (r= -0.34).

In fully adjusted models, there was a 9% increase in risk of stillbirth per 3.6 ppb IQR increase in O₃ exposure (HR =1.09, 95% CI: 1.01, 1.18) or a 3% increase in risk per unit increase in O₃ exposure (Table 3). This did not appreciably change in the multi-pollutant model (HR =1.09, 95% CI: 1.01, 1.18) that included PM_{2.5} and NO₂ as covariates. Our stratified analyses suggest differences in the association of O₃ with stillbirth based upon both race/ethnicity and gestational age. When stratified by maternal race/ethnicity, the association was stronger among Hispanic women (HR =1.14, 95% CI: 1.02, 1.27 per IQR increase) and weaker among non-Hispanic black (HR =1.04, 95% CI: 0.91, 1.19) or non-Hispanic white (HR =1.07, 95% CI: 0.90, 1.28) women. In addition, the risk of stillbirth increased by 13% per IQR increase among women with pregnancies shorter than 37 weeks (HR =1.13, 95% CI:

1.04, 1.23) versus 5% among longer-term pregnancies (HR =1.05, 95% CI: 0.87, 1.27) (Table 3). In the sensitivity analysis restricted to women who lived within 10 km from the nearest monitoring station, little difference in the association between ozone and stillbirth was observed (adjusted HR=1.09, 95% CI: 1.01, 1.17). There was also little difference in the primary association when the analysis was restricted to records that had LMP estimates of gestation (HR=1.10, 95% CI: 1.01, 1.19).

DISCUSSION

A growing number of studies suggest a positive association between maternal exposure to ambient air pollutants and stillbirth but the evidence for O₃ is limited. In this study, we examined the risk of stillbirth associated with O₃ exposure during pregnancy in a racially and ethnically diverse urban area (Harris County, Texas where Houston is located) with historic non-attainment O₃ levels. Further, we evaluated the association between O₃ and stillbirth using survival analysis, which allowed us to evaluate the same exposure windows at different gestational ages that may result in a stillbirth.

We found a 9% increased risk of stillbirth per 3.6 ppb increase in time-varying average intensity of O₃ exposure; for ease of comparison to previous findings, this represents a HR of 1.28 (95% CI: 1.04, 1.57) per 10 ppb increase in O₃ exposure. Previous studies are mixed; three studies, conducted in Taiwan in 2011 (17), California in 2015 (16) and Wuhan, China in 2018 (23), reported null findings for entire pregnancy exposures. However, our findings confirm the strong associations reported by Mendola et al. in a U.S.-wide study for

exposures over the entire pregnancy (RR = 1.39, 95% CI: 1.05, 1.84 per 7.8 ppb IQR increase) (22). The biological mechanisms underlining the O₃-stillbirth association are not yet well-understood, though animal studies report evidence of reduced birth weight (41) and reduced post-natal weight gain (42) in offspring following gestational O₃ exposures. The O₃-stillbirth association is likely mediated by maternal inflammatory responses, which affect fetal growth, and pregnant women are more likely to be exposed than non-pregnant women due to their high alveolar ventilation (43).

We also found that the risk of stillbirth increased by 13% per IQR increase for women with pregnancies shorter than 37 weeks and by 6% among longer-term pregnancies. Hwang et al. previously reported null estimates for the association with O₃ exposures over the entire pregnancy (OR =1.00, 95% CI: 0.91, 1.09 per 10 ppb among preterm births and OR=0.93, 95% CI: 0.85, 1.03 among term births) (17). Racial and ethnic disparities in the risk of stillbirth are well-documented (44-46) and previous studies have reported that associations between ambient air pollution and adverse birth outcomes are modified by maternal race/ethnicity (47-49). The only previous study to examine race/ethnicity as an effect measure modifier for the O₃-stillbirth association found little evidence in support of this hypothesis (16). In contrast, while we cannot rule out the role of chance, the association between O₃ and stillbirth in our population was considerably higher among Hispanic women (14% increase in risk of stillbirth per IQR increase, which translates to 44% (95% CI: 1.06, 1.96) per 10 ppb), with more modest associations among non-Hispanic black and non-Hispanic white women. In our study, Hispanic women were not exposed to higher

concentrations of O₃ (mean (SD) = 37.65 (2.67) ppb) compared to non-Hispanic black (37.80 (2.77) ppb) and non-Hispanic white women (38.52 (2.76) ppb). Further, while the majority of Hispanic women (58.5%) were foreign-born, there were little differences in risk estimates between this group and Hispanic women born in the U.S. (foreign-born: HR=1.12 (95% CI: 0.96, 1.31) per IQR increase; U.S.-born: HR=1.18 (95% CI: 1.00, 1.39).

A major strength of our study was our use of a survival analysis model with time-varying O₃ exposures that allowed us to account for average intensities of exposure for different exposure periods based on the gestational age of the fetus. In addition, we used a cohort with a large sample size and evaluated a wide array of clinical and sociodemographic characteristics as potential confounders in a racially and ethnically diverse population. This is one of two studies (22) of the O₃-stillbirth association to adjust for maternal smoking. However, we were unable to account for occupational or leisure time exposures, though there is evidence to suggest that adjustment for these factors may not impact the effect estimate (50). Our study location, Harris County, was uniquely suited for studying O₃ exposures given its non-attainment status and the higher density of ambient air monitors (48 monitors in total, over a study area of 1777 square miles) as compared to previous studies (16, 17). Our results are likely generalizable to other U.S.-based populations with similar exposure levels, i.e., counties currently designated as non-attainment areas for either the 2008 (n=160) (32) or 2015 (n=201) (33) 8-hour O₃ standard.

We used inverse distance weighting (IDW) to assign exposures; O₃ exposure estimates derived using this method were found to be highly correlated with those derived through ordinary kriging in a study of a large pregnancy cohort in Mexico City (51). We also accounted for spatial variability by restricting our study sample to women living within 10 km of a monitoring station in our sensitivity analysis but found little difference in the results. Our exposure assessment is limited by the fact that we were unable to account for residential mobility. However, a study by Lupo et al. found the likelihood of misclassification of air pollution exposure due to maternal residential mobility in a Texas population to be small as there were no significant differences in exposure assessment between address at delivery and address at conception (52). To the extent that the proportion of women who moved during pregnancy was similar between mothers with stillbirths and mothers with live births, it is possible our study underestimated the association between O₃ exposure and risk of stillbirth due to non-differential exposure misclassification. This is the first study to account for differences in time-varying O₃ exposures over different gestational lengths between stillbirths and live births and our findings indicate that maternal exposure to O₃ is associated with increased risk of stillbirth, with Hispanic mothers and women with pregnancies of shorter gestational length being at particular risk.

Table 1. Selected Sociodemographic Characteristics and Pregnancy Conditions of Women with Stillbirths or Live Births in Harris County, Texas, 2008—2013.

| Characteristic | Stillbirths (n = 1,599) | | Live Births (N = 356,767) | |
|---------------------------------------------|----------------------------|------|------------------------------|-------|
| | No. of women | (%) | No. of women | (%) |
| Maternal age (years) | | | | |
| <20 | 179 | 11.2 | 38918 | 10.9 |
| 20-24 | 363 | 22.7 | 86520 | 24.3 |
| 25-29 | 390 | 24.4 | 98786 | 27.7 |
| 30-34 | 309 | 19.3 | 83094 | 23.3 |
| 35-39 | 191 | 11.9 | 40155 | 11.3 |
| ≥40 | 68 | 4.3 | 9291 | 2.6 |
| Missing | 99 | 6.2 | 3 | < 0.1 |
| Maternal Race | | | | |
| Non-Hispanic White | 269 | 16.8 | 83143 | 23.3 |
| Non-Hispanic Black | 529 | 33.1 | 63980 | 17.9 |
| Hispanic | 725 | 45.3 | 184117 | 51.6 |
| Other/Unknown | 76 | 4.8 | 25527 | 7.2 |
| Maternal Education | | | | |
| High school or less | 987 | 61.7 | 192599 | 54.0 |
| Some college | 370 | 23.1 | 85703 | 24.0 |
| College or beyond | 224 | 14.0 | 77963 | 21.9 |
| Missing | 18 | 1.1 | 502 | 0.1 |
| Prenatal Care visits | | | | |
| None | 43 | 2.7 | 14730 | 4.1 |
| <10 | 1026 | 64.2 | 191524 | 53.7 |
| ≥10 | 204 | 12.8 | 146545 | 41.1 |
| Missing | 326 | 20.4 | 3968 | 1.1 |
| Smoking | | | | |
| No smoking before or during pregnancy | 1519 | 95.0 | 343662 | 96.3 |
| Smoked 3 months before and during pregnancy | 79 | 4.9 | 13003 | 3.6 |
| Missing | 1 | 0.1 | 102 | < 0.1 |
| Fetal Sex | | | | |
| Male | 855 | 53.5 | 181756 | 51.0 |
| Female | 742 | 46.4 | 175011 | 49.1 |
| Missing | 2 | 0.1 | | |
| Pre-pregnancy BMI (kg/m²) | | | | |
| <18.5 | 36 | 2.3 | 14640 | 4.1 |

| Characteristic | Stillbirths (n = 1,599) | | Live Births (N = 356,767) | |
|-----------------------|------------------------------------|------------|--------------------------------------|------------|
| | No. of women | (%) | No. of women | (%) |
| 18.5 to 24.9 | 491 | 30.7 | 163355 | 45.8 |
| 25.0 to 29.9 | 397 | 24.8 | 94180 | 26.4 |
| 30.0 to 34.9 | 224 | 14.0 | 47306 | 13.3 |
| ≥ 35 | 224 | 14.0 | 33408 | 9.4 |
| Missing | 227 | 14.2 | 3878 | 1.1 |

BMI = body mass index

Table 2. Estimated Average Air Pollutant Exposures Across Pregnancy among Women with Stillbirths or Live Births in Harris County, Texas, 2008—2013.

| | Stillbirths (n= 1,599) | | | | | Live births (n=356,767) | | | | |
|----------------------------------------|------------------------|-----------------------------|-----------------------------|-----------------------------|-------|-------------------------|-----------------------------|-----------------------------|-----------------------------|-------|
| | Min | 25 th Percentile | 50 th Percentile | 75 th Percentile | Max | Min | 25 th Percentile | 50 th Percentile | 75 th Percentile | Max |
| O ₃ (ppb) | 26.33 | 35.69 | 37.71 | 40.00 | 52.50 | 11.00 | 36.09 | 37.88 | 39.70 | 55.47 |
| PM _{2.5} (µg/m ³) | 7.78 | 10.79 | 11.50 | 12.23 | 15.05 | 7.92 | 11.04 | 11.55 | 11.95 | 14.88 |
| NO ₂ (ppb) | 2.19 | 7.57 | 9.88 | 12.01 | 18.47 | 3.77 | 8.37 | 9.92 | 11.62 | 19.77 |
| Apparent temperature (F) | 50.71 | 65.10 | 72.39 | 79.86 | 91.95 | 50.12 | 68.90 | 73.20 | 77.27 | 92.03 |

Table 3. Crude and Adjusted^a Hazard Ratios for the Association between O₃ Exposure and Stillbirth among Women in Harris County, Texas, 2008—2013.

| Pollutant | Crude model | | Adjusted ^a model | | | | | |
|------------------------------------|-------------|------------|-----------------------------|------------|--------------------|------------|-----------------|------------|
| | HR | 95% CI | All deliveries | | Preterm deliveries | | Term deliveries | |
| | HR | 95% CI | HR | 95% CI | HR | 95% CI | HR | 95% CI |
| O ₃ (per unit increase) | 0.99 | 0.98, 1.01 | 1.03 | 1.00, 1.05 | 1.04 | 1.01, 1.06 | 1.01 | 0.96, 1.07 |
| O ₃ (per 3.6 ppb) | 1.00 | 0.95, 1.05 | 1.09 | 1.01, 1.18 | 1.13 | 1.04, 1.23 | 1.05 | 0.87, 1.27 |

HR = hazard ratio; CI = confidence interval

^aAdjusted for apparent temperature, maternal age, race/ethnicity, education, smoking, pre-pregnancy BMI and prenatal care utilization.

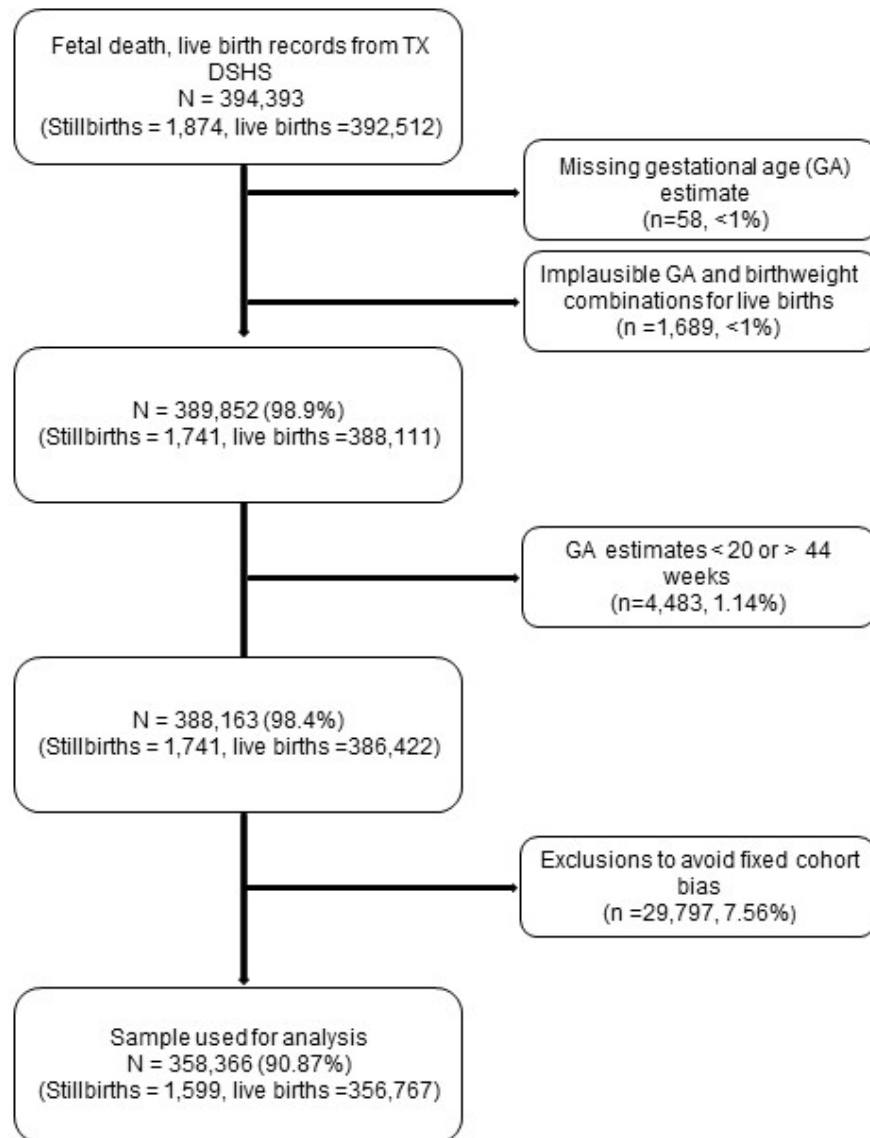


Figure 1. Flowchart detailing exclusions of fetal death and live birth records obtained from Texas DSHS for Harris County, TX, 2008—2013.

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CHAPTER III: Temperature, placental abruption and stillbirth

Environmental Health Perspectives

ABSTRACT

Background: Pregnant women may be especially vulnerable to changes in ambient temperature and warming climates. Recent evidence suggests that temperature increases are associated with placental abruption, a risk factor for stillbirth.

Objectives: In the first study to focus on stillbirths caused by placental abruption, we investigated the effect of acute exposures to apparent temperature on stillbirths in Harris County, Texas, 2008-2013.

Methods: We conducted a case-crossover study to investigate the association of temperature and stillbirth among 1599 women experiencing a stillbirth, 189 caused by placental abruption. We used data from the National Climatic Data Center to estimate maternal exposure to daily average apparent temperature over the days (lag days 1 through 6) preceding the stillbirth event. We employed symmetric bidirectional sampling to select six control periods one to three weeks before and after each event. We applied conditional logistic regression to examine associations between increases of apparent temperature and stillbirths caused by placental abruptions, as well as all-cause stillbirths. Models were adjusted for fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂) and ozone (O₃).

Results: We found that a 10°F increase in apparent temperature was positively associated with stillbirths caused by placental abruption on lag days 1, 2 and 3. The risk was highest (OR= 1.29, 95% confidence interval (CI): 1.02, 1.63, per 10°F increase) when exposure was

examined as a moving average over lag days 1-3. We observed a slightly elevated risk (OR= 1.06, 95% CI: 0.99, 1.13, per 10°F increase) for all-cause stillbirth on lag day 1 and no evidence of an association on subsequent lag days.

Conclusions: We found evidence of an association between apparent temperature increases in the few days preceding an event and risk of stillbirths caused by placental abruption and the risk was independent of maternal ambient air pollutant exposures.

INTRODUCTION

Pregnant women are particularly vulnerable to environmental stressors associated with climate change, such as heat exposures (Rylander et al. 2013, Poursafa et al. 2015, Kuehn and McCormick 2017). A growing number of studies have examined the association between ambient temperature and adverse pregnancy outcomes including preterm birth and low birth weight (Strand et al. 2011, Zhang et al. 2017). Recent studies provide evidence of an increased risk of stillbirth associated with increased ambient temperature during pregnancy. These investigations have varied in design and have mostly relied on trimester-specific temperature fluctuations or extremes to characterize exposure (Strand et al. 2012, Arroyo et al. 2016, Li et al. 2018). There is some evidence suggesting that shorter time periods, for example, up to a week preceding an event, might be more relevant for estimating the effect of temperature exposures on adverse birth outcomes (Basu et al. 2010). Yet, studies investigating the acute effect of elevated ambient temperature on stillbirth are limited; a 2016 case-crossover study in California by Basu et al. (2016) reported a 10.4% (95% confidence interval (CI): 4.4%, 16.8%) increase in stillbirth risk associated with a 10 degrees Fahrenheit

(°F) increase in apparent temperature averaged over lag days 2 to 6. Ha et al. (2017) temperature also reported a 6% (3%, 9%) increase in risk associated with a 1 degree Celsius (°C) (i.e., 1.8 degrees Fahrenheit; °F) increase in temperature during the week preceding delivery in a case-crossover analysis among a U.S.-wide cohort. Finally, a case-crossover study in Quebec, Canada, examined daily maximum temperatures and reported a 16% (2%, 33%) increase in risk associated with a 28°C daily maximum temperature relative to 20°C (or 82.4 °F relative to 68 °F) on the day before intrauterine fetal death(Auger et al. 2017).

The literature also provides suggestive evidence of an association between maternal exposure to ambient air pollutants and stillbirth (Glinianaia et al. 2004, Lacasana et al. 2005, Siddika et al. 2016). Two recent studies evaluating acute exposures found that short-term increases short-term increases in ambient air pollutants, such as fine particulate matter (PM_{2.5}), nitrogen dioxide (NO₂) and Ozone (O₃), immediately before delivery were associated with an increased of stillbirth (Faiz et al. 2013, Mendola et al. 2017).

While causes of stillbirth are varied and may include placental, fetal or umbilical cord abnormalities (Smith and Fretts 2007, Stillbirth Collaborative Research Network Writing Group 2011), maternal medical conditions and obstetric complications, pathologic studies have examined causal or contributory links between placental abruptions and stillbirth (Ptacek et al. 2014). A recent systematic review found that abruption was the most frequently reported risk factor for stillbirth, among other neonatal and perinatal outcomes (Downes et al. 2017). Placental abruption may occur if the integrity of the placenta is compromised by, for

example, heat and dehydration, since pregnant women's ability to regulate their body temperature may be compromised given their unique physiological characteristics (Strand et al. 2011). Interestingly, in the single study investigating the association between elevated ambient temperatures and placental abruption to date, He et al. (2018) reported a 7% (0.99%, 1.16%) increase in risk of abruption associated with a weekly maximum of 30 degrees Celsius ($^{\circ}\text{C}$) compared to 15°C (or 86°F compared to 59°F) during the week before an abruption event, and the risk was independent of exposures to ambient air pollutants. Further, heat stress may also lead to placental inflammation (Schifano et al. 2013), which is associated with placental abruption and could lead to preterm labor and premature rupture of membranes, which some fetuses might not be able to tolerate (Pinar et al. 2014).

Given the limited evidence regarding the ambient temperature-stillbirth association, as well as the putative link between temperature, placental abruption and stillbirth, we designed a case-crossover study with a symmetric bidirectional sampling approach to examine the associations between temperature and stillbirths caused by placental abruptions among women in Harris County, Texas. The underlying hypothesis was that women who experience higher temperatures in the few days before delivery are more likely to have a stillborn delivery than women who do not experience such temperatures. This study was approved by The University of Texas Health Science Center at Houston (UTHealth) Committee for the Protection of Human Subjects and the Texas Department of State Health Services (DSHS) Institutional Review Board.

METHODS

Study Population

Using fetal death records from the Texas DSHS, we abstracted the following information for 1,874 singleton stillborn deliveries occurring between January 1, 2008 and December 31, 2013 for all mothers residing in Harris County, Texas: maternal age (<20, 20-24, 25-29, 30-34, 35-39 and ≥ 40 years), maternal race/ethnicity (non-Hispanic white, non-Hispanic black, Hispanic and other/unknown), and maternal education (high school or less, some college, college or beyond). We also abstracted information on smoking (no smoking before or during pregnancy, smoking three months before and during pregnancy), pre-pregnancy body mass index ((BMI)(weight (kg)/height (m²); classified as <18.5, 18.5 to 24.9, 25.0 to 29.9, 30.0 to 34.9 and ≥ 35), residential address and placental abruption. Following exclusions for missing gestational age and birth weight, for gestational age that was not between 20 and 44 weeks and to avoid fixed cohort bias (Strand et al. 2011), a total of 1,599 stillbirths remained for analysis. We classified the cause of stillbirths as placental abruption if the fetal death certificate indicated placental abruption as either the initiating or contributing cause of death. Of the 1599 cases of stillbirth, 189 (11.82%) were caused by placental abruption.

The average period for delivery following an intrauterine death has been estimated at 48 hours (Gardosi et al. 1998) and the median time at less than 24 hours (Genest et al. 1992). We therefore defined each case period starting on lag day 1 (one day preceding the stillborn delivery) through lag day 6. We used a symmetric bidirectional sampling approach (Maclure

and Mittleman 2000) to assign six control periods per each case period, selecting three control periods on the first, second and third preceding weeks and three control periods over the first, second and third subsequent weeks of the stillbirth event. We also defined control periods as lag days 1 through 6.

Apparent temperature and air pollution data

We obtained meteorological data for January 1, 2007 to December 31, 2013 from the National Climatic Data Center (2017) for seven weather stations from the Houston-Galveston-Brazoria region, which is spread over eight contiguous counties, including Harris County, where the study population comes from. We calculated mean daily apparent temperature (in degrees Celsius; °C) using hourly ambient and dew point temperature and based on methods previously described by Basu et al. (2008); we then converted the data to degrees Fahrenheit (°F). There were little differences in the mean daily temperatures and standard deviations across the seven meteorological stations so the apparent temperature exposure estimates for each day of the pregnancy were developed using a single meteorological station in Harris County. We also obtained validated hourly concentration measurements from all active Texas Commission on Environmental Quality (TCEQ) monitoring stations in the study area for PM_{2.5} (reported in $\mu\text{g}/\text{m}^3$) (n=13), O₃ (ppb) (n=48) and NO₂ (ppb) (n=21) after excluding two PM_{2.5} monitors, one O₃ monitor and one NO₂ monitor that had more than 25% missing observations over the study period. We computed the daily average PM_{2.5} and NO₂ concentrations and the maximum average eight-hour O₃ concentration for each monitoring station. Using data from the three monitoring stations

closest to the mother's geocoded residential address, we assigned exposure estimates for each day of pregnancy from conception until delivery using inverse distance interpolation (Waller and Gotway 2004).

Statistical analysis

We used conditional logistic regression models to compute odds ratios and 95% confidence intervals (CI) representing the association between apparent temperature and stillbirths caused by placental abruptions. In crude models, we examined temperature exposures on each of lag days 1 to 6. We also examined moving exposures, i.e., means of lag days 1 to 2, 1 to 3, 1 to 4, 1 to 5 and 1 to 6. We also ran multi-pollutant models adjusting for PM_{2.5}, NO₂ and O₃. Finally, we ran the same models to examine associations among all-cause stillbirths (n=1599). The case-crossover design automatically adjusts for sociodemographic characteristics or maternal risk factors that are relatively constant, such as race/ethnicity or smoking status, since each case of stillbirth serves as its own matched control (Maclure and Mittleman 2000). In sensitivity analyses, we examined whether removing lag day 1 exposures from moving exposure averages over subsequent lag days would affect the risk estimates, to account for the estimated 48 hour average time between intrauterine death and delivery (Gardosi et al. 1998). In other words, we examined moving exposures averages of lag days 2 to 3, 2 to 4, 2 to 5 and 2 to 6. All statistical analyses were conducted using SAS software (Version 9.4, SAS Institute, Cary, North Carolina).

RESULTS

Selected maternal characteristics are presented in Table 1. The mean (SD) age for all women with stillborn deliveries was 27 (6.6). The majority of women had less than a high school education and approximately half were of Hispanic origin. The distribution of mean daily apparent temperature and daily air pollutant exposures over lag days 1 through 6 for case and control periods of stillbirths caused by placental abruption are presented in Table 2. The mean (SD) apparent temperature for case periods was between 75 (18.1) °F on lag day 4 and 77 (16.9) °F on lag day 1. Among control periods, the mean (SD) apparent temperature was between 74 (18.2) °F on lag day 4 and 75 (17.8) °F on lag day 3. Apparent temperature was moderately negatively correlated with NO₂ ($r = -0.53$) and weakly correlated with PM_{2.5} ($r = 0.29$) and O₃ ($r = 0.13$) concentrations (cumulative of lag days 1 to 6) among stillbirth cases caused by placental abruption. .

In unadjusted analyses among stillbirths caused by placental abruption, we observed 25%, 27% and 11% increased risk of stillbirth associated with a 10 °F increase in apparent temperature on lag day 1 (OR = 1.25, 95% CI: 1.06, 1.47), lag day 2 (OR=1.27, 95% CI: 1.08, 1.50) and lag day 3 (OR=1.11, 95% CI: 0.95, 1.31) respectively, with little evidence of an association on subsequent lag days (Table 3). In a multi-pollutant model that adjusted for PM_{2.5}, NO₂ and O₃, the risk of stillbirth associated with a 10 °F increase in apparent temperature was similar on lag day 1 (OR = 1.20, 95% CI 0.99, 1.45), lag day 2 (OR = 1.24, 95% CI 1.02, 1.51) and lag day 3 (OR = 1.19, 95% CI 0.97, 1.45) (Table 3). Similar results were observed when exposure was operationalized using moving averages (i.e., means of lag

days 1 to 2, 1 to 3, 1 to 4, 1 to 5 and 1 to 6), with the strongest risk associated with a 10 °F increase in mean apparent temperature during lag days 1 to 3 (OR =1.29, 95% CI 1.02, 1.63).

In the sensitivity analysis where lag day 1 was excluded from the moving average for exposure, we observed similar estimates for the risk of stillbirth caused by placental abruption for mean of lag days 2 to 3 (adjusted OR = 1.26, 95% CI: 1.01, 1.56), mean of lag days 2 to 4 (adjusted OR = 1.23, 95% CI: 0.97, 1.55), mean of lag days 2 to 5 (adjusted OR=1.16, 95% CI: 0.91, 1.48) and mean of lag days 2 to 6 (adjusted OR=1.13, 95% CI: 0.87, 1.46). In the analysis of all-cause stillbirths, we found a slightly elevated risk of stillbirth (OR = 1.06, 95% CI: 0.99, 1.13) associated with a 10 °F increase on lag day 1, and null associations on subsequent lag days (data not shown). The results of the sensitivity analysis among all stillbirths did not differ from those of the main analysis (data not shown).

DISCUSSION

This was the first investigation of the temperature-stillbirth association with a focus on stillbirths caused by placental abruption. We found increased risks for stillbirth caused by placental abruption associated with increased mean apparent temperature in the four days preceding stillbirth, with the highest risks (29% and 26%) associated with mean apparent temperatures over lag days 1 to 3 and lag days 1 to 4, respectively. Risk estimates appeared to be independent of ambient air pollution exposures (i.e., PM_{2.5}, NO₂ and O₃). Further, in contrast to two previous investigations using a similar case-crossover design (Basu et al. 2016, Ha et al. 2017), we observed only limited evidence of an association between ambient temperature and all-cause stillbirth. Because previous investigations did

not have information related to the cause of stillbirth, further comparison with our study is not possible.

While no previous studies have examined the effect of temperature on stillbirths caused by placental abruption, our findings are supported by recent evidence from He et al. (2018) on the association between elevated maximum weekly temperatures and the risk for placental abruption at term. While we cannot rule out the role of chance, our findings of an association exclusively among stillbirths caused by placental abruption and not among all-cause stillbirths point to the important role of placental abruption in the association between temperature and stillbirths.

One major strength of this investigation was the use of a case-crossover design, which minimized confounding and provided ample sample size to examine associations among a relatively small proportion of stillbirths caused by placental abruption. Further, a symmetric bidirectional sampling approach for selecting control periods before and after each case period minimized bias from temporal trends in temperature levels (Maclure and Mittleman 2000). The case-crossover design also allowed us to minimize potential exposure misclassification of air pollutants due to residential mobility during pregnancy, since it covered a short period of time (no more than three weeks) before and after the event. However, while it is possible that some women may have still moved during this narrow period, there might not be a significant difference in exposure assessment between address at

delivery and address at conception, as suggested by Lupo et al. (2010) in a study of residential mobility of pregnant women in Texas.

We did not have information on other placental causes of stillbirth reported on the fetal death certificate, which would have enabled us to better understand the link between temperature, placental pathology and stillbirth. Further, there is evidence that fetal death certificates might not accurately report the true cause of death (placental or otherwise) (Greb et al. 1987, Lydon-Rochelle et al. 2005, Duke et al. 2008, Heuser et al. 2010). However, because the assignment of a case or control status in this study was independent of exposure status, selection bias arising from relying on fetal death records is unlikely to have occurred. Another limitation is that while our apparent temperature exposure metric incorporated ambient and dew point temperature, we did not have information on indoor temperature and the use of air conditioning systems in the home, the frequency of which might be unique to the study area. We also lacked information on activity patterns, such as time spent outdoors, although any exposure misclassification this may have introduced would have likely been non-differential and thus, bias estimates toward the null.

To our knowledge, this is the first study in the published literature to examine the effect of acute apparent temperature on stillbirths caused by placental abruptions. While we did not observe an elevated risk for all-cause stillbirths, we found evidence of an increased risk for stillbirths caused by placental abruption associated with temperature increases in the

few days preceding an event, and the risk was independent of maternal exposures to ambient air pollutants.

Table 1. Selected Sociodemographic Characteristics of Women with Stillbirths Caused by Placental Abruptions and All-Cause Stillbirths in Harris County, Texas, 2008—2013.

| Characteristic | Stillbirths caused by placental abruption | All-cause Stillbirths |
|---------------------------------------------|----------------------------------------------|--------------------------|
| | <i>n</i> (%) | <i>n</i> (%) |
| Total | 189 (100) | 1,599 (100) |
| Maternal age (years) | | |
| Mean ± SD | 27.6 ± 6.7 | 27.4 ± 6.6 |
| <20 | 24 (12.7) | 179 (11.2) |
| 20-24 | 45 (23.8) | 363 (22.7) |
| 25-29 | 40 (21.2) | 390 (24.4) |
| 30-34 | 40 (21.2) | 309 (19.3) |
| 35-39 | 26 (13.8) | 191 (11.9) |
| ≥40 | 6 (3.2) | 68 (4.3) |
| Missing | 8 (4.2) | 99 (6.2) |
| Maternal Race | | |
| Non-Hispanic White | 34 (18.0) | 269 (16.8) |
| Non-Hispanic Black | 74 (39.2) | 529 (33.1) |
| Hispanic | 76 (40.2) | 725 (45.3) |
| Other/Unknown | 5 (2.7) | 76 (4.8) |
| Maternal Education | | |
| High school or less | 107 (56.6) | 987 (61.7) |
| Some college | 55 (29.1) | 370 (23.1) |
| College or beyond | 26 (13.8) | 224 (14.0) |
| Missing | 1 (0.5) | 18 (1.1) |
| Prenatal Care visits | | |
| None | 4 (2.1) | 43 (2.7) |
| <10 | 117 (61.9) | 1026 (64.2) |
| ≥10 | 25 (13.2) | 204 (12.8) |
| Missing | 43 (22.8) | 326 (20.4) |
| Smoking | | |
| No smoking before or during pregnancy | 177 (93.7) | 1519 (95.0) |
| Smoked 3 months before and during pregnancy | 12 (6.4) | 79 (4.9) |
| Missing | | 1 (0.06) |
| Pre-pregnancy BMI (kg/m²) | | |

| Characteristic | Stillbirths caused by placental abruption | All-cause Stillbirths |
|----------------|----------------------------------------------|--------------------------|
| | <i>n</i> (%) | <i>n</i> (%) |
| <18.5 | 2 (1.1) | 36 (2.3) |
| 18.5 to 24.9 | 71 (37.6) | 491 (30.7) |
| 25.0 to 29.9 | 37 (19.6) | 397 (24.8) |
| 30.0 to 34.9 | 28 (14.8) | 224 (14.0) |
| ≥ 35 | 25 (13.2) | 224 (14.0) |
| Missing | 26 (13.8) | 227 (14.2) |

Note: BMI, body mass index.

Table 2. Estimated mean daily apparent temperature exposures on lag days 1 through 6 for case and control periods of stillbirths caused by placental abruption, Harris County, Texas, 2008—2013.

| Lag day | Case Periods | | | | | | Control Periods | | | | | |
|---------|--------------|------|-------------|------|------|-------|-----------------|------|-------------|------|------|-------|
| | Mean ± SD | Min | Percentiles | | | Max | Mean ± SD | Min | Percentiles | | | Max |
| | | | 25 | 50 | 75 | | | | 25 | 50 | 75 | |
| 1 | 76.7 ± 16.9 | 34.2 | 63.1 | 79.2 | 91.6 | 99.7 | 74.6 ± 17.8 | 25.7 | 61.3 | 77.0 | 90.3 | 100.6 |
| 2 | 76.8 ± 16.2 | 32.4 | 65.5 | 78.1 | 91.4 | 101.1 | 74.6 ± 17.8 | 25.7 | 60.3 | 77.8 | 90.3 | 101.1 |
| 3 | 75.7 ± 16.8 | 36.5 | 62.4 | 78.6 | 90.0 | 99.3 | 74.7 ± 17.8 | 26.1 | 61.2 | 77.7 | 90.5 | 101.1 |
| 4 | 74.9 ± 18.1 | 32.0 | 60.1 | 80.1 | 89.8 | 99.1 | 74.4 ± 18.2 | 25.7 | 60.3 | 77.4 | 90.9 | 101.1 |
| 5 | 74.6 ± 17.9 | 26.8 | 59.7 | 77.9 | 90.3 | 99.3 | 74.4 ± 18.2 | 25.7 | 60.3 | 77.4 | 90.9 | 101.1 |
| 6 | 74.9 ± 17.3 | 32.9 | 62.8 | 76.6 | 90.3 | 100.6 | 74.4 ± 18.3 | 25.7 | 59.9 | 77.4 | 90.9 | 101.1 |

Table 3. Crude and adjusted^a odds ratios (OR) and 95% confidence intervals (CI) for stillbirths caused by placental abruptions associated with 10°F increases in apparent temperature by lag day(s), Harris County, Texas, 2008—2013.

| Lag day(s) | Crude | Adjusted |
|---------------------|-------------------|-------------------|
| | OR (95% CI) | OR (95% CI) |
| 1 | 1.25 (1.06, 1.47) | 1.20 (0.99, 1.45) |
| 2 | 1.27 (1.08, 1.50) | 1.24 (1.02, 1.51) |
| 3 | 1.11 (0.95, 1.31) | 1.19 (0.97, 1.45) |
| 4 | 1.04 (0.89, 1.23) | 1.07 (0.88, 1.29) |
| 5 | 1.02 (0.87, 1.19) | 0.98 (0.82, 1.17) |
| 6 | 1.06 (0.90, 1.24) | 1.00 (0.83, 1.20) |
| 1 and 2 | 1.23 (1.03, 1.47) | 1.15 (0.93, 1.41) |
| 1, 2 and 3 | 1.30 (1.07, 1.58) | 1.29 (1.02, 1.63) |
| 1, 2, 3 and 4 | 1.27 (1.04, 1.57) | 1.26 (0.99, 1.62) |
| 1, 2, 3, 4 and 5 | 1.25 (1.00, 1.55) | 1.20 (0.93, 1.56) |
| 1, 2, 3, 4, 5 and 6 | 1.25 (0.99, 1.56) | 1.16 (0.89, 1.52) |

^a adjusted for PM_{2.5} (µg/m³), NO₂ (ppb) and O₃ (ppb)

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CHAPTER IV: PM_{2.5} METAL CONSTITUENT EXPOSURE AND STILLBIRTH RISK IN HARRIS COUNTY, TEXAS

Environmental Research

ABSTRACT

There is limited evidence of the role of exposure to chemical constituents of fine particulate matter (PM_{2.5}) in increased risk for stillbirth. We extracted information from birth and fetal death records in Harris County, Texas between 2008 and 2013 and obtained PM_{2.5} metal data from a centrally located air monitoring station. For each case and six linked controls, we estimated maternal exposures to PM_{2.5} mass and metal constituents of PM_{2.5} over the risk period, as defined by the gestational length of each case, and applied conditional logistic regression. We observed null associations when we modeled exposures as continuous variables. We found the risk for stillbirth slightly increased with exposure to high ($\geq 95^{\text{th}}$ percentile, or $\geq 13.68 \mu\text{g}/\text{m}^3$) levels of PM_{2.5} mass. There were also elevated risks (21% to 36%) associated with high exposures ($\geq 95^{\text{th}}$ percentile) to metal constituents of PM_{2.5} (Al, Cr, Cu, Fe, Pb, Mn, Ni, Se, Ti and Zn), compared to low, with the strongest association observed for Ni (OR = 1.36, 95% confidence interval (CI): 1.03, 1.79).

INTRODUCTION

Studies examining the association between maternal exposure to fine particulate matter (aerodynamic diameter $< 2.5 \mu\text{m}$; PM_{2.5}) and stillbirth provide equivocal findings (Faiz et al. 2012, Faiz et al. 2013, DeFranco et al. 2015, Green et al. 2015, Mendola et al. 2017,

Ebisu et al. 2018, Yang et al. 2018) and two recent meta-analyses reported elevated but not statistically significant summary risk estimates (Zhu et al. 2015, Siddika et al. 2016). The chemical variation of PM_{2.5} constituents could vary locally as well as by study region, due to differences in the mix of air pollutant sources across locations (Symanski et al. 2014). In turn, this may explain the inconsistency of findings from investigations of the association between PM_{2.5} and adverse birth outcomes (Sun et al. 2016). Several studies have examined associations between chemical constituents of PM_{2.5} and low birth weight and preterm birth (Darrow et al. 2009, Bell et al. 2010, Ebisu and Bell 2012, Basu et al. 2014, Laurent et al. 2014), yet, to our knowledge, only one recently published investigation has examined the impact of PM_{2.5} chemical constituents on stillbirth (Ebisu et al. 2018). Given the paucity of studies in the literature, we examined the association between metal constituents of PM_{2.5} and stillbirth in Harris County, Texas, which includes Houston, the fourth largest city in the United States (U.S.) with a high density of industrial activity (e.g., petrochemical complexes) and heavily trafficked roadways (Sexton et al. 2007), and where a recent study found evidence of exposure to heavy metals (cadmium (Cd), arsenic (As), Pb, and Ni) among economically disadvantaged pregnant women (Whitworth et al. 2017).

MATERIALS AND METHODS

In a previous retrospective cohort study, we obtained fetal death and live birth records from the Texas Department of State Health Services (DSHS) for all singleton pregnancies in Harris County, Texas from January 2008 to December 2013. We excluded records with missing gestational age and weight, as well as live births with implausible gestational age

and birth weight combinations (Alexander et al. 1996). To avoid fixed cohort bias (Strand et al. 2011), we further limited the study population to women with conception dates between 20 weeks before January 1, 2008 and 44 weeks before December 31, 2013, based on the shortest and longest gestational ages in the study. Following these exclusions, we extracted maternal and fetal characteristics from vital statistics records for 1,599 stillbirths and 324,188 full-term (≥ 37 weeks of gestation) live births. After excluding records with missing data (27% of stillbirths and 2% of live births) on risk factors of interest, we nested a case-control study within the entire cohort by selecting six full-term controls (i.e., full-term live births) per case (i.e., stillbirth at ≥ 20 weeks of gestation). The University of Texas Health Science Center at Houston (UTHealth) Committee for the Protection of Human Subjects and the Texas DSHS Institutional Review Board approved this study.

For each case mother and her six linked controls, we estimated maternal exposures to $PM_{2.5}$ over the risk period, defined by the gestational age of each case. For example, if the gestational period for a case mother was 25 weeks, then the risk period for that case and her linked controls was limited to 25 weeks. We evaluated chemically speciated data (reported as 24-hour averages in $\mu g/m^3$) from three stationary monitors located in Harris County (maintained by the Texas Commission on Environmental Quality) and chose one station that reported no more than 10% of the measurements for all metal constituents below the method detection limit (MDL). We focused our investigation on 10 metals: aluminum (Al), chromium (Cr), copper (Cu), iron (Fe), lead (Pb), manganese (Mn), nickel (Ni), strontium (Sr), titanium (Ti) and zinc (Zn). There were little (5%) missing data over the 6-year study

period. We assigned measurements below the federal MDL (EPA 2018) a value of ½ of the MDL (Hornung and Reed 1990). We also retrieved average daily ambient temperature and dew point temperature data for a meteorological station operating in Harris County (National Climatic Data Center 2017) . As with our exposure assessment for PM_{2.5}, we estimated daily average apparent temperature (reported in degrees Celsius; °C) over the risk period as defined by the gestational age of the cases.

We used conditional logistic regression to examine the association between PM_{2.5} mass and metal constituents of PM_{2.5} and stillbirth. We used continuous (per unit and interquartile range (IQR) increase) and a dichotomized (cut-off point at the 95th percentile) exposure metrics to examine associations between each pollutant and risk for stillbirth. We adjusted for apparent temperature and several maternal risk factors *a priori*, as recorded in birth and fetal death records: maternal age, race/ethnicity, education, smoking, pre-pregnancy body mass index (BMI) (weight (kg)/height (m²)) and number of prenatal care visits (none, < 10 visits, ≥10 visits). All statistical analyses were conducted using SAS software (Version 9.4, SAS Institute, Cary, North Carolina).

RESULTS

Selected maternal and fetal characteristics for cases and controls are presented in Table 1. Over half of all women were of Hispanic origin, had less than a high school education and were between the ages of 20 and 29. Characteristics among cases and controls were mostly similar, though 62% of cases had a BMI ≥25 kg/m² compared to 50% of

controls, and the majority of cases (81%) had fewer than 10 prenatal care visits, compared to 53% of controls. Table 2 provides summary statistics for exposures to PM_{2.5} mass and metal constituents.

| Characteristic | Cases | Controls | Total |
|---------------------------------------------|------------------|-----------------|---------------|
| | (n = 1,172) % | (N = 7032) % | (N=8204) % |
| Maternal age (years) | | | |
| <20 | 10.6 | 11.0 | 11.0 |
| 20-24 | 23.3 | 24.5 | 24.3 |
| 25-29 | 26.9 | 26.7 | 26.7 |
| 30-34 | 20.8 | 24.2 | 23.7 |
| 35-39 | 13.3 | 11.3 | 11.6 |
| ≥40 | 5.1 | 2.3 | 2.7 |
| Maternal Race | | | |
| Non-Hispanic White | 18.3 | 23.4 | 22.7 |
| Non-Hispanic Black | 30.5 | 17.4 | 19.3 |
| Hispanic | 46.0 | 51.6 | 50.8 |
| Other/Unknown | 5.3 | 7.5 | 7.2 |
| Maternal Education | | | |
| High school or less | 55.5 | 54.0 | 54.2 |
| Some college | 27.7 | 23.5 | 24.1 |
| College or beyond | 16.8 | 22.6 | 21.7 |
| Prenatal Care visits | | | |
| None | 2.7 | 3.5 | 3.4 |
| <10 | 81.1 | 53.1 | 57.1 |
| ≥10 | 16.2 | 43.4 | 39.5 |
| Smoking | | | |
| No smoking before or during pregnancy | 94.5 | 96.5 | 96.2 |
| Smoked 3 months before and during pregnancy | 5.5 | 3.5 | 3.8 |
| Pre-pregnancy BMI (kg/m²) | | | |
| <18.5 | 2.6 | 4.6 | 4.3 |
| 18.5 to 24.9 | 35.8 | 45.1 | 43.7 |
| 25.0 to 29.9 | 29.3 | 27.5 | 27.8 |
| 30.0 to 34.9 | 15.7 | 13.8 | 14.0 |
| ≥ 35 | 16.7 | 9.1 | 10.2 |

BMI = body mass index

Table 1. Selected maternal and fetal characteristics of cases and controls in Harris County, Texas, 2008—2013.

| Pollutant ($\mu\text{g}/\text{m}^3$) | Mean (S.D.) | 5th percentil e | 25th percentil e | median | 75th percentil e | 95th percentil e |
|------------------------------------------------------------|------------------------|-------------------------------------------|--------------------------------------------|---------------|--------------------------------------------|--------------------------------------------|
| PM _{2.5} mass | 11.59 (1.13) | 9.92 | 10.88 | 11.55 | 12.19 | 13.68 |
| Al | 0.31 (0.67) | 0.029 | 0.050 | 0.104 | 0.163 | 2.273 |
| Cr | 0.21 (0.62) | 0.001 | 0.001 | 0.001 | 0.002 | 1.995 |
| Cu | 0.26 (0.76) | 0.004 | 0.006 | 0.009 | 0.012 | 2.502 |
| Fe | 0.42 (0.84) | 0.074 | 0.108 | 0.144 | 0.189 | 2.955 |
| Pb | 0.23 (0.69) | 0.002 | 0.003 | 0.004 | 0.005 | 2.314 |
| Mn | 0.21 (0.61) | 0.003 | 0.004 | 0.006 | 0.008 | 1.929 |
| Ni | 0.16 (0.46) | 0.001 | 0.001 | 0.002 | 0.002 | 1.449 |
| Sr | 0.22 (0.63) | 0.001 | 0.002 | 0.002 | 0.003 | 2.139 |
| Ti | 0.24 (0.69) | 0.004 | 0.006 | 0.011 | 0.015 | 2.283 |
| Zn | 0.23 (0.59) | 0.020 | 0.024 | 0.027 | 0.032 | 1.980 |

Table 2. Summary statistics of maternal exposures to pollutants, Harris County, Texas, 2008—2013.

We observed null associations when examining PM_{2.5} exposures as continuous variables. In crude models, we observed a 19% increase in the risk for stillbirth (OR = 1.19, 95% confidence interval (CI): 0.91, 1.55) with high exposure to PM_{2.5} ($\geq 13.68 \mu\text{g}/\text{m}^3$), but the risk was attenuated in a fully adjusted model (OR = 1.05, 95% CI: 0.79, 1.38) (Table 3). We found elevated risks for stillbirths associated with high exposures to Al, Cr, Cu, Fe, Pb, Mn, Sr, Ti and Zn in crude models and the risk increased (21% - 36%) in fully adjusted models, though estimates were imprecise. The strongest association was observed for PM_{2.5}

Ni, where we observed a 36% increase (adjusted OR = 1.36, 95% CI: 1.03, 1.79) in stillbirth risk associated with high exposures ($\geq 1.45 \mu\text{g}/\text{m}^3$).

| Pollutant | Crude Models | | Adjusted Models | |
|------------------------|--------------|------------|-----------------|------------|
| | OR | 95% CI | OR | 95% CI |
| PM _{2.5} mass | 1.19 | 0.91, 1.55 | 1.05 | 0.79, 1.38 |
| Al | 1.16 | 0.89, 1.52 | 1.22 | 0.91, 1.62 |
| Cr | 1.21 | 0.93, 1.58 | 1.27 | 0.96, 1.68 |
| Cu | 1.15 | 0.88, 1.50 | 1.21 | 0.91, 1.61 |
| Fe | 1.17 | 0.90, 1.53 | 1.25 | 0.94, 1.66 |
| Pb | 1.19 | 0.91, 1.56 | 1.24 | 0.93, 1.64 |
| Mn | 1.17 | 0.90, 1.53 | 1.22 | 0.92, 1.62 |
| Ni | 1.28 | 0.99, 1.66 | 1.36 | 1.03, 1.79 |
| Sr | 1.17 | 0.90, 1.54 | 1.22 | 0.92, 1.62 |
| Ti | 1.17 | 0.90, 1.53 | 1.23 | 0.93, 1.63 |
| Zn | 1.23 | 0.94, 1.60 | 1.29 | 0.98, 1.71 |

^aadjusted for age, race, education, number of prenatal care visits, smoking, BMI and apparent temperature

Table 3. Crude and Adjusted^a odds ratios (OR) and 95% confidence intervals (CI) for the associations between maternal exposure to PM_{2.5} and stillbirth, Harris County, Texas, 2008-2013.

DISCUSSION

Among a cohort of pregnant women living in Harris County, Texas, we found little evidence of an association with PM_{2.5} mass, but compelling evidence for metal constituents, notwithstanding some precision in the estimates. Direct comparison of our results with those of previous studies are complicated by differences in categorization of exposure as well as variations in PM composition and sources across the U.S. Five previous studies reported modest associations between gestational exposure to PM_{2.5} and stillbirth (Faiz et al. 2012, DeFranco et al. 2015, Green et al. 2015, Mendola et al. 2017, Ebisu et al. 2018). One of these (DeFranco et al. 2015) utilized an exposure metric similar to ours and reported a 21%

(adjusted OR =1.21, 95% CI: 0.96, 1.53) increased risk for stillbirth associated with exposures at or above 15.67 $\mu\text{g}/\text{m}^3$ over the entire pregnancy. Further, Yang et al. reported a relatively strong association (OR = 1.60, 95% CI: 1.34, 1.91 per a 10 $\mu\text{g}/\text{m}^3$ increase in entire pregnancy $\text{PM}_{2.5}$ exposures) (Yang et al. 2018).

Because the toxicity of $\text{PM}_{2.5}$ depends on its chemical composition, we also evaluated associations between 10 metal constituents and risk for stillbirth. We observed elevated risks with entire pregnancy exposures for several metal constituents of $\text{PM}_{2.5}$ (Al, Cr, Cu, Fe, Pb, Mn, Ni, Sr, Ti and Zn). Ebisu et al. reported elevated risks for stillbirth associated with exposures to Fe (OR=1.11, 95% CI: 1.06, 1.17 per 0.015 $\mu\text{g}/\text{m}^3$ IQR increase) and Ti (OR=1.10, 95% CI: 1.04, 1.17 per 0.012 $\mu\text{g}/\text{m}^3$ IQR increase) (Ebisu et al. 2018). Whereas our estimated odds ratio for Ni was 1.36, they found no association between Ni exposure and stillbirth. There is likely some degree of heterogeneity in PM metal profiles between the two study areas; their sources, concentrations and compositional percentages are likely different. The mean ambient air concentrations observed in our study were several orders of magnitude higher for these metal constituents, though we observed lower IQRs for all except Al. For example, while the mean (SD) ambient concentration level for Ni in our study was 0.16 (0.46), Ebisu et al. reported a mean (SD) Ni concentration of 0.0029 (0.0023).

The biological pathways through which specific constituents of $\text{PM}_{2.5}$ may impact stillbirth are unclear. Evidence from toxicological studies suggests that metal constituents of $\text{PM}_{2.5}$ can cause oxidative stress leading to DNA damage and placental inflammation (Wei et

al. 2009, Møller et al. 2014). Further, pulmonary inflammation in the mother from PM_{2.5} exposures could lead to reduced oxygen level for the fetus (Sun et al. 2016). These mechanisms have been linked to outcomes such as preterm birth and low birth weight (Ferguson and Chin 2017, Klepac et al. 2018) and could possibly explain the association between PM_{2.5} and stillbirth.

One strength of our study is its location in a large urban area of the U.S. that has a high density of industries and heavily trafficked roadways with documented poor air quality (Sexton et al. 2006, Sexton et al. 2007). Another strength of the study is ample sample size from a large cohort of fetal deaths and live births. Additionally, we used a truncated risk period to assess exposure of controls that approximates the risk period of linked cases, which allowed us to account for the same potential for exposure during pregnancy between cases and controls. As is common to many air pollution and registry-based epidemiologic studies, we could not account for time-activity patterns, such as time spent outdoors, or behavioral risk factors, such as alcohol use during pregnancy. While the former might introduce non-differential exposure misclassification, adjusting for behavioral risk factors might not impact effect estimates, as suggested by Ritz and Wilhelm (2008). Second, while there is growing interest in identifying the putative role of specific PM chemical constituents in exacerbating health risks, routine data of speciated measurements of PM_{2.5} in the US remain limited. Despite Harris County being one of the most monitored areas in the U.S., with an extensive air monitoring network of 15 active PM_{2.5} monitors during the study period, speciated PM_{2.5} data were only available from a single monitor. While based on a centrally located monitor in

Harris County, we recognize that our exposure assessment did not capture the spatial variability in outdoor air levels of PM_{2.5} constituents (Darrow et al. 2011, Ebisu et al. 2014), potentially introducing exposure misclassification, although the errors would have been the same for controls as for cases.

CONCLUSION

We found that women in our study with high exposures to PM_{2.5} experienced slightly elevated risk for stillbirths. Notwithstanding the spatially limited speciated PM_{2.5} data, there was evidence of increased risk associated with maternal exposures to some metal constituents of PM_{2.5}. Petrochemical industries and metal recycling facilities in the Greater Houston Area are possible sources for metal emissions, as well as traffic-related emissions (Buzcu et al. 2003). A lack of zoning in the area means that industrial sources of pollution are often dispersed and close to residential neighborhoods (Qian 2010). Future studies, applying exposure assessment methods to better capture the spatial heterogeneity of PM_{2.5} constituents, are warranted in large urban centers characterized by myriad and diverse sources of PM. In Houston in particular, a source appointment approach might help identify emission sources for PM_{2.5} constituents with the goal of mitigating exposures in residential neighborhoods.

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CHAPTER V: CONCLUSIONS

Previous investigations of the air pollution-stillbirth association have relied on pre-defined exposure periods, such as trimester-specific exposures or whole pregnancy exposures, and findings among studies are equivocal; it is not clear which exposure periods are the most relevant to fetal survival. One important limitation in assessing gestational exposures relates to defining risk periods over the duration of pregnancy, which could vary in length from 20 to 37 weeks or longer (Pedersen 2016).

This was the first investigation to use survival analysis for examining associations between time-varying O₃ exposure and stillbirth, which allowed us to evaluate exposures while accounting for different gestational lengths between stillbirths and live births. Similarly, we also used truncated exposure periods for stillbirth and live births to examine the effect of PM_{2.5} mass and PM_{2.5} metals on stillbirths in a case control design. Finally, we evaluated confounding from ambient air pollutants exposures in multi-pollutant models, as well as a wide range of maternal characteristics and risk factors for stillbirth. We also evaluated effect measure modifying potential of gestational length and maternal race/ethnicity in a racially and ethnically diverse urban center with documented health disparities.

Our findings suggest that maternal exposure to O₃ during pregnancy is associated with increased risk of stillbirth, and that Hispanic women and women with shorter gestation periods (i.e., less than 37 weeks of gestation) might be more at risk. We also found evidence of an association between high exposure to metal constituents of PM_{2.5} (Al, Cr, Cu, Fe, Pb,

Mn, Ni, Se, Ti and Zn) and stillbirth. Further studies employing a source appointment approach for fine particulate matter pollution are warranted, particularly in urban centers such as Harris County, an area characterized by a high density of industrial activity and heavily-trafficked roadways.

In addition to evaluating ambient air pollution exposures, this was also the first investigation to examine the association between increases in apparent temperature in the week preceding delivery and stillbirths caused by placental abruption, using a case-crossover design with symmetric bidirectional sampling of controls, which minimized confounding from maternal characteristics and bias from temporal trends in temperature. We found evidence of a positive association between apparent temperature increases in the few days preceding delivery and the risk of stillbirth caused by placental abruption, and no evidence of an association with all-cause stillbirths. Future studies should examine other aspects of placental pathology that might be relevant to the temperature-stillbirth association.

Overall, this project addresses an important methodological limitation in the extent literature on ambient air pollution and stillbirth by accounting for the differences in gestational lengths when comparing exposures between stillbirths and live births. Further, the evidence of an acute effect from temperature on stillbirths exclusively among those caused by placental abruptions underscores the importance of placental abruption in the association between temperature and stillbirth.

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