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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

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IN HARRIS COUNTY, TEXAS

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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.

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EXPOSURE TO AMBIENT AIR POLLUTION AND FETAL DEATH

IN HARRIS COUNTY, TEXAS

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The University of Texas
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The evidence from studies of maternal ambient air pollutant exposure (including O_3, 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 (O_3), fine particulate matter ($PM_{2.5}$), nitrogen dioxide (NO_2) and $PM_{2.5}$ metals from the local monitoring network.

In one study, we used Cox survival models to examine associations between time-varying O_3 exposure and stillbirth with adjustment for $PM_{2.5}$ and NO_2 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 O_3 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 (≥95th percentile) levels of $PM_{2.5}$ mass. There were also elevated risks (21% to 36%) associated with high exposures (≥95th 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 PM_{10}, 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 (NOx) (Landgren 1996, Pereira et al. 1998, Bobak and Leon 1999, Hwang et al. 2011, Faiz et al. 2012, Faiz et al. 2013) sulfur dioxide (SO_2) (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 (O_3) (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 Paolo, 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 O_3, 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 O_3 and time to a stillbirth event. We estimated weekly maternal residential O_3 concentrations from conception until delivery and used Cox survival models to examine associations between time-varying O_3 exposure and stillbirth. We further evaluated the effect measure modifying potential of maternal race/ethnicity on the association between O_3 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 per1000 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 (O_3) 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 O_3 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 O_3 exposure Further, results from a multi-pollutant model suggested little evidence of confounding due to other routinely monitored air pollutants (i.e., $PM_{2.5}$, PM_{10}, SO_2, 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 PM2.5 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 $\mu g/m^3$ 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 O_3 exposures. The O_3-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-

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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

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ABSTRACT

This study is the first to use time-to-event analyses to examine stillbirth risk associated with prenatal ozone (O_3) exposure. The study was conducted in a racially and ethnically diverse urban area (Harris County, Texas) with historic non-attainment O_3 levels. We obtained birth and fetal death records from 2008-2013 and estimated weekly maternal residential O_3 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 O_3 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 O_3 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 O_3 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 (NOx) (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 O_3 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 O_3 exposure (22). Further, results from a multi-pollutant model suggested little evidence of confounding due to other routinely monitored air pollutants (i.e., $PM_{2.5}$, PM_{10}, SO_2, and NOx).

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 O_3 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 O_3 since 1992 because it has failed to meet subsequent National Ambient Air Quality Standards (NAAQS) (30), which stipulate that an

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area will meet the standard for O_3 if the three-year average of the annual fourth-highest daily maximum 8-hour average at every O_3 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 O_3 based on the 2008 8-hour O_3 standard of 0.075 parts per million (ppm) (32) and in marginal non-attainment based on the 2015 8-hour O_3 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 O_3 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, 35-30 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 O_3 (reported in parts per billion; ppb), $PM_{2.5}$ ($\mu g/m^3$), and NO_2 (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 O_3, 15 stations for $PM_{2.5}$ and 22 stations for NO_2. All monitors measured pollutants continuously and year round. We excluded one O_3 monitor, two $PM_{2.5}$ monitors and one NO_2 monitor that each had more than 25% missing observations over the study period. We calculated the maximum average eight-hour O_3 concentration within a 24-hour period, and the daily average $PM_{2.5}$ and NO_2 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 O_3 concentration or the daily average $PM_{2.5}$ or NO_2 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 O_3 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 O_3. 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 NO_2) 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 O_3 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

O_3, 11.50 µg/m^3 (1.44) and 11.55 µg/m^3 (0.91) for $PM_{2.5}$ and 9.88 ppb (4.44) and 9.92 ppb

(3.25) for NO_2. O_3 exposure was negatively correlated with NO_2 (r= -0.50) and $PM_{2.5}$ was

weakly correlated with NO_2 (r= 0.26); there was no correlation between O_3 and $PM_{2.5}$ (r=

0.06). Apparent temperature was weekly correlated with O_3 (r= 0.36) and $PM_{2.5}$ (r= 0.33) and

negatively correlated with NO_2 (r= -0.34).

In fully adjusted models, there was a 9% increase in risk of stillbirth per 3.6 ppb IQR

increase in O_3 exposure (HR =1.09, 95% CI: 1.01, 1.18) or a 3% increase in risk per unit

increase in O_3 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 NO_2 as covariates. Our

stratified analyses suggest differences in the association of O_3 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 sensitively 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 O_3 is limited. In this study, we examined the risk of stillbirth associated with O_3 exposure during pregnancy in a racially and ethnically diverse urban area (Harris County, Texas where Houston is located) with historic non-attainment O_3 levels. Further, we evaluated the association between O_3 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 O_3 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 O_3 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

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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 O_3-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 O_3 exposures. The O_3-

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 O_3-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 O_3 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 O_3 (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 O_3 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 O_3-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 O_3 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 O_3 standard.

We used inverse distance weighting (IDW) to assign exposures; O_3 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 O_3 exposure and risk of stillbirth due to non-differential exposure misclassification. This is the first study to account for differences in time-varying O_3 exposures over different gestational lengths between stillbirths and live births and our findings indicate that maternal exposure to O_3 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/m^2)				
<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	25th Percentile	50th Percentile	75th Percentile	Max	Min	25th Percentile	50th Percentile	75th 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
$PM_{2.5}$ ($\mu g/m^3$)	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 O_3 Exposure and Stillbirth among Women in Harris County, Texas, 2008—2013.

	Crude model		Adjusted[a] model					
			All deliveries		Preterm deliveries		Term deliveries	
Pollutant	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
[a]Adjusted for apparent temperature, maternal age, race/ethnicity, education, smoking, pre-pregnancy BMI and prenatal care utilization.
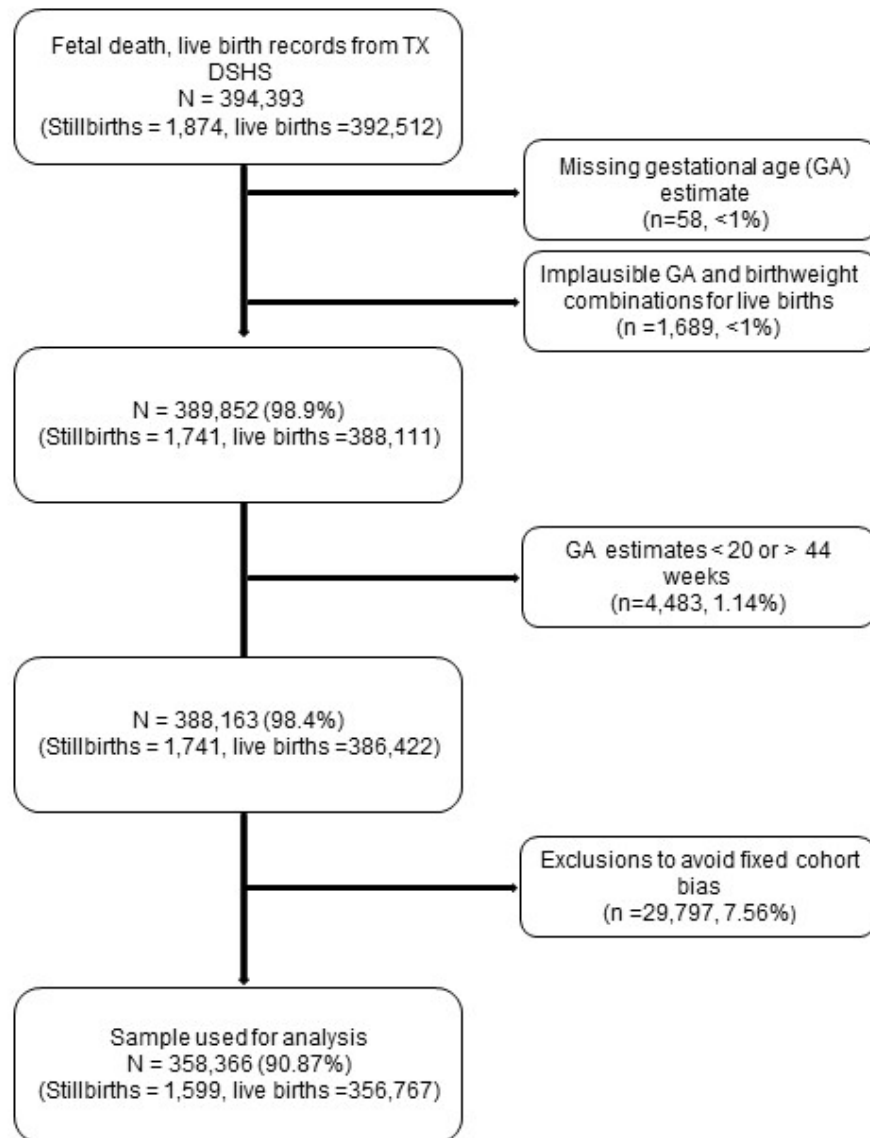
Figure 1. Flowchart detailing exclusions of fetal death and live birth records obtained from Texas DSHS for Harris County, TX, 2008—2013.

1. Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. Epidemiology (Cambridge, Mass). 2004;15(1):36-45. doi:10.1097/01.ede.0000101023.41844.ac [doi].

2. Li X, Huang S, Jiao A, Yang X, Yun J, Wang Y et al. Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis. Environmental pollution (Barking, Essex : 1987). 2017;227:596-605. doi:10.1016/j.envpol.2017.03.055.

3. Maisonet M, Correa A, Misra D, Jaakkola JJK. A review of the literature on the effects of ambient air pollution on fetal growth. Environmental research. 2004;95(1):106-15. doi:http://dx.doi.org.www5.sph.uth.tmc.edu:2048/10.1016/j.envres.2004.01.001.

4. Sapkota AC, Adam P; Nachman, Keeve E; Cohen, Aaron J; Ritz, Beate. Exposure to particulate matter and adverse birth outcomes: A comprehensive review and meta-analysis. Air Quality, Atmosphere, & Health. 2012;5(4):369-81. doi:http://dx.doi.org/10.1007/s11869-010-0106-3.

5. Stieb DM, Chen L, Eshoul M, Judek S. Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis. Environ Res. 2012;117:100-11. doi:10.1016/j.envres.2012.05.007.

6. Stillerman KP, Mattison DR, Giudice LC, Woodruff TJ. Environmental exposures and adverse pregnancy outcomes: a review of the science. Reproductive sciences (Thousand Oaks, Calif). 2008;15(7):631-50. doi:10.1177/1933719108322436.

7. Vrijheid M, Martinez D, Manzanares S, Dadvand P, Schembari A, Rankin J et al. Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis. Environ Health Perspect. 2011;119(5):598-606. doi:10.1289/ehp.1002946.

8. Zhu X, Liu Y, Chen Y, Yao C, Che Z, Cao J. Maternal exposure to fine particulate matter (PM2.5) and pregnancy outcomes: a meta-analysis. Environ Sci Pollut Res Int. 2015;22(5):3383-96. doi:10.1007/s11356-014-3458-7.

9. Klepac P, Locatelli I, Korosec S, Kunzli N, Kukec A. Ambient air pollution and pregnancy outcomes: A comprehensive review and identification of environmental public health challenges. Environ Res. 2018;167:144-59. doi:10.1016/j.envres.2018.07.008.

10. Glinianaia SV, Rankin J, Bell R, Pless-Mulloli T, Howel D. Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence. Epidemiology. 2004;15(1):36-45. doi:10.1097/01.ede.0000101023.41844.ac.

11. Lacasana M, Esplugues A, Ballester F. Exposure to ambient air pollution and prenatal and early childhood health effects. Eur J Epidemiol. 2005;20(2):183-99.

12. Siddika N, Balogun HA, Amegah AK, Jaakkola JJ. Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence. Occup Environ Med. 2016;73(9):573-81. doi:10.1136/oemed-2015-103086.

13. DeFranco E, Hall E, Hossain M, Chen A, Haynes EN, Jones D et al. Air Pollution and Stillbirth Risk: Exposure to Airborne Particulate Matter during Pregnancy Is Associated with Fetal Death. PloS one. 2015;10(3):e0120594. doi:10.1371/journal.pone.0120594 [doi].

14. Faiz AS, Rhoads GG, Demissie K, Kruse L, Lin Y, Rich DQ. Ambient air pollution and the risk of stillbirth. American Journal of Epidemiology. 2012;176(4):308-16. doi:10.1093/aje/kws029 [doi].

15. Faiz AS, Rhoads GG, Demissie K, Lin Y, Kruse L, Rich DQ. Does ambient air pollution trigger stillbirth? Epidemiology (Cambridge, Mass). 2013;24(4):538-44. doi:10.1097/EDE.0b013e3182949ce5 [doi].

16. Green R, Sarovar V, Malig B, Basu R. Association of Stillbirth With Ambient Air Pollution in a California Cohort Study. American Journal of Epidemiology. 2015. doi:kwu460 [pii].

17. Hwang BF, Lee YL, Jaakkola JJ. Air pollution and stillbirth: a population-based case-control study in Taiwan. Environmental health perspectives. 2011;119(9):1345-9. doi:10.1289/ehp.1003056 [doi].

18. Kim OJ, Ha EH, Kim BM, Seo JH, Park HS, Jung WJ et al. PM10 and pregnancy outcomes: a hospital-based cohort study of pregnant women in Seoul. Journal of occupational and environmental medicine. 2007;49(12):1394-402. doi:10.1097/JOM.0b013e3181594859.

19. Pereira LAA, Loomis D, Conceição GMS, Braga AsLF, Arcas RnM, Kishi HS et al. Association between Air Pollution and Intrauterine Mortality in São Paulo, Brazil. Environmental health perspectives. 1998;106(6):325-9. doi:10.2307/3434038.

20. Landgren O. Environmental pollution and delivery outcome in southern Sweden: a study with central registries. Acta paediatrica (Oslo, Norway : 1992). 1996;85(11):1361-4.

21. Bobak M, Leon DA. Pregnancy Outcomes and Outdoor Air Pollution: An Ecological Study in Districts of the Czech Republic 1986-8. Occupational and environmental medicine. 1999;56(8):539-43. doi:10.2307/27731170.

22. Mendola P, Ha S, Pollack AZ, Zhu Y, Seeni I, Kim SS et al. Chronic and Acute Ozone Exposure in the Week Prior to Delivery Is Associated with the Risk of Stillbirth. International journal of environmental research and public health. 2017;14(7). doi:10.3390/ijerph14070731.

23. Yang S, Tan Y, Mei H, Wang F, Li N, Zhao J et al. Ambient air pollution the risk of stillbirth: A prospective birth cohort study in Wuhan, China. International journal of hygiene and environmental health. 2018;221(3):502-9. doi:10.1016/j.ijheh.2018.01.014.

24. Erickson AC, Arbour L. The shared pathoetiological effects of particulate air pollution and the social environment on fetal-placental development. Journal of environmental and public health. 2014;2014:901017. doi:10.1155/2014/901017 [doi].

25. Sram RJ. Impact of Air Pollution on Reproductive Health. Environmental health perspectives. 1999;107(11):A542-A3. doi:10.2307/3454450.

26. Pedersen M. Is it still important to study if ambient air pollution triggers stillbirth? Occup Environ Med. 2016;73(9):571-2. doi:10.1136/oemed-2016-103625.

27. Strand LB, Barnett AG, Tong S. Maternal exposure to ambient temperature and the risks of preterm birth and stillbirth in Brisbane, Australia. Am J Epidemiol. 2012;175(2):99-107. doi:10.1093/aje/kwr404.

28. Ryerson T, Trainer M, Angevine W, Brock C, Dissly R, Fehsenfeld F et al. Effect of petrochemical industrial emissions of reactive alkenes and NOx on tropospheric ozone formation in Houston, Texas. Journal of Geophysical Research: Atmospheres. 2003;108(D8).

29. Kleinman LI, Daum P, Imre D, Lee YN, Nunnermacker L, Springston S et al. Ozone production rate and hydrocarbon reactivity in 5 urban areas: A cause of high ozone concentration in Houston. Geophysical Research Letters. 2002;29(10):105-1--4.

30. EPA. Green Book, National Area and County-Level Multi-Pollutant Information, Texas Whole or Part County Nonattainment Status by Year Since 1992 for all Criteria Pollutants. 2018. https://www3.epa.gov/airquality/greenbook/phistory_tx.html. Accessed 10/04 2018.

31. EPA. Table of Historical Ozone National Ambient Air Quality Standards (NAAQS). 2018. https://www.epa.gov/ozone-pollution/table-historical-ozone-national-ambient-air-quality-standards-naaqs. Accessed 10/04 2018.

32. EPA. Green Book 8–Hr Ozone (2008) Designated Area/State Information, as of September 30, 2018. 2018. https://www3.epa.gov/airquality/greenbook/hbtc.html

Accessed 10/04 2018.

33. EPA. Green Book 8–Hr Ozone (2015) Designated Area/State Information, as of September 30, 2018. 2018. https://www3.epa.gov/airquality/greenbook/jbtc.html. Accessed 10/04 2018.

34. Tex. Admin. Code 181.(10).

35. Tex. Admin. Code 181.7(b).

36. Alexander GR, Himes JH, Kaufman RB, Mor J, Kogan M. A United States national reference for fetal growth. Obstetrics and gynecology. 1996;87(2):163-8. doi:10.1016/0029-7844(95)00386-x.

37. Strand LB, Barnett AG, Tong S. Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes. BMC medical research methodology. 2011;11:49-2288-11-49. doi:10.1186/1471-2288-11-49 [doi].

38. National Climatic Data C. Land-Based Datasets and Products. 2017. https://www.ncdc.noaa.gov/data-access/land-based-station-data/land-based-datasets. Accessed Web Page 2015.

39. Waller LA, Gotway CA. Applied spatial statistics for public health data. John Wiley & Sons; 2004.

40. Rothman KJ, Greenland S, Lash TL. Modern epidemiology. Lippincott Williams & Wilkins; 2008.

41. Dell'Omo G, Fiore M, Petruzzi S, Alleva E, Bignami G. Neurobehavioral development of CD-1 mice after combined gestational and postnatal exposure to ozone. Arch Toxicol. 1995;69(9):608-16.

42. Bignami G, Musi B, Dell'Omo G, Laviola G, Alleva E. Limited effects of ozone exposure during pregnancy on physical and neurobehavioral development of CD-1 mice. Toxicol Appl Pharmacol. 1994;129(2):264-71.

43. Salam MT, Millstein J, Li YF, Lurmann FW, Margolis HG, Gilliland FD. Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study. Environ Health Perspect. 2005;113(11):1638-44. doi:10.1289/ehp.8111.

44. MacDorman MF. Race and ethnic disparities in fetal mortality, preterm birth, and infant mortality in the United States: an overview. Semin Perinatol. 2011;35(4):200-8. doi:10.1053/j.semperi.2011.02.017.

45. Rowland Hogue CJ, Silver RM. Racial and ethnic disparities in United States: stillbirth rates: trends, risk factors, and research needs. Semin Perinatol. 2011;35(4):221-33. doi:10.1053/j.semperi.2011.02.019.

46. Spong CY, Iams J, Goldenberg R, Hauck FR, Willinger M. Disparities in perinatal medicine: preterm birth, stillbirth, and infant mortality. Obstetrics and gynecology. 2011;117(4):948-55. doi:10.1097/AOG.0b013e318211726f.

47. Bell ML, Belanger K, Ebisu K, Gent JF, Lee HJ, Koutrakis P et al. Prenatal exposure to fine particulate matter and birth weight: variations by particulate constituents and sources. Epidemiology. 2010;21(6):884-91. doi:10.1097/EDE.0b013e3181f2f405.

48. Green RS, Malig B, Windham GC, Fenster L, Ostro B, Swan S. Residential exposure to traffic and spontaneous abortion. Environ Health Perspect. 2009;117(12):1939-44. doi:10.1289/ehp.0900943.

49. Ng C, Malig B, Hasheminassab S, Sioutas C, Basu R, Ebisu K. Source apportionment of fine particulate matter and risk of term low birth weight in California: Exploring modification by region and maternal characteristics. The Science of the total environment. 2017;605-606:647-54. doi:10.1016/j.scitotenv.2017.06.053.

50. Ritz B, Wilhelm M, Hoggatt KJ, Ghosh JK. Ambient air pollution and preterm birth in the environment and pregnancy outcomes study at the University of California, Los Angeles. Am J Epidemiol. 2007;166(9):1045-52. doi:10.1093/aje/kwm181.

51. Rivera-Gonzalez LO, Zhang Z, Sanchez BN, Zhang K, Brown DG, Rojas-Bracho L et al. An assessment of air pollutant exposure methods in Mexico City, Mexico. J Air Waste Manag Assoc. 2015;65(5):581-91. doi:10.1080/10962247.2015.1020974.

52. Lupo PJ, Symanski E, Chan W, Mitchell LE, Waller DK, Canfield MA et al. Differences in exposure assignment between conception and delivery: the impact of maternal mobility. Paediatric and perinatal epidemiology. 2010;24(2):200-8. doi:10.1111/j.1365-3016.2010.01096.x.

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 (NO_2) and ozone (O_3).

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

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(°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 dioxine (NO_2) and Ozone (O_3), 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 (°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, 35-30 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 (m^2); 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 $\mu g/m^3$) (n=13), O_3 (ppb) (n=48) and NO_2 (ppb) (n=21) after excluding two $PM_{2.5}$ monitors, one O_3 monitor and one NO_2 monitor that had more than 25% missing observations over the study period. We computed the daily average $PM_{2.5}$ and NO_2 concentrations and the maximum average eight-hour O_3 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 $PM_{2.5}$, NO_2 and O_3. 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 NO_2 ($r = -0.53$) and weakly correlated with $PM_{2.5}$ ($r = 0.29$) and O_3 ($r = 0.13$) 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 $PM_{2.5}$, NO_2 and O_3, 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., $PM_{2.5}$, NO_2 and O_3). 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
	n (%)	*n* (%)
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
	n (%)	n (%)
<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.

	Case Periods						Control Periods					
			Percentiles						Percentiles			
Lag day	Mean ± SD	Min	25	50	75	Max	Mean ± SD	Min	25	50	75	Max
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.

	Crude	Adjusted
Lag day(s)	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/m^3), NO_2 (ppb) and O_3 (ppb)

Arroyo, V., Diaz, J., Carmona, R., Ortiz, C. and Linares, C. (2016). "Impact of air pollution and temperature on adverse birth outcomes: Madrid, 2001-2009." Environ Pollut 218: 1154-1161.

Auger, N., Fraser, W. D., Smargiassi, A., Bilodeau-Bertrand, M. and Kosatsky, T. (2017). "Elevated outdoor temperatures and risk of stillbirth." Int J Epidemiol 46(1): 200-208.

Basu, R., Feng, W.-Y. and Ostro, B. D. (2008). "Characterizing temperature and mortality in nine California counties." Epidemiology: 138-145.

Basu, R., Malig, B. and Ostro, B. (2010). "High ambient temperature and the risk of preterm delivery." American Journal of Epidemiology 172(10): 1108-1117.

Basu, R., Sarovar, V. and Malig, B. J. (2016). "Association Between High Ambient Temperature and Risk of Stillbirth in California." Am J Epidemiol 183(10): 894-901.

Downes, K. L., Shenassa, E. D. and Grantz, K. L. (2017). "Neonatal Outcomes Associated With Placental Abruption." Am J Epidemiol 186(12): 1319-1328.

Duke, W., Williams, L. and Correa, A. (2008). "Using active birth defects surveillance programs to supplement data on fetal death reports: Improving surveillance data on stillbirths." Birth Defects Research Part A: Clinical and Molecular Teratology 82(11): 799-804.

Faiz, A. S., Rhoads, G. G., Demissie, K., Lin, Y., Kruse, L. and Rich, D. Q. (2013). "Does ambient air pollution trigger stillbirth?" Epidemiology (Cambridge, Mass.) 24(4): 538-544.

Gardosi, J., Mul, T., Mongelli, M. and Fagan, D. (1998). "Analysis of birthweight and gestational age in antepartum stillbirths." British journal of obstetrics and gynaecology 105(5): 524-530.

Genest, D. R., A., W. M. and Greene, M. F. (1992). "Estimating the time of death in stillborn fetuses: I. Histologic evaluation of fetal organs; an autopsy study of 150 stillborns." Obstetrics & Gynecology 80(4): 593-600

Glinianaia, S. V., Rankin, J., Bell, R., Pless-Mulloli, T. and Howel, D. (2004). "Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence." Epidemiology (Cambridge, Mass.) 15(1): 36-45.

Greb, A. E., Pauli, R. M. and Kirby, R. S. (1987). "Accuracy of fetal death reports: comparison with data from an independent stillbirth assessment program." American journal of public health 77(9): 1202-1206.

Ha, S., Liu, D., Zhu, Y., Soo Kim, S., Sherman, S., Grantz, K. L. and Mendola, P. (2017). "Ambient Temperature and Stillbirth: A Multi-Center Retrospective Cohort Study." Environ Health Perspect 125(6): 067011.

He, S., Kosatsky, T., Smargiassi, A., Bilodeau-Bertrand, M. and Auger, N. (2018). "Heat and pregnancy-related emergencies: Risk of placental abruption during hot weather." Environ Int 111: 295-300.

Heuser, C. C., Hunn, J., Varner, M., Hossain, S., Vered, S. and Silver, R. M. (2010). "Correlation Between Stillbirth Vital Statistics and Medical Records." Obstetrics & Gynecology 116(6): 1296-1301.

Kuehn, L. and McCormick, S. (2017). "Heat Exposure and Maternal Health in the Face of Climate Change." Int J Environ Res Public Health 14(8).

Lacasana, M., Esplugues, A. and Ballester, F. (2005). "Exposure to ambient air pollution and prenatal and early childhood health effects." European journal of epidemiology 20(2): 183-199.

Li, S., Chen, G., Jaakkola, J. J. K., Williams, G. and Guo, Y. (2018). "Temporal change in the impacts of ambient temperature on preterm birth and stillbirth: Brisbane, 1994-2013." Sci Total Environ 634: 579-585.

Lupo, P. J., Symanski, E., Chan, W., Mitchell, L. E., Waller, D. K., Canfield, M. A. and Langlois, P. H. (2010). "Differences in exposure assignment between conception and delivery: the impact of maternal mobility." Paediatr Perinat Epidemiol 24(2): 200-208.

Lydon-Rochelle, M. T., Cardenas V Fau - Nelson, J. L., Nelson Jl Fau - Tomashek, K. M., Tomashek Km Fau - Mueller, B. A., Mueller Ba Fau - Easterling, T. R. and Easterling, T. R. (2005). "Validity of maternal and perinatal risk factors reported on fetal death certificates." American Journal of Public Health 95(11): 1948-1951.

Maclure, M. and Mittleman, M. A. (2000). "Should we use a case-crossover design?" Annu Rev Public Health 21: 193-221.

Maclure, M. and Mittleman, M. A. (2000). "Should we use a case-crossover design?" Annu. Rev. Public Health 21(0163-7525 (Print)): 193-221.

Mendola, P., Ha, S., Pollack, A. Z., Zhu, Y., Seeni, I., Kim, S. S., Sherman, S. and Liu, D. (2017). "Chronic and Acute Ozone Exposure in the Week Prior to Delivery Is Associated with the Risk of Stillbirth." Int J Environ Res Public Health 14(7).

National Climatic Data Center. (2017). "Land-Based Datasets and Products." Retrieved Web Page, 2015, from https://www.ncdc.noaa.gov/data-access/land-based-station-data/land-based-datasets.

Pinar, H., Goldenberg, R. L., Koch, M. A., Heim-Hall, J., Hawkins, H. K., Shehata, B., Abramowsky, C., Parker, C. B., Dudley, D. J. and Silver, R. M. (2014). "Placental findings in singleton stillbirths." Obstetrics and gynecology 123(2 0 1): 325.

Poursafa, P., Keikha, M. and Kelishadi, R. (2015). "Systematic review on adverse birth outcomes of climate change." Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences 20(4): 397.

Ptacek, I., Sebire, N., Man, J., Brownbill, P. and Heazell, A. (2014). "Systematic review of placental pathology reported in association with stillbirth." Placenta 35(8): 552-562.

Rylander, C., Odland, J. O. and Sandanger, T. M. (2013). "Climate change and the potential effects on maternal and pregnancy outcomes: an assessment of the most vulnerable--the mother, fetus, and newborn child." Glob Health Action 6: 19538.

Schifano, P., Lallo, A., Asta, F., De Sario, M., Davoli, M. and Michelozzi, P. (2013). "Effect of ambient temperature and air pollutants on the risk of preterm birth, Rome 2001–2010." Environment international 61: 77-87.

Siddika, N., Balogun, H. A., Amegah, A. K. and Jaakkola, J. J. (2016). "Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence." Occup Environ Med 73(9): 573-581.

Smith, G. C. and Fretts, R. C. (2007). "Stillbirth." The Lancet 370(9600): 1715-1725.

Stillbirth Collaborative Research Network Writing Group (2011). "Causes of death among stillbirths." Jama 306(22): 2459.

Strand, L. B., Barnett, A. G. and Tong, S. (2011). "The influence of season and ambient temperature on birth outcomes: a review of the epidemiological literature." Environ Res 111(3): 451-462.

Strand, L. B., Barnett, A. G. and Tong, S. (2011). "Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes." BMC medical research methodology 11: 49-2288-2211-2249.

Strand, L. B., Barnett, A. G. and Tong, S. (2012). "Maternal exposure to ambient temperature and the risks of preterm birth and stillbirth in Brisbane, Australia." Am J Epidemiol 175(2): 99-107.

Waller, L. A. and Gotway, C. A. (2004). Applied spatial statistics for public health data, John Wiley & Sons.

Zhang, Y., Yu, C. and Wang, L. (2017). "Temperature exposure during pregnancy and birth outcomes: An updated systematic review of epidemiological evidence." Environ Pollut 225: 700-712.

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 (≥95th percentile, or ≥13.68 µg/m^3) levels of PM$_{2.5}$ mass. There were also elevated risks (21% to 36%) associated with high exposures (≥95th 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 µm; 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 ($\geq$ 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 $\geq$ 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 (m^2)) 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/m^2 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 (n = 1,172)	Controls (N = 7032)	Total (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 (µg/m³)	Mean (S.D.)	5th percentile	25th percentile	median	75th percentile	95th percentile
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$13.68 µg/m³), but the risk was attenuated in a fully adjusted model (OR = 1.05, 95% CI: 0.79, 1.38) (Table 3). We found elevated risks for stillbirths associated with high exposures to Al, Cr, Cu, Fe, Pb, Mn, Sr, Ti and Zn in crude models and the risk increased (21% - 36%) in fully adjusted models, though estimates were imprecise. The strongest association was observed for PM$_{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 (≥ 1.45 µg/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

[a]adjusted 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 µg/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 µg/m^3 increase in entire pregnancy PM$_{2.5}$ exposures) (Yang et al. 2018).

Because the toxicity of 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 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 µg/m^3 IQR increase) and Ti (OR=1.10, 95% CI: 1.04, 1.17 per 0.012 µg/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 PM$_{2.5}$ may impact stillbirth are unclear. 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.

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.

Alexander, G. R., Himes, J. H., Kaufman, R. B., Mor, J. and Kogan, M. (1996). "A United States national reference for fetal growth." Obstet Gynecol 87(2): 163-168.

Basu, R., Harris, M., Sie, L., Malig, B., Broadwin, R. and Green, R. (2014). "Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California." Environmental research 128: 42-51.

Bell, M. L., Belanger, K., Ebisu, K., Gent, J. F., Lee, H. J., Koutrakis, P. and Leaderer, B. P. (2010). "Prenatal exposure to fine particulate matter and birth weight: variations by particulate constituents and sources." Epidemiology 21(6): 884-891.

Buzcu, B., Fraser, M. P., Kulkarni, P. and Chellam, S. (2003). "Source identification and apportionment of fine particulate matter in Houston, TX, using positive matrix factorization." Environmental Engineering Science 20(6): 533-545.

Darrow, L. A., Klein, M., Flanders, W. D., Waller, L. A., Correa, A., Marcus, M., Mulholland, J. A., Russell, A. G. and Tolbert, P. E. (2009). "Ambient air pollution and preterm birth: a time-series analysis." Epidemiology (Cambridge, Mass.) 20(5): 689-698.

Darrow, L. A., Klein, M., Strickland, M. J., Mulholland, J. A. and Tolbert, P. E. (2011). "Ambient air pollution and birth weight in full-term infants in Atlanta, 1994-2004." Environmental health perspectives 119(5): 731-737.

DeFranco, E., Hall, E., Hossain, M., Chen, A., Haynes, E. N., Jones, D., Ren, S., Lu, L. and Muglia, L. (2015). "Air Pollution and Stillbirth Risk: Exposure to Airborne Particulate Matter during Pregnancy Is Associated with Fetal Death." PloS one 10(3): e0120594.

Ebisu, K., Belanger, K. and Bell, M. L. (2014). "The Association between Airborne PM2.5 Chemical Constituents and Birth Weight-Implication of Buffer Exposure Assignment." Environ Res Lett 9(8).

Ebisu, K. and Bell, M. L. (2012). "Airborne PM2.5 chemical components and low birth weight in the northeastern and mid-Atlantic regions of the United States." Environmental health perspectives 120(12): 1746-1752.

Ebisu, K., Malig, B., Hasheminassab, S., Sioutas, C. and Basu, R. (2018). "Cause-specific stillbirth and exposure to chemical constituents and sources of fine particulate matter." Environ Res 160: 358-364.

EPA. (2018). "Sampling Methods for PM2.5 Speciation Parameters, AQS Reference Table." Retrieved 10/21, 2018, from https://aqs.epa.gov/aqsweb/documents/codetables/methods_speciation.html.

Faiz, A. S., Rhoads, G. G., Demissie, K., Kruse, L., Lin, Y. and Rich, D. Q. (2012). "Ambient air pollution and the risk of stillbirth." American Journal of Epidemiology 176(4): 308-316.

Faiz, A. S., Rhoads, G. G., Demissie, K., Lin, Y., Kruse, L. and Rich, D. Q. (2013). "Does ambient air pollution trigger stillbirth?" Epidemiology (Cambridge, Mass.) 24(4): 538-544.

Ferguson, K. K. and Chin, H. B. (2017). "Environmental chemicals and preterm birth: Biological mechanisms and the state of the science." Current epidemiology reports 4(1): 56-71.

Green, R., Sarovar, V., Malig, B. and Basu, R. (2015). "Association of Stillbirth With Ambient Air Pollution in a California Cohort Study." American Journal of Epidemiology.

Hornung, R. and Reed, L. (1990). "Estimation of Average Concentrations in the Presence of Nondetectable Values." Appl. Occup. and Environ. Hyg. 5(1): 46-51.

Klepac, P., Locatelli, I., Korosec, S., Kunzli, N. and Kukec, A. (2018). "Ambient air pollution and pregnancy outcomes: A comprehensive review and identification of environmental public health challenges." Environ Res 167: 144-159.

Laurent, O., Hu, J., Li, L., Cockburn, M., Escobedo, L., Kleeman, M. J. and Wu, J. (2014). "Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001-2008." Environ Res 134: 488-495.

Mendola, P., Ha, S., Pollack, A. Z., Zhu, Y., Seeni, I., Kim, S. S., Sherman, S. and Liu, D. (2017). "Chronic and Acute Ozone Exposure in the Week Prior to Delivery Is Associated with the Risk of Stillbirth." Int J Environ Res Public Health 14(7).

Møller, P., Danielsen, P. H., Karottki, D. G., Jantzen, K., Roursgaard, M., Klingberg, H., Jensen, D. M., Christophersen, D. V., Hemmingsen, J. G. and Cao, Y. (2014). "Oxidative stress and inflammation generated DNA damage by exposure to air pollution particles." Mutation Research/Reviews in Mutation Research 762: 133-166.

National Climatic Data Center. (2017). "Land-Based Datasets and Products."   Retrieved Web Page, 2015, from https://www.ncdc.noaa.gov/data-access/land-based-station-data/land-based-datasets.

Qian, Z. (2010). "Without zoning: Urban development and land use controls in Houston." Cities 27(1): 31-41.

Ritz, B. and Wilhelm, M. (2008). "Ambient air pollution and adverse birth outcomes: methodologic issues in an emerging field." Basic & clinical pharmacology & toxicology 102(2): 182-190.

Sexton, K., Delclos, G., Abramson, S., Bondy, M., Fraser, M. and Ward, J. (2006). A closer look at air pollution in Houston. Identifying priority health risks: Report of the mayor's task force on the health effects of air pollution. . Houston, Texas, University of Texas Health Science Center, Institute for Health Policy.

Sexton, K., Linder, S. H., Marko, D., Bethel, H. and Lupo, P. J. (2007). "Comparative assessment of air pollution-related health risks in Houston." Environ Health Perspect 115(10): 1388-1393.

Siddika, N., Balogun, H. A., Amegah, A. K. and Jaakkola, J. J. (2016). "Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence." Occup Environ Med 73(9): 573-581.

Strand, L. B., Barnett, A. G. and Tong, S. (2011). "Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes." BMC medical research methodology 11: 49-2288-2211-2249.

Sun, X., Luo, X., Zhao, C., Zhang, B., Tao, J., Yang, Z., Ma, W. and Liu, T. (2016). "The associations between birth weight and exposure to fine particulate matter (PM2.5) and its chemical constituents during pregnancy: A meta-analysis." Environ Pollut 211: 38-47.

Symanski, E., Davila, M., McHugh, M. K., Waller, D. K., Zhang, X. and Lai, D. (2014). "Maternal exposure to fine particulate pollution during narrow gestational periods and newborn health in Harris County, Texas." Maternal and child health journal 18(8): 2003-2012.

Wei, Y., Han, I.-K., Shao, M., Hu, M., Zhang, J. and Tang, X. (2009). "PM2. 5 constituents and oxidative DNA damage in humans." Environmental science & technology 43(13): 4757-4762.

Whitworth, K. W., Han, I., Afshar, M., Mei, Y., Berens, P. D., Sharma, S. V. and Symanski, E. (2017). "Accessing Disadvantaged Pregnant Women in Houston, Texas, and Characterizing Biomarkers of Metal Exposure: A Feasibility Study." Int J Environ Res Public Health 14(5).

Yang, S., Tan, Y., Mei, H., Wang, F., Li, N., Zhao, J., Zhang, Y., Qian, Z., Chang, J. J., Syberg, K. M., Peng, A., Mei, H., Zhang, D., Zhang, Y., Xu, S., Li, Y., Zheng, T. and Zhang, B. (2018). "Ambient air pollution the risk of stillbirth: A prospective birth cohort study in Wuhan, China." Int J Hyg Environ Health 221(3): 502-509.

Zhu, X., Liu, Y., Chen, Y., Yao, C., Che, Z. and Cao, J. (2015). "Maternal exposure to fine particulate matter (PM2.5) and pregnancy outcomes: a meta-analysis." Environ Sci Pollut Res Int 22(5): 3383-3396.

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 O_3 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 O_3 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.

REFERENCES

Arroyo, V., Diaz, J., Carmona, R., Ortiz, C. and Linares, C. (2016). "Impact of air pollution and temperature on adverse birth outcomes: Madrid, 2001-2009." Environ Pollut 218: 1154-1161.

Auger, N., Fraser, W. D., Smargiassi, A., Bilodeau-Bertrand, M. and Kosatsky, T. (2017). "Elevated outdoor temperatures and risk of stillbirth." Int J Epidemiol 46(1): 200-208.

Basu, R., Harris, M., Sie, L., Malig, B., Broadwin, R. and Green, R. (2014). "Effects of fine particulate matter and its constituents on low birth weight among full-term infants in California." Environmental research 128: 42-51.

Basu, R., Malig, B. and Ostro, B. (2010). "High ambient temperature and the risk of preterm delivery." American Journal of Epidemiology 172(10): 1108-1117.

Basu, R., Sarovar, V. and Malig, B. J. (2016). "Association Between High Ambient Temperature and Risk of Stillbirth in California." Am J Epidemiol 183(10): 894-901.

Bell, M. L., Belanger, K., Ebisu, K., Gent, J. F., Lee, H. J., Koutrakis, P. and Leaderer, B. P. (2010). "Prenatal exposure to fine particulate matter and birth weight: variations by particulate constituents and sources." Epidemiology 21(6): 884-891.

Bignami, G., Musi, B., Dell'Omo, G., Laviola, G. and Alleva, E. (1994). "Limited effects of ozone exposure during pregnancy on physical and neurobehavioral development of CD-1 mice." Toxicol Appl Pharmacol 129(2): 264-271.

Bobak, M. and Leon, D. A. (1999). "Pregnancy Outcomes and Outdoor Air Pollution: An Ecological Study in Districts of the Czech Republic 1986-8." Occupational and environmental medicine 56(8): 539-543.

Darrow, L. A., Klein, M., Flanders, W. D., Waller, L. A., Correa, A., Marcus, M., Mulholland, J. A., Russell, A. G. and Tolbert, P. E. (2009). "Ambient air pollution and preterm birth: a time-series analysis." Epidemiology (Cambridge, Mass.) 20(5): 689-698.

DeFranco, E., Hall, E., Hossain, M., Chen, A., Haynes, E. N., Jones, D., Ren, S., Lu, L. and Muglia, L. (2015). "Air Pollution and Stillbirth Risk: Exposure to Airborne Particulate Matter during Pregnancy Is Associated with Fetal Death." PloS one 10(3): e0120594.

Dell'Omo, G., Fiore, M., Petruzzi, S., Alleva, E. and Bignami, G. (1995). "Neurobehavioral development of CD-1 mice after combined gestational and postnatal exposure to ozone." Arch Toxicol 69(9): 608-616.

Downes, K. L., Shenassa, E. D. and Grantz, K. L. (2017). "Neonatal Outcomes Associated With Placental Abruption." Am J Epidemiol 186(12): 1319-1328.

Ebisu, K. and Bell, M. L. (2012). "Airborne PM2.5 chemical components and low birth weight in the northeastern and mid-Atlantic regions of the United States." Environmental health perspectives 120(12): 1746-1752.

Ebisu, K., Malig, B., Hasheminassab, S., Sioutas, C. and Basu, R. (2018). "Cause-specific stillbirth and exposure to chemical constituents and sources of fine particulate matter." Environ Res 160: 358-364.

Erickson, A. C. and Arbour, L. (2014). "The shared pathoetiological effects of particulate air pollution and the social environment on fetal-placental development." Journal of environmental and public health 2014: 901017.

Faiz, A. S., Rhoads, G. G., Demissie, K., Kruse, L., Lin, Y. and Rich, D. Q. (2012). "Ambient air pollution and the risk of stillbirth." American Journal of Epidemiology 176(4): 308-316.

Faiz, A. S., Rhoads, G. G., Demissie, K., Lin, Y., Kruse, L. and Rich, D. Q. (2013). "Does ambient air pollution trigger stillbirth?" Epidemiology (Cambridge, Mass.) 24(4): 538-544.

Ferguson, K. K. and Chin, H. B. (2017). "Environmental chemicals and preterm birth: Biological mechanisms and the state of the science." Current epidemiology reports 4(1): 56-71.

Glinianaia, S. V., Rankin, J., Bell, R., Pless-Mulloli, T. and Howel, D. (2004). "Particulate air pollution and fetal health: a systematic review of the epidemiologic evidence." Epidemiology (Cambridge, Mass.) 15(1): 36-45.

Green, R., Sarovar, V., Malig, B. and Basu, R. (2015). "Association of Stillbirth With Ambient Air Pollution in a California Cohort Study." American Journal of Epidemiology.

Gregory, E. C., MacDorman, M. F. and Martin, J. A. (2014). "Trends in fetal and perinatal mortality in the United States, 2006-2012." NCHS data brief (169)(169): 1-8.

Ha, S., Liu, D., Zhu, Y., Soo Kim, S., Sherman, S., Grantz, K. L. and Mendola, P. (2017). "Ambient Temperature and Stillbirth: A Multi-Center Retrospective Cohort Study." Environ Health Perspect 125(6): 067011.

He, S., Kosatsky, T., Smargiassi, A., Bilodeau-Bertrand, M. and Auger, N. (2018). "Heat and pregnancy-related emergencies: Risk of placental abruption during hot weather." Environ Int 111: 295-300.

Hwang, B. F., Lee, Y. L. and Jaakkola, J. J. (2011). "Air pollution and stillbirth: a population-based case-control study in Taiwan." Environmental health perspectives 119(9): 1345-1349.

Kim, O. J., Ha, E. H., Kim, B. M., Seo, J. H., Park, H. S., Jung, W. J., Lee, B. E., Suh, Y. J., Kim, Y. J., Lee, J. T., Kim, H. and Hong, Y. C. (2007). "PM10 and pregnancy outcomes: a hospital-based cohort study of pregnant women in Seoul." J Occup Environ Med 49(12): 1394-1402.

Kleinman, L. I., Daum, P., Imre, D., Lee, Y. N., Nunnermacker, L., Springston, S., Weinstein-Lloyd, J. and Rudolph, J. (2002). "Ozone production rate and hydrocarbon reactivity in 5 urban areas: A cause of high ozone concentration in Houston." Geophysical Research Letters 29(10): 105-101-105-104.

Klepac, P., Locatelli, I., Korosec, S., Kunzli, N. and Kukec, A. (2018). "Ambient air pollution and pregnancy outcomes: A comprehensive review and identification of environmental public health challenges." Environ Res 167: 144-159.

Kuehn, L. and McCormick, S. (2017). "Heat Exposure and Maternal Health in the Face of Climate Change." Int J Environ Res Public Health 14(8).

Landgren, O. (1996). "Environmental pollution and delivery outcome in southern Sweden: a study with central registries." Acta Pædiatrica 85(11): 1361-1364.

Laurent, O., Hu, J., Li, L., Cockburn, M., Escobedo, L., Kleeman, M. J. and Wu, J. (2014). "Sources and contents of air pollution affecting term low birth weight in Los Angeles County, California, 2001-2008." Environ Res 134: 488-495.

Li, S., Chen, G., Jaakkola, J. J. K., Williams, G. and Guo, Y. (2018). "Temporal change in the impacts of ambient temperature on preterm birth and stillbirth: Brisbane, 1994-2013." Sci Total Environ 634: 579-585.

Li, X., Huang, S., Jiao, A., Yang, X., Yun, J., Wang, Y., Xue, X., Chu, Y., Liu, F. and Liu, Y. (2017). "Association between ambient fine particulate matter and preterm birth or term low birth weight: An updated systematic review and meta-analysis." Environmental Pollution 227: 596-605.

MacDorman, M. F. and Gregory, E. C. W. (2015). "Fetal and Perinatal Mortality: United States, 2013." National Vital Statistics Reports 64(8): 1-24.

Maisonet, M., Correa, A., Misra, D. and Jaakkola, J. J. K. (2004). "A review of the literature on the effects of ambient air pollution on fetal growth." Environmental research 95(1): 106-115.

Mendola, P., Ha, S., Pollack, A. Z., Zhu, Y., Seeni, I., Kim, S. S., Sherman, S. and Liu, D. (2017). "Chronic and Acute Ozone Exposure in the Week Prior to Delivery Is Associated with the Risk of Stillbirth." Int J Environ Res Public Health 14(7).

Møller, P., Danielsen, P. H., Karottki, D. G., Jantzen, K., Roursgaard, M., Klingberg, H., Jensen, D. M., Christophersen, D. V., Hemmingsen, J. G. and Cao, Y. (2014). "Oxidative stress and inflammation generated DNA damage by exposure to air pollution particles." Mutation Research/Reviews in Mutation Research 762: 133-166.

Pedersen, M. (2016). "Is it still important to study if ambient air pollution triggers stillbirth?" Occup Environ Med 73(9): 571-572.

Pereira, L. A. A., Loomis, D., Conceição, G. M. S., Braga, A. s. L. F., Arcas, R. n. M., Kishi, H. S., Singer, J., Böhm, G. r. M. and Saldiva, P. H. N. (1998). "Association between Air Pollution and Intrauterine Mortality in São Paulo, Brazil." Environmental health perspectives 106(6): 325-329.

Pinar, H., Goldenberg, R. L., Koch, M. A., Heim-Hall, J., Hawkins, H. K., Shehata, B., Abramowsky, C., Parker, C. B., Dudley, D. J. and Silver, R. M. (2014). "Placental findings in singleton stillbirths." Obstetrics and gynecology 123(2 0 1): 325.

Poursafa, P., Keikha, M. and Kelishadi, R. (2015). "Systematic review on adverse birth outcomes of climate change." Journal of research in medical sciences: the official journal of Isfahan University of Medical Sciences 20(4): 397.

Ptacek, I., Sebire, N., Man, J., Brownbill, P. and Heazell, A. (2014). "Systematic review of placental pathology reported in association with stillbirth." Placenta 35(8): 552-562.

Ryerson, T., Trainer, M., Angevine, W., Brock, C., Dissly, R., Fehsenfeld, F., Frost, G., Goldan, P., Holloway, J. and Hübler, G. (2003). "Effect of petrochemical industrial emissions of reactive alkenes and NOx on tropospheric ozone formation in Houston, Texas." Journal of Geophysical Research: Atmospheres 108(D8).

Rylander, C., Odland, J. O. and Sandanger, T. M. (2013). "Climate change and the potential effects on maternal and pregnancy outcomes: an assessment of the most vulnerable--the mother, fetus, and newborn child." Glob Health Action 6: 19538.

Salam, M. T., Millstein, J., Li, Y. F., Lurmann, F. W., Margolis, H. G. and Gilliland, F. D. (2005). "Birth outcomes and prenatal exposure to ozone, carbon monoxide, and particulate matter: results from the Children's Health Study." Environ Health Perspect 113(11): 1638-1644.

Sapkota, A. C., Adam P; Nachman, Keeve E; Cohen, Aaron J; Ritz, Beate (2012). "Exposure to particulate matter and adverse birth outcomes: A comprehensive review and meta-analysis." Air Quality, Atmosphere, & Health 5(4): 369-381.

Schifano, P., Lallo, A., Asta, F., De Sario, M., Davoli, M. and Michelozzi, P. (2013). "Effect of ambient temperature and air pollutants on the risk of preterm birth, Rome 2001–2010." Environment international 61: 77-87.

Siddika, N., Balogun, H. A., Amegah, A. K. and Jaakkola, J. J. (2016). "Prenatal ambient air pollution exposure and the risk of stillbirth: systematic review and meta-analysis of the empirical evidence." Occup Environ Med 73(9): 573-581.

Smith, G. C. and Fretts, R. C. (2007). "Stillbirth." The Lancet 370(9600): 1715-1725.

Sram, R. J. (1999). "Impact of Air Pollution on Reproductive Health." Environmental health perspectives 107(11): A542-A543.

Stieb, D. M., Chen, L., Eshoul, M. and Judek, S. (2012). "Ambient air pollution, birth weight and preterm birth: a systematic review and meta-analysis." Environ Res 117: 100-111.

Stillbirth Collaborative Research Network Writing Group (2011). "Causes of death among stillbirths." Jama 306(22): 2459.

Stillerman, K. P., Mattison, D. R., Giudice, L. C. and Woodruff, T. J. (2008). "Environmental exposures and adverse pregnancy outcomes: a review of the science." Reprod Sci 15(7): 631-650.

Strand, L. B., Barnett, A. G. and Tong, S. (2011). "The influence of season and ambient temperature on birth outcomes: a review of the epidemiological literature." Environ Res 111(3): 451-462.

Strand, L. B., Barnett, A. G. and Tong, S. (2012). "Maternal exposure to ambient temperature and the risks of preterm birth and stillbirth in Brisbane, Australia." Am J Epidemiol 175(2): 99-107.

Sun, X., Luo, X., Zhao, C., Zhang, B., Tao, J., Yang, Z., Ma, W. and Liu, T. (2016). "The associations between birth weight and exposure to fine particulate matter (PM2.5) and its chemical constituents during pregnancy: A meta-analysis." Environ Pollut 211: 38-47.

Symanski, E., Davila, M., McHugh, M., Waller, D., Zhang, X. and Lai, D. (2014). "Maternal Exposure to Fine Particulate Pollution During Narrow Gestational Periods and Newborn Health in Harris County, Texas." Maternal and child health journal 18(8): 2003-2012.

Texas Department of State Health Services. (2015a). "Annual Reports: 2006 Texas Vital Statistics - Deaths." from http://www.dshs.state.tx.us/chs/vstat/vs06/data.shtm#death

Texas Department of State Health Services. (2015b). "Annual Reports: 2010 Texas Vital Statistics - Deaths." from http://www.dshs.state.tx.us/chs/vstat/vs10/data.shtm#death

Texas Department of State Health Services. (2015c). "Annual Reports: 2012 Texas Vital Statistics - Dealths."   Retrieved Report, from http://www.dshs.state.tx.us/chs/vstat/vs12/data.shtm#death.

Texas Department of State Health Services. (2015d). "Annual Reports: 2013 Texas Vital Statistics - Dealths."   Retrieved Report, from http://www.dshs.state.tx.us/chs/vstat/vs13/data.aspx#death.

Vrijheid, M., Martinez, D., Manzanares, S., Dadvand, P., Schembari, A., Rankin, J. and Nieuwenhuijsen, M. (2011). "Ambient air pollution and risk of congenital anomalies: a systematic review and meta-analysis." Environ Health Perspect 119(5): 598-606.

Wei, Y., Han, I.-K., Shao, M., Hu, M., Zhang, J. and Tang, X. (2009). "PM2. 5 constituents and oxidative DNA damage in humans." Environmental science & technology 43(13): 4757-4762.

Yang, S., Tan, Y., Mei, H., Wang, F., Li, N., Zhao, J., Zhang, Y., Qian, Z., Chang, J. J., Syberg, K. M., Peng, A., Mei, H., Zhang, D., Zhang, Y., Xu, S., Li, Y., Zheng, T. and Zhang, B. (2018). "Ambient air pollution the risk of stillbirth: A prospective birth cohort study in Wuhan, China." Int J Hyg Environ Health 221(3): 502-509.

Zhang, Y., Yu, C. and Wang, L. (2017). "Temperature exposure during pregnancy and birth outcomes: An updated systematic review of epidemiological evidence." Environ Pollut 225: 700-712.

Zhu, X., Liu, Y., Chen, Y., Yao, C., Che, Z. and Cao, J. (2015). "Maternal exposure to fine particulate matter (PM2.5) and pregnancy outcomes: a meta-analysis." Environ Sci Pollut Res Int 22(5): 3383-3396.