Distribution Agreement

Signature:

____________________________ ____________________________

Yue Xie Date

Preterm birth, stillbirth and ambient air pollution in Georgia, 2006 to 2013

By

Yue Xie

Master of Science in Public Health

Biostatistics and Bioinformatics

____

Howard H. Chang, Ph.D.

(Thesis Advisor)

____

Matthew J. Strickland, Ph.D.

(Reader)

Preterm birth, stillbirth and ambient air pollution in Georgia, 2006 to 2013

By

Yue Xie

B.A.

Muhlenberg College

2019

Thesis Advisor: Howard H. Chang, Ph.D.

Reader: Matthew J. Strickland, Ph.D.

An abstract of
A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University in
partial fulfillment of the requirements for the degree of
Master of Science in Public Health in
Biostatistics and Bioinformatics
2021

Abstract

Preterm birth, stillbirth and ambient air pollution in Georgia, 2006 to 2013

By Yue Xie

Background: Previous epidemiologic studies suggest associations between ambient air pollution exposure during pregnancy and adverse birth outcomes, including preterm births (PTB) and stillbirth (STB); but mixed findings exist.

Objective: We investigated associations between 8 ambient air pollutants over 6 exposure windows, and risks of PTB (< 37 weeks of gestation) and STB in Georgia.

Methods: Singleton fetal death records (n = 5,797) and live birth records (n = 1,055,744) with 20 - 44 weeks of gestation and estimated date of conception between 1st January 2006, and 30th December 2013 were obtained the State Office of Vital Records, Georgia Department of Public Health. Daily concentrations of $PM_{2.5}$, CO, OC, EC, O_3, NO_2, NO_3, and NO_x were estimated by combining numerical model simulations with measurements from stationary monitors at 12-km resolution. Cox proportional hazard models with time-varying covariates were used to examine average pollutant concentration during trimester 1, trimester 2, trimester 3, the entire pregnancy, 1-week lag and 4-week lag. Models were adjusted for seasonality and year of conception, maternal race, ethnicity, marital status, median house income, tobacco usage during pregnancy, and infant sex.

Results: Associations ($p < 0.05$) were observed for several pollutants in the STB analysis for trimester 2 and pregnancy-wide average exposures. NOx, O3, and EC were found to elevate the risk of STB. For example, hazard ratios for an interquartile range increase in ozone during the second trimester and entire pregnancy were 1.15 (CI: 1.04-1.26) and 1.12 (CI: 1:02-1.22). Most associations between PTB and pollutants were null.

Conclusions: Exposure to ambient air pollutants during pregnancy may be associated with elevating the risk of STB in Georgia.

Preterm birth, stillbirth and ambient air pollution in Georgia, 2006 to 2013

By

Yue Xie

B.A.

Muhlenberg College

2019

Thesis Advisor: Howard H. Chang, Ph.D.

Reader: Matthew J. Strickland, Ph.D.

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University in
partial fulfillment of the requirements for the degree of
Master of Science in Public Health in
Biostatistics and Bioinformatics
2021

Acknowledgement

First and foremost, I would like to appreciate my parents who have supported me to pursue my career in public health. I would like to give huge praise to my thesis advisor, Dr. Howard Chang, for his constant direction and guidance. He is a great mentor to students and is always available when you need him for help. His knowledge, enthusiasm, and patience for this project motivated me to move forward. I am so grateful that I got to work with him throughout my journey at Emory University.

This study would not have been completed without the help from Rohan D'Souza. Thanks for all the preparation and groundwork we accomplished at the very beginning of this study. I would also like to thank Sodahm Yoo (Robin), my groupmate on Dr. Chang’s team. We were able to collaborate and learn from each other during this process. I also want to thank my friends who have been on my side in this difficult time.

In the end, I want to appreciate all the faculty members and staff of the Rollins School of Public Health Department of Biostatistics and Bioinformatics for their contributions to our overall community.

Table of Contents

1. INTRODUCTION

Associations between adverse birth outcomes and exposure to ambient air pollution during pregnancy have been studied extensively (Bekkar et al., 2020; Stieb et al., 2012). Stillbirth (STB) and preterm birth (PTB) are two more frequently studied outcomes. In the United States, PTB affected 1 of every 10 births (10%) and has lifelong health impacts (CDC, 2020). STB affected about 1 in 160 births (0.63%) and approximately 24,000 STB were reported every year (CDC, 2020) in the States. Nationally, the rate of STB and PTB has remained stable during recent years and it is essential to identify the underlying causes, especially for potentially modifiable risk factors such as ambient air pollution. Within the current literature, common pollutants of interest that have been examined in relation to STB and PTB include particulate matter with an aerodynamic diameter ≤ 2.5 μm ($PM_{2.5}$), nitrogen oxides (NO_x), sulfur dioxide (SO_2), carbon monoxide (CO), and ozone (O_3) (Rammah et al., 2019). These pollutants represent a diverse set of emission sources, particularly in an urban environment.

Despite the large number of epidemiologic studies performed in various locations around the world, reported associations across different pollutants and exposure windows during pregnancy often show mixed findings. For example, a systematic review in 2012 for PTB (Stieb et al.) indicated the lack of consistent results for ozone and sulfur dioxide and more research on variation in effects by exposure period should be further explored. A more recent review for studies conducted in the US (Bekkar et al., 2020) noted that only 6 out of 11 studies reported positive association between PTB and average $PM_{2.5}$ exposures during the entire pregnancy but the other studies reported no association with exposure measures over different exposure periods. Studies on STB are less numerous. One study from New Jersey found no association of STB with trimester-wide or pregnancy-wide exposure to $PM_{2.5}$ but noted a significant association with carbon monoxide (CO), nitrogen dioxide (NO_2), and sulfur dioxide (SO_2). Two other studies indicated a positive association but in various other exposure windows (Bekkar et al., 2020).

One of the main limitations of previous studies is that they often applied logistic regression to analyze PTB or STB as a binary outcome. Because ambient air pollution is a time-varying exposure, the exposure windows of interest for each birth can vary based on the duration of pregnancy (Rammah et al., 2019). Survival analysis with time-varying covariate can accommodate time-varying air pollution exposures during pregnancy to examine both trimester-wide, pregnancy-wide and short-term exposures on the risks for STB or PTB.

In this study, our primary objective was to conduct time-to-event analyses to examine the risk of PTB and STB associated with pollutant exposure in Georgia during the period 2006 to 2013. We extend the previous state-wide analysis of PTB in Georgia from 2002 to 2006 (Hao et al., 2016), which observed positive associations between several pollutants. For example, associations with CO exposure during the first, second, and third trimesters and entire pregnancy with odds ratio of 1.005 (95% CI: 1.001 -1.009), 1.007 (95% CI: 1.002 -1.011), 1.010 (95% CI: 1.006-1.014), and 1.011 (95% CI: 1.006 -1.017) for interquartile range (IQR) increases were uncovered.

This PTB analysis using more recent birth records is of interest because of air quality has improved in this region. The large state-wide analysis on STB is also new.

2. METHODS

2.1 Study population

All live birth and fetal death records were provided by the State Office of Vital Records, Georgia Department of Public Health (DPH). Only singleton live births (n = 1,055,744) with gestational weeks of 20 - 44 and an estimated conception date between January 1st, 2006 and December 31st, 2013 in Georgia were included in the PTB analyses. For records with missing gestational age, an alternate gestational age estimate was obtained based on self-reported last menstrual period (LMP) and birthdate. We excluded births with (a) birth weight < 250 g or > 7500 g or missing (0.006%); (b) missing geocode data at the census tract level (0.36%); (c) in counties where the number of births is less than 300 (0.12%); and (d) missing maternal and pregnancy covariates of interest (5.02%). In total, 997,571 records were eligible for the preterm analysis and 93,194 (9.34%) were preterm births (gestational weeks <37).

STB was defined as a pregnancy loss after 20 completed gestational weeks. A total of 5,797 STB records (0.55% of the live births) were identified from the Georgia fetal death records with an estimated conception date between January 1st, 2006 and December 31st. After applying the same exclusion criteria, we identified 3,098 eligible STB records (46.6%) due to a large number of missing information on maternal characteristics and geocode. A case-control study was conducted for STB due to the rarity of the outcome. For each STB, we randomly selected up to 5 live birth records in the same county, in the same conception year, and have gestational age greater or equal than the STB case. 4 STB were excluded due to the lack of a match (gestational age ≥ 43). Only 5 STB were unable to match with 5 controls (0.2%), and among them, 3 were matched with 2 controls. The final case-control dataset includes 18,552 records.

2.2 Exposure assessment

Daily air pollution concentrations $PM_{2.5}$, elemental carbon (EC), CO, organic carbon (OC), O_3, NO_2, Nitrate (NO_3), and NO_x from a recent data fusion product that combines measurements from monitoring network and simulations from the Community Multi-scale Air Quality model (CMAQ), which incorporates information on emission, meteorology, and atmospheric chemistry (Senthilkumar et al., 2019). The data fusion products have excellent spatial out-of-sample prediction performance at locations without monitors, for example, O_3 (R2 = 0.83), $PM_{2.5}$ (R2 = 0.74), and NO_2 (R2 = 0.72). Gridded air quality estimates at 12-km by 12-km spatial resolution were linked to the maternal residential address census tract.

We treated gestational age as time-to-event data. The analysis assumes all births became at risk at week 20. For preterm analyses, term births (gestational weeks ≥ 37) were censored at week 37 and for stillbirth analyses, event time can occur up to week 44. Pollution concentrations were treated as time-varying covariates if the exposure window varies across the at-risk period. Breslow approximation was used for tied survival times in completed weeks. Let t be the completed gestational week for an ongoing pregnancy. We examined 6 exposure windows defined as follows: trimester 1 (gestational weeks 3 to 13). (2) trimester 2 (week 14 to *t* or 26); (3) trimester 3 (week 27 to *t*); (4) entire pregnancy (week 1 to *t*); (5) a 1-week lag (week *t*); and (6) a 4-week lag (week *t* – 4 to *t*).

2.3 Statistical Analysis

The following maternal and fetal characteristics were adjusted in our analyses: maternal age (in years: 10-19, 20–24, 25–29, 30–34, 35–39, 40-45, 46-50, or >50), maternal race (White, Black, Native American & Alaskan, Asian Pacific Islander, Multiracial), maternal ethnicity (non-Hispanic, Hispanic), marital status (unmarried, married), self-reported tobacco use (not indicated, indicated), median house income quantiles, fetal/infant sex (male, female). Since ambient air pollution is often related to seasonality, we controlled for conception year (2006-2013) for preterm analyses, and conception season: spring (March-May), summer (June – August), fall (September – November), and winter (December – February).

Due to the large sample size for a state-wide analysis, associations between PTB and air pollution were conducted using a two-stage approach. In the first stage, separate Cox proportional hazard models were fitted for each county (n=150) to obtain log hazard ratios and the corresponding standard errors. Then, a random-effect meta-analysis was applied to pool county-specific estimates. Between-county heterogeneity was estimated using the restricted maximum likelihood (REML) method.

We conducted a state-wide STB case-control analysis by fitting Cox proportional hazard model where each matched case-control set was treated as a separate stratum.

All other covariates in the PTB model were included except the matching variable year of conception and county.

We also performed sensitivity analyses for both PTB and STB, including performing a logistic regression, using natural cubic splines to model non-linear effects of maternal age and conception date. Our data was compiled using SAS version 9.4, SAS Institute, Inc., Cary, NC, USA and analyses were generated using R version 4.0.2, R Core Team (2020).

3. RESULTS

Table 1 and 2 provide descriptive characteristics for preterm, full term, and stillbirth fetuses. The mean length of gestation was 34 (standard deviation (sd) = 3.3) weeks for preterm birth, 28 (sd = 6.7) for stillbirth, and 39 (sd = 1) for full-term infants. Among all live births, 9.3% were preterm infants and among all STB records, 84.2% percent of STB occurred before week 37. Approximately 76.6% of births and 71.5% STB were given by women from 20 to 35 years old. The PTB rates decreased throughout the years from 9.53% in 2006 to 8.70% in 2013. Higher risk of PTB and STB was associated with infant sex (male), maternal race (Black), marital status (unmarried), used tobacco during pregnancy and median household income. Higher risk of STB was also associated with maternal ethnicity (non-Hispanic). Adjusted hazard ratios for maternal and pregnancy characteristics are given in Table 6 in the Appendix.

Table 4 in the Appendix gives summary statistics of total-pregnancy exposure for each pollutant by three conception years (2006, 2009, 2013). Exposures to all pollutants decreased considerably over the study period. We observed moderate to high correlations between pollutants. For example, for pregnancy-wide exposures in PTB analyses, NO_x was correlated with NO_2 (r = 0.89) and NO_3 (r = 0.46). $PM_{2.5}$ was correlated with NO_2 (r = 0.50) and NO_3 (r = 0.29). The correlations for pregnancy-wide exposures were similar for STB. The complete correlation matrix for PTB is given in Table 7 in the Appendix.

Table 1: Characteristics of preterm analyses in Georgia, 2006-2013

	Preterm infants (N=93194)	Term infants (N=904377)	Total (N=997571)
Gestational age (weeks)			
Mean (SD)	33.8 (3.3)	38.9 (1.0)	38.4 (2.1)
Infant sex			
Male	48999 (52.6%)	460441 (50.9%)	509440 (51.1%)
Female	44195 (47.4%)	443936 (49.1%)	488131 (48.9%)
Conception season			
Spring	23636 (25.4%)	225852 (25.0%)	249488 (25.0%)
Summer	22749 (24.4%)	221123 (24.5%)	243872 (24.4%)
Fall	23086 (24.8%)	226698 (25.1%)	249784 (25.0%)
Winter	23723 (25.5%)	230704 (25.5%)	254427 (25.5%)
Maternal age (years)			
10-19	10998 (11.8%)	92712 (10.3%)	103710 (10.4%)
20-24	25301 (27.1%)	239199 (26.4%)	264500 (26.5%)
25-29	24116 (25.9%)	252955 (28.0%)	277071 (27.8%)
30-34	19182 (20.6%)	203059 (22.5%)	222241 (22.3%)
35-39	10656 (11.4%)	96566 (10.7%)	107222 (10.7%)
40-45	2820 (3.0%)	19195 (2.1%)	22015 (2.2%)
45-49	118 (0.1%)	683 (0.1%)	801 (0.1%)
50+	3 (0.0%)	8 (0.0%)	11 (0.0%)

Maternal race			
White	45139 (48.4%)	529346 (58.5%)	574485 (57.6%)
Black	42047 (45.1%)	303491 (33.6%)	345538 (34.6%)
Native American, Alaskan	2637 (2.8%)	34489 (3.8%)	37126 (3.7%)
Multiracial	3303 (3.5%)	36286 (4.0%)	39589 (4.0%)
API	68 (0.1%)	765 (0.1%)	833 (0.1%)
Maternal ethnicity			
Non-Hispanic	80973 (86.9%)	759612 (84.0%)	840585 (84.3%)
Hispanic	12221 (13.1%)	144765 (16.0%)	156986 (15.7%)
Marital status			
Unmarried	49537 (53.2%)	401601 (44.4%)	451138 (45.2%)
Married	43657 (46.8%)	502776 (55.6%)	546433 (54.8%)
Tobacco usage during pregnancy			
Not Indicated	85688 (91.9%)	849148 (93.9%)	934836 (93.7%)
Indicated	7506 (8.1%)	55229 (6.1%)	62735 (6.3%)
Median household income			
[5816,35344]	27462 (29.5%)	217771 (24.1%)	245233 (24.6%)
(35344, 45758]	23603 (25.3%)	223952 (24.8%)	247555 (24.8%)
(45758,61444]	14400 (15.5%)	145640 (16.1%)	160040 (16.0%)
(61444,207500]	27729 (29.8%)	317014 (35.1%)	344743 (34.6%)

Table 2: Characteristics of Stillbirth Analyses in Georgia, 2006-2013

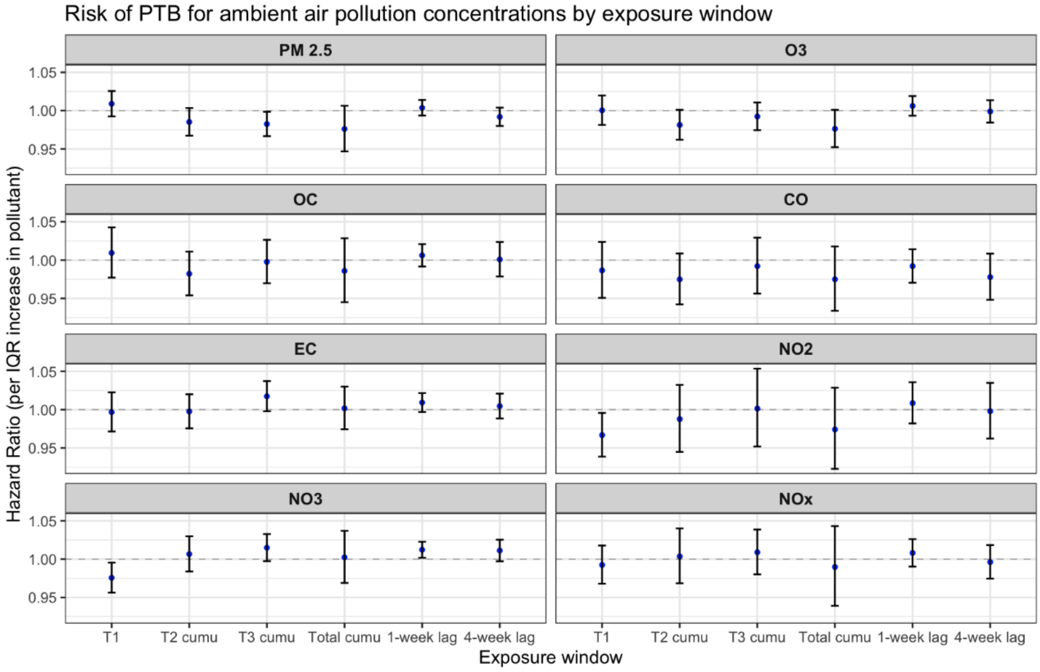
	Control (N=15458)	Stillbirth (N=3094)	Total (N=18552)
Gestational age (weeks)			
Mean (SD)	38.7 (1.7)	28.1 (6.7)	36.9 (5.1)
Infant sex			
Male	7887 (51.0%)	1645 (53.2%)	9532 (51.4%)
Female	7571 (49.0%)	1449 (46.8%)	9020 (48.6%)

Conception season			
Spring	3816 (24.7%)	739 (23.9%)	4555 (24.6%)
Summer	3788 (24.5%)	741 (23.9%)	4529 (24.4%)
Fall	3901 (25.2%)	796 (25.7%)	4697 (25.3%)
Winter	3953 (25.6%)	818 (26.4%)	4771 (25.7%)
Maternal age (years)			
10-19	1514 (9.8%)	400 (12.9%)	1914 (10.3%)
20-24	4184 (27.1%)	831 (26.9%)	5015 (27.0%)
25-29	4233 (27.4%)	768 (24.8%)	5001 (27.0%)
30-34	3548 (23.0%)	614 (19.8%)	4162 (22.4%)
35-39	1621 (10.5%)	375 (12.1%)	1996 (10.8%)
40-45	358 (2.3%)	106 (3.4%)	464 (2.5%)
Maternal race			
White	8380 (54.2%)	1114 (36.0%)	9494 (51.2%)
Black	5895 (38.1%)	1864 (60.2%)	7759 (41.8%)
Native American, Alaskan	577 (3.7%)	68 (2.2%)	645 (3.5%)
Multiracial	590 (3.8%)	45 (1.5%)	635 (3.4%)
API	16 (0.1%)	3 (0.1%)	19 (0.1%)
Maternal ethnicity			
Non-Hispanic	13314 (86.1%)	2938 (95.0%)	16252 (87.6%)
Hispanic	2144 (13.9%)	156 (5.0%)	2300 (12.4%)
Marital status			
Unmarried	7251 (46.9%)	1846 (59.7%)	9097 (49.0%)
Married	8207 (53.1%)	1248 (40.3%)	9455 (51.0%)
Tobacco usage during pregnancy			
Not Indicated	14486 (93.7%)	2785 (90.0%)	17271 (93.1%)
Indicated	972 (6.3%)	309 (10.0%)	1281 (6.9%)
Median household income			
[5816,35344]	4140 (26.8%)	995 (32.2%)	5135 (27.7%)
(35344, 45758]	3868 (25.0%)	789 (25.5%)	4657 (25.1%)
(45758,61444]	2437 (15.8%)	439 (14.2%)	2876 (15.5%)
(61444,207500]	5013 (32.4%)	871 (28.2%)	5884 (31.7%)

3. 1 Ambient Air Pollution and Preterm Birth

Figure 1 shows the hazard ratios for PTB associated with each of the 8 pollutants and 6 exposure windows examined. Each hazard ratio was scaled by the exposure's interquartile range across the entire state (Table 3). In fully adjusted models, we found a 1.2% increase (HR = 1.012, 95% CI: 1.00 - 1.02) in the risk of preterm per 0.76 $\mu g/m^3$ increase in NO_3 exposure for 1-week lag averages. There was no other consistent association to a particular exposure window in this analysis. No significant associations were identified for EC, OC, CO, and NO_x exposures and PTB. Some protective effects were detected for $PM_{2.5}$, NO_2, and NO_3 exposures. In trimester 1, there was a 2% decrease (HR = 0.99, 95% CI: 0.96 - 0.10) in risk of PTB per 0.71 $\mu g/m^3$ increase in NO_3 and a 4% decrease (HR = 0.96, 95% CI: 0.94 - 0.10) in risk of PTB per 0.33-ppb increase in NO_2. $PM_{2.5}$ also had a protective effect for PTB during trimester 3 with a 2% decrease (HR=0.98, 95% CI: 0.97 - 0.10) in risk of preterm per 3.54 $\mu g/m^3$ increase in $PM_{2.5}$ exposure. The sensitivity analyses were conducted for $PM_{2.5}$ to compare the exposure effect during the first and third trimester and the results from logistic regression were similar to the survival analyses.

Figure 1: Hazard Ratio (per IQR increase) of preterm births for ambient air pollution concentrations by exposure window in Georgia



T1 indicates trimester 1 average; T2: trimester 2 cumulative averages; T3: trimester 3 cumulative averages; Total cumu: Total cumulative averages.

Table 3: Interquartile range of gestational air pollutant exposures during pregnancy in preterm and stillbirth studies

	T1	T2	T3	Tot Preg	1-week lag	4-week lag
$PM_{2.5}$ (µg/m^3)						
Stillbirth	3.141	2.992	3.101	2.802	3.959	3.16
Preterm	3.461	3.33	3.544	3.207	4.316	3.558
CO (ppm)						
Stillbirth	0.336	0.326	0.323	0.321	0.327	0.323
Preterm	0.381	0.368	0.361	0.368	0.365	0.364
EC (µg/m3)						
Stillbirth	0.398	0.373	0.37	0.366	0.394	0.38
Preterm	0.405	0.399	0.4	0.393	0.417	0.399
NO_2 (ppb)						
Stillbirth	12.854	12.465	12.175	12.289	12.562	12.519
Preterm	12.687	12.547	12.529	12.322	12.68	12.579
NO_3 (ppm)						

Stillbirth	0.635	0.621	0.641	0.535	0.67	0.65
Preterm	0.709	0.686	0.726	0.592	0.762	0.728
NO_x (ppb)						
Stillbirth	28.197	27.539	26.669	27.833	26.655	27.451
Preterm	28.39	28.064	27.35	28.655	26.758	27.487
OC (µg/m3)						
Stillbirth	1.681	1.552	1.463	1.621	1.63	1.533
Preterm	2.728	2.727	2.614	2.759	2.549	2.627
O_3 (ppm)						
Stillbirth	0.013	0.012	0.013	0.009	0.015	0.013
Preterm	0.014	0.013	0.014	0.009	0.016	0.014

T1 indicates trimester 1; T2: trimester 2; T3: trimester 3; Tot Preg: entire pregnancy.

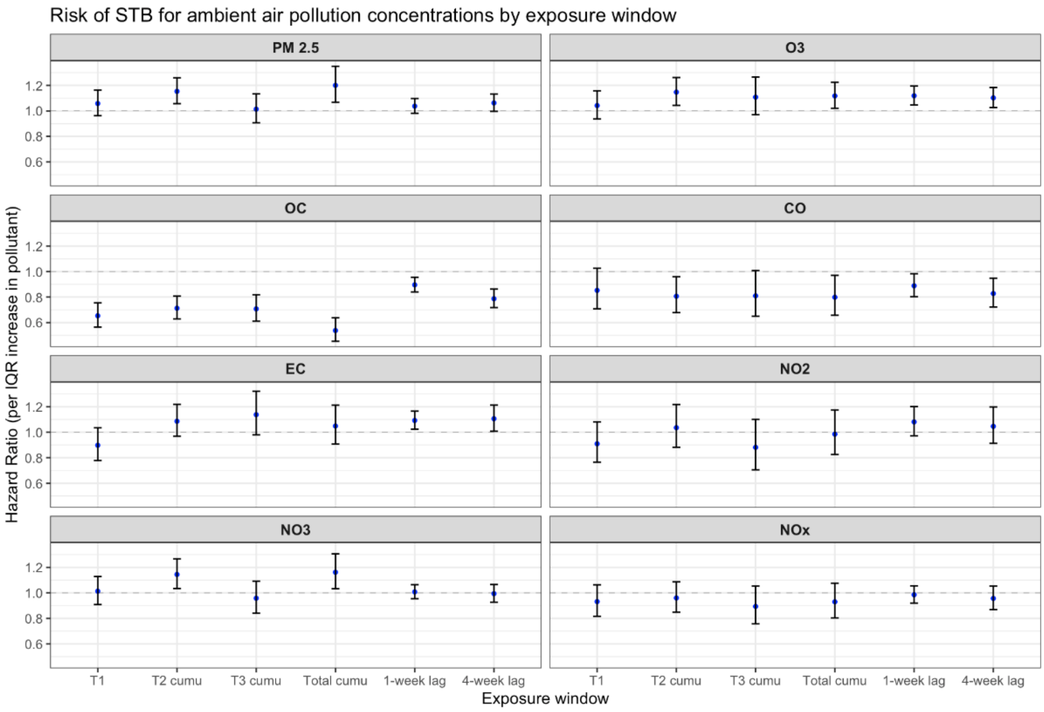
3.2 Ambient Air Pollution and Stillbirth

Figure 2 shows the hazard ratios for STB associated with each of the 8 pollutants and 6 exposure windows examined. Each hazard ratio was scaled by the exposure's interquartile range over the entire state (Table 3). For $PM_{2.5}$, O_3, and NO_3, we found evidence of susceptible exposure windows for trimester 2 and cumulative pregnancy-wide exposures. In fully adjusted models, there was a 15% increase (HR = 1.15, 95% CI: 1.06 -1.26) in risk of STB per 2.99 µg/m^3 increase in $PM_{2.5}$ exposure during trimester 2 and a 20% increase (HR = 1.20, 95% CI: 1.07 - 1.35) per 2.80 µg/m^3 increase in $PM_{2.5}$ exposure for cumulative exposures over the entire pregnancy. Similarly, O_3 had elevated risks of 15% (HR = 1.15, CI: 1.04 - 1.26) and 12% (HR = 1.12, CI: 1.02 - 1.22) for STB in trimester 2 and in entire pregnancy per IQR increase. For NO_3, hazard ratios of 1.14 (CI: 1.03 - 1.27) in trimester 2 and 1.16 (CI: 1.03 - 1.31) in entire pregnancy per IQR increase were noted.

For the trimester 1 exposure window, we found both negative and protective effects between air pollution and STB. There was a 12% increase (HR = 1.12, CI: 1.05 - 1.20) in the risk of STB per 0.015 ppm increase in O_3 for 1-week lag means and a 10% increase (HR = 1.10, CI: 1.03 - 1.18) per 0.013 ppm increase for 4-week lags. EC also has a similar effect for 1-week lags and 4-week lags.

Interestingly, we found OC had consistent protective associations with STB across all exposure windows. OC was also the only pollutant with an effect on the first trimester of gestation. CO also had protective associations with STB in lagged exposure window, trimester 2 and entire pregnancy. NO_2 and NO_x exposures at any time during pregnancy were not found to be associated with STB.

Figure 2: Hazard Ratio (per IQR increase) of stillbirths for ambient air pollution concentrations by exposure window in Georgia



4. DISCUSSION

Our study analyzed eight air pollutants and six exposure windows using time-dependent Cox proportional hazard model across the state of Georgia. Particularly, there is a limited number of studies on the association between stillbirth and various pollutants, especially for particulate matter species. The previous Georgia study during an earlier period reported positive associations between various pollutants and PTB (Hao et al., 2016). This is in contrast to our overall null findings. This may be due to the decrease in ambient air pollution levels, resulting in reduced statistical power. It is also possible that the air pollution mixture has become less toxic or there exists a threshold effect.

Our STB analyses generated more distinct results. Our finding that cumulative O_3 exposure over the pregnancy had a 12% increase in risk of STB is consistent with another time-to-event study in Texas which reported a 9% increase in the STB risk per IQR (Rammah et al., 2019) and a US-wide study (relative risk = 1.39, 95% CI:1.05 - 1.84, per 7.8-ppb increase) (Mendola et al, 2017). Contrary to some studies that indicated trimester 1 was the most susceptible exposure window for STB (Hwang et al., 2011), we only found OC to have a protective association with STB in trimester 1. Our study also provide evidence that $PM_{2.5}$ and NO_3 may elevate risks of STB during the second and total trimester.

The main strengths of our study include the large sample size associated with a state-wide analysis and the use of ambient air pollution data products that provide complete spatial and temporal coverage. We also accounted for maternal and socioeconomic characteristics, temporal confounders, and differences in time-varying exposures over multiple gestational lengths between PTB, STB and term births. There were some limitations to this study. First, some maternal health and pregnancy conditions, for example, maternal body mass index, were not collected in the Georgia birth records. These conditions can potentially contribute to adverse birth outcomes and be correlated with air pollution exposures. The obtained STB records from DPH (0.55%) was a little less than the expected number reported in US (0.63%). Also, due to incomplete data on maternal characteristics, the STB sample included in this study was relatively small. Since only 46.5% of the total STB samples were studied, we may lose information on particular risk factors and their association to the outcome. Though missing covariate information may be associated with air pollution exposures. Third, the Breslow approximation was used for tied gestational age and should be compared to exact method for discrete-time models. We also did not examine models with multiple pollutants or multiple exposure windows, even though correlations between pollutants and exposure windows can be moderate to high. Lastly, effect heterogeneity across counties was not studied in our model. Associations between air pollution and adverse birth outcomes may vary in space due to differences in emission sources that contribute to the air pollution mixture.

REFERENCES

1. Bekkar, B., Pacheco, S., Basu, R., & DeNicola, N. (2020). Association of Air Pollution and Heat Exposure With Preterm Birth, Low Birth Weight, and Stillbirth in the US. *JAMA Network Open*, *3*(6), e208243. https://doi.org/10.1001/jamanetworkopen.2020.8243
2. Hao, H., Chang, H. H., Holmes, H. A., Mulholland, J. A., Klein, M., Darrow, L. A., & Strickland, M. J. (2016). Air Pollution and Preterm Birth in the U.S. State of Georgia (2002–2006): Associations with Concentrations of 11 Ambient Air Pollutants Estimated by Combining Community Multiscale Air Quality Model (CMAQ) Simulations with Stationary Monitor Measurements. *Environmental Health Perspectives*, *124*(6), 875–880. https://doi.org/10.1289/ehp.1409651
3. Hwang, B. F., Lee, Y. L., & Jaakkola, J. J. (2011). Air Pollution and Stillbirth: A Population-Based Case–Control Study in Taiwan. *Environmental Health Perspectives*, *119*(9), 1345–1349. https://doi.org/10.1289/ehp.1003056
4. Mendola, P., Ha, S., Pollack, A., Zhu, Y., Seeni, I., Kim, S., Sherman, S., & Liu, D. (2017). 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*, *14*(7), 731. https://doi.org/10.3390/ijerph14070731
5. *Preterm Births | CDC*. (2020, October 30). Centers for Disease Control and Prevention. https://www.cdc.gov/reproductivehealth/maternalinfanthealth/pretermbirth.htm#:%7E:text=Preterm%20birth%20is%20when%20a,born%20in%20the%20United%20States
6. R: A Language and Environment for Statistical Computing [computer program]. Version R 4.0.2. Vienna, Austria: R Foundation for Statistical Computing; 2020.
7. Rammah, A., Whitworth, K. W., Han, I., Chan, W., & Symanski, E. (2019). Time-Varying Exposure to Ozone and Risk of Stillbirth in a Nonattainment Urban Region. *American Journal of Epidemiology*, *188*(7), 1288–1295. https://doi.org/10.1093/aje/kwz095
8. SAS [computer program]. Version 9.4. Cary, NC: SAS Institute Inc; 2014.
9. Senthilkumar, N., Gilfether, M., Metcalf, F., Russell, A. G., Mulholland, J. A., & Chang, H. H. (2019). Application of a Fusion Method for Gas and Particle Air Pollutants between Observational Data and Chemical Transport Model Simulations Over the Contiguous United States for 2005–2014. International Journal of Environmental Research and Public Health, 16(18), 3314. https://doi.org/10.3390/ijerph16183314
10. Stieb, D. M., Chen, L., Eshoul, M., & Judek, S. (2012). Ambient air pollution, birth weight and preterm birth: A systematic review and meta-analysis. *Environmental Research*, *117*, 100–111. https://doi.org/10.1016/j.envres.2012.05.007
11. *What is Stillbirth? | CDC*. (2020, November 16). Centers for Disease Control and Prevention. https://www.cdc.gov/ncbddd/stillbirth/facts.html#ref

Appendix

Table 4: Exposure characteristics for entire pregnancy and by selected years of conception

	Entire Pregnancy	2006	2009	2013
$PM_{2.5}$				
Mean (SD)	11.1 ± 2.4	13.7 ± 2.1	10.2 ± 1.2	8.8 ± 0.8
EC				
Mean (SD)	0.6 ± 0.3	0.7 ± 0.2	0.5 ± 0.2	0.4 ± 0.2
NO_3				
Mean (SD)	0.9 ± 0.4	1.1 ± 0.4	0.9 ± 0.4	0.8 ± 0.4
OC				
Mean (SD)	3.2 ± 1.6	4.2 ± 0.8	3.6 ± 1.1	1.6 ± 0.3
NO_x				
Mean (SD)	28.5 ± 18.8	34.8 ± 22.6	24.5 ± 16.8	26.7 ± 17.2
NO_2				
Mean (SD)	15.7 ± 7.9	19.3 ± 9.5	13.6 ± 6.9	13.5 ± 6.3
CO				
Mean (SD)	0.6 ± 0.2	0.8 ± 0.3	0.5 ± 0.2	0.4 ± 0.1
O_3				
Mean (SD)	0.041 ± 0.006	0.044 ± 0.006	0.038 ± 0.005	0.037 ± 0.003

Table 5: Exposure characteristics for entire pregnancy and by selected years of conception

	Entire Pregnancy	2006	2009	2013
$PM_{2.5}$ ($\mu g/m^3$)				
Mean (SD)	10.6 ± 2.4	13.5 ± 2.4	10.0 ± 1.3	8.7 ± 0.9
EC				
Mean (SD)	0.6 ± 0.3	0.7 ± 0.2	0.5 ± 0.2	0.4 ± 0.2
NO_3				
Mean (SD)	0.8 ± 0.4	1.0 ± 0.4	0.9 ± 0.4	0.8 ± 0.4
OC				
Mean (SD)	2.6 ± 1.2	4.1 ± 0.8	3.5 ± 1.1	1.6 ± 0.3
NO_x				
Mean (SD)	28.1 ± 19.3	33.4 ± 23.9	25.0 ± 17.8	26.6 ± 18.1
NO_2				
Mean (SD)	15.2 ± 7.9	18.5 ± 9.9	13.5 ± 7.0	13.4 ± 6.6
CO				
Mean (SD)	0.5 ± 0.2	0.8 ± 0.3	0.5 ± 0.2	0.4 ± 0.1
O_3				
Mean (SD)	0.041 ± 0.006	0.044 ± 0.007	0.038 ± 0.005	0.037 ± 0.004

Table 6: Adjusted regression estimates and associated 95% confidence intervals of risk factors associated with preterm birth in Fulton County, Georgia and overall stillbirths in Georgia, 2006-2013

	Hazard Ratio PTB	Hazard Ratio STB
Infant sex		
Female	0.93 (0.89, 0.97)	0.91 (0.84, 0.99)
Conception season		
Summer	1.02 (0.96, 1.09)	1.09 (0.96, 1.23)
Fall	0.97 (0.9, 1.04)	1.20 (1.05, 1.37)
Winter	1.01 (0.95, 1.07)	1.14 (1.01, 1.28)
Maternal age (years)		
[20 - 24]	0.93 (0.87, 1)	0.80 (0.7, 0.92)
[25 - 29]	0.99 (0.92, 1.06)	0.88 (0.76, 1.01)
[30 - 34]	1.04 (0.96, 1.12)	0.92 (0.78, 1.07)
[35 - 39]	1.18 (1.08, 1.28)	1.28 (1.08, 1.52)
[40 - 45]	1.64 (1.46, 1.84)	1.51 (1.17, 1.96)
Maternal race		
Black	1.59 (1.49, 1.68)	2.34 (2.11, 2.6)
Native American/Alaskan	0.94 (0.84, 1.05)	0.92 (0.71, 1.21)
Multiracial	1.21 (1.09, 1.34)	0.66 (0.48, 0.91)
API	1.25 (0.74, 2.12)	1.82 (0.52, 6.33)
Maternal ethnicity		
Hispanic	0.98 (0.91, 1.06)	0.43 (0.36, 0.52)
Marital status		
Married	0.76 (0.72, 0.8)	0.76 (0.69, 0.84)
Tobacco usage during pregnancy		
Tobacco usage indicated	1.58 (1.43, 1.73)	1.72 (1.48, 1.98)
Median household income		
(35344, 45758]	0.92 (0.86, 0.98)	0.95 (0.85, 1.07)
(45758, 61444]	0.86 (0.8, 0.93)	0.85 (0.73, 0.98)
(61444, 207500]	0.83 (0.78, 0.87)	0.87 (0.76, 0.98)

Table 7: Exposure correlation between air pollutants in entire pregnancy in PTB analyses in Georgia, 2006-2013

	$PM_{2.5}$	NO_2	NO_3	NO_x	OC	CO	O_3
$PM_{2.5}$							
NO_2	0.51						
NO_3	0.29	0.6					
NO_x	0.38	0.96	0.61				
OC	0.7	0.37	0.43	0.28			
CO	0.66	0.85	0.57	0.81	0.6		
O_3	0.6	-0.08	-0.34	0.26	0.2	0.01	
EC	0.62	0.87	0.53	0.85	0.47	0.82	0.02