

# **Original Contribution**

# Time-Varying Exposure to Ozone and Risk of Stillbirth in a Nonattainment Urban Region

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In a racially and ethnically diverse urban area (Harris County, Texas) with historic nonattainment  $O_3$  levels, we obtained birth and fetal death records from 2008–2013 and estimated maternal residential  $O_3$  concentrations from conception until delivery using inverse-distance interpolation from the local air monitoring network. We examined multipollutant models (with fine particulate matter 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 3.6-partsper-billion increase in  $O_3$  exposure. The risk was higher among women with pregnancies of <37 gestational weeks (hazard ratio (HR) = 1.13, 95% CI: 1.04, 1.23) compared with 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 also conducted a case-crossover analysis and detected no associations with short-term exposure. To our knowledge, this study is the first to use time-to-event analyses to examine stillbirth risk associated with time-varying prenatal ozone ( $O_3$ ) exposure over pregnancy. Our findings indicate that maternal  $O_3$  exposure over pregnancy is associated with stillbirth risk and that Hispanic women and women with shorter pregnancies might be at particular risk.

air pollution; ozone; stillbirth

Abbreviations: CI, confidence interval; HR, hazard ratio; IQR, interquartile range; LMP, last menstrual period; NO<sub>2</sub>, nitrogen dioxide; O<sub>3</sub>, ozone; ppb, parts per billion; PM<sub>2.5</sub>, particulate matter with an aerodynamic diameter less than or equal to  $2.5 \mu m$ ; ppb, parts per billion; SD, standard deviation

Associations between maternal exposure to ambient air pollution during pregnancy and adverse birth outcomes, such as low birth weight, intrauterine growth restriction and preterm birth, 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 (1, 10, 11). Investigations of the associations between poor air quality and stillbirth have examined particulate matter with an aerodynamic diameter  $\leq$ 10 µm (PM<sub>10</sub>) or  $\leq$ 2.5 µm (PM<sub>2.5</sub>) (12–18), nitrogen oxides (13, 14, 16, 18–20), sulfur dioxide (13–15, 19, 20), carbon monoxide (13–16, 18), and ozone (O<sub>3</sub>) (15, 16, 18, 21, 22).

While the literature generally reports suggestive evidence of an association between prenatal exposures to ambient air pollution and stillbirth (11), findings vary by air pollutant and exposure window. In focusing on  $O_3$  exposure experienced over the entire pregnancy, where results are equivocal, a case-control study of stillbirths conducted in Taiwan reported an odds ratio of 0.97 (95% confidence interval (CI): 0.91, 1.04) per 10-parts-per-billion (ppb) increase in  $O_3$  exposure (16). Two later cohort studies of women living in Wuhan, China, and California produced similar results (15, 22). However, in a recent US-wide study, Mendola et al. (21) reported an elevated risk of stillbirth (relative risk = 1.39, 95% CI: 1.05, 1.84) with a 7.8-ppb increase in  $O_3$  exposure. Further, results from a multipollutant model suggested little evidence of confounding due to other routinely monitored air pollutants.

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) (23). Other limitations relate to assessing exposure periods for the duration of pregnancy that can vary in length from 20 weeks 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, given that the highest risks are present in the first trimester and decline thereafter (23, 24).

Given the relatively sparse number of studies and equivocal findings from the investigations that have been carried out, our primary objective was to conduct a retrospective cohort study (23) using time-to-event analyses to examine the risk of stillbirth associated with maternal O<sub>3</sub> exposure in Harris County, Texas, a large urban center currently in nonattainment for this pollutant based on National Ambient Air Quality Standards for  $O_3$  (25, 26). Further, given the ethnically diverse population, a secondary objective was to examine differences in this association among Hispanic women, non-Hispanic black women, and non-Hispanic white women. Our third objective was to examine potential differences in susceptibility to chronic O<sub>3</sub> exposure based on the gestational age of the fetus. Finally, we examined the impact of acute O<sub>3</sub> exposure on stillbirth in a case-crossover analysis.

#### **METHODS**

# Study population

We obtained 394,393 records for singleton livebirths 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. The state of Texas defines a stillbirth as an unintended intrauterine fetal death after no less than 20 completed weeks of gestation (27). A fetal death certificate is required if the death involves a fetus weighing 350 grams or more or, if the weight is unknown, of gestational age of 20 weeks or more (28). 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 Institutional Review Board.

We abstracted the following maternal and fetal characteristics from birth and fetal death records: maternal age (in years: <20, 20-24, 25-29, 30-34, 35-39, or  $\geq 40$ ), 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 vs. smoking at least 3 months before pregnancy and/ or during pregnancy), prepregnancy weight and height (from which we computed body mass index as weight (kg)/height (m)<sup>2</sup> and categorized it as <18.5, 18.5–24.9, 25.0–29.9, 30.0–34.9, or  $\geq$ 35.0), fetal sex, fetal 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 6-year period. We excluded records with missing gestational age and weight (<1%) as well as those with gestational ages outside the range of 20–44 weeks (1.1%). In addition, we excluded birth records with implausible birth weight-gestational age data (<1%) (29) as well as those with estimated 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%) (30). Following these exclusions, there were 1,599 stillbirths and 356,767 livebirths remaining for analysis (Figure 1).

# Air pollution and temperature data

We obtained hourly data for  $O_3$  (ppb),  $PM_{2.5}$  (µg/m<sup>3</sup>), and nitrogen dioxide (NO2; ppb) from all active Texas Commission on Environmental Quality monitors in the greater Houston area, which comprises 8 counties (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<sub>2</sub>. All monitors measured pollutants continuously and year round. We excluded 1 O<sub>3</sub> monitor, 2 PM<sub>2.5</sub> monitors, and 1 NO<sub>2</sub> monitor that each had more than 25% missing observations over the study period. We calculated the maximum 8-hour average O<sub>3</sub> concentration within a 24-hour period, and the daily average PM<sub>2.5</sub> and NO<sub>2</sub> concentrations from each monitoring station. We also obtained data from 7 weather stations in the study area on apparent temperature (reported in degrees Fahrenheit), a measure that reflects overall temperature discomfort and incorporates temperature and humidity, from the National Climatic Data Center (31). We computed daily average apparent temperature for each weather station from January 1, 2007, to December 31, 2013. Because there was little variability (0.15%-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 (power (p) = 2) (32) of the maximum 8-hour average O<sub>3</sub> concentration or the daily average PM<sub>2.5</sub> or NO<sub>2</sub> concentrations for the 3 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 fetal death. We constructed exposure estimates for each pollutant by computing weekly averages until the week of delivery (or death for stillbirths) and then averaged estimates for each applicable gestational period. This means that for every woman, we computed an exposure measure representing average intensity of exposure to each pollutant 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 gestation, when there was a delivery that resulted in a livebirth or stillbirth. We used the same method for apparent temperature.

# Statistical analysis

Time-varying  $O_3$  exposures over pregnancy. We considered gestational age when the stillbirth occurred as time-to-event data and examined O<sub>3</sub> exposure as a time-varying covariate in a single-pollutant survival model. Mothers with livebirths were removed from the population at risk at their week of delivery. We computed hazard ratios and 95% confidence intervals to

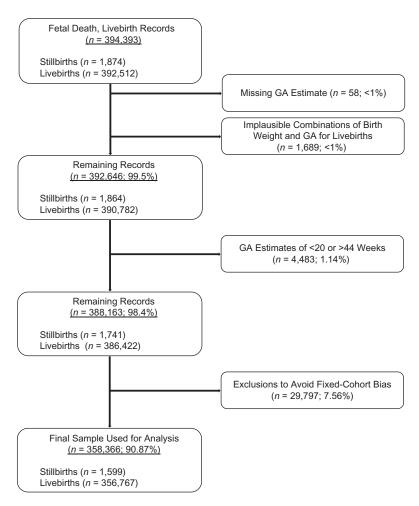


Figure 1. Flowchart detailing exclusions of fetal death and livebirth records obtained from Texas Department of State Health Services for Harris County, Texas, 2008-2013. GA, gestational age.

estimate the risk of stillbirth associated with both a unit increase and an interquartile-range increase in exposure to O<sub>3</sub>. We identified the following variables as risk factors for stillbirth a priori and included them as adjustments in final models: apparent temperature, maternal age, race/ethnicity, education, smoking, prepregnancy body mass index, and number of prenatal care visits. 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% (33), but none did and we did not include them in final models. Finally, we evaluated potential confounding due to exposure to other ambient air pollutants (i.e., PM<sub>2.5</sub> and NO<sub>2</sub>) in multipollutant models. Observations with missing covariate data (n = 8,125) were excluded.

We explored the potential for effect measure modification due to race/ethnicity using stratified analyses of the full models. We also stratified by gestational age groups (gestational age of <37 completed weeks vs. gestational age of  $\ge$ 37 completed weeks). Additionally, we conducted 2 sensitivity analyses. First, we examined the robustness of the exposure assessment by restricting the study population to women who lived within 10 km of the nearest O<sub>3</sub> 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.

Short-term  $O_3$  exposure. We also examined the association between acute O<sub>3</sub> exposure and stillbirth in a case-crossover analysis of all 1,599 stillbirth cases. We used symmetric bidirectional sampling (34) to select 6 control periods per case, 1 week apart each, for the 3 weeks preceding and the 3 weeks following the date of a stillborn delivery. We considered exposures on lag day 1 through 6 and also examined moving average exposures over lag days 1-2, 1-3, 1-4, 1-5, and 1-6. We applied conditional logistic regression to obtain odds ratios and 95% confidence intervals, and models adjusted for daily average apparent temperature. All statistical analyses were performed using SAS, version 9.4 (SAS Institute, Inc., 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 (standard deviation (SD), 6.64) weeks for stillbirths and 39 (SD, 2.23) weeks for livebirths. Mean birth weight was 1,291 (SD, 1,083) g for stillbirths and 3,253 (SD, 550) g for livebirths; 82.5% of stillbirths and 9.1% of livebirths were preterm. Table 1 presents a breakdown of other fetal and maternal characteristics among stillbirths and livebirths. Approximately half of women who delivered a live or stillborn infant were aged 20-29 years (47% of stillbirths, 52% of livebirths) and had less than a high-school education (62% of stillbirths and 54% of livebirths).

Table 2 presents selected percentiles of the distribution of estimated mean concentrations of air pollutant exposures during pregnancy. The median exposure among stillbirths and livebirths, respectively, was 37.71 ppb (interquartile range (IQR), 4.31) and 37.88 ppb (IQR, 3.61) for  $O_3$ , 11.50  $\mu$ g/m<sup>3</sup> (IQR, 1.44) and  $11.55 \,\mu\text{g/m}^3$  (IQR, 0.91) for PM<sub>2.5</sub>, and 9.88 ppb (IQR, 4.44) and 9.92 ppb (IQR, 3.25) for NO<sub>2</sub>. O<sub>3</sub> exposure was negatively correlated with NO<sub>2</sub> (r = -0.50), and PM<sub>2.5</sub> was weakly correlated with NO<sub>2</sub> (r = 0.26); there was no correlation between O<sub>3</sub> and  $PM_{2.5}$  (r = 0.06). Apparent temperature was weakly correlated with  $O_3$  (r = 0.36) and  $PM_{2.5}$  (r = 0.33) and negatively correlated with NO<sub>2</sub> (r = -0.34).

### Time-varying exposure analyses

In fully adjusting models, there was a 9% increase in risk of stillbirth per 3.6-ppb interquartile-range increase in O<sub>3</sub> exposure (hazard ratio (HR) = 1.09, 95% CI: 1.01, 1.18) or a 3% increase in risk per unit increase in O<sub>3</sub> exposure (Table 3). This did not appreciably change in the multipollutant model (HR = 1.09, 95% CI: 1.01, 1.18) that included PM<sub>2.5</sub> and NO<sub>2</sub> as covariates.

Our stratified analyses suggest differences in the association of O<sub>3</sub> 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) and non-Hispanic white (HR = 1.07, 95% CI: 0.90, 1.28) women. In addition, the risk of stillbirth increased by 13% per interquartile-range increase among women with pregnancies shorter than 37 weeks (HR = 1.13, 95% CI: 1.04, 1.23) versus 5% among longer term pregnancies (HR = 1.05, 95% CI: 0.87, 1.27) (Table 3).

In the sensitivity analysis restricted to women who lived within 10 km of 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 included estimated LMP (HR = 1.10, 95% CI: 1.01, 1.19).

#### Short-term exposure analyses

We detected little difference in the selected percentiles of the distributions of acute O<sub>3</sub> exposures by lag day between

case and control periods (Web Table 1, available at https:// academic.oup.com/aje). There was little evidence of an association between interquartile-range increases in daily maximum 8-hour average O<sub>3</sub> exposure and stillbirth in the casecrossover analysis by lag day 1 through lag day 6 (Web Table 2). Null associations were also observed for lagged exposure averages.

#### DISCUSSION

A growing number of studies suggest a positive association between maternal exposure to ambient air pollutants and stillbirth, but the evidence for O<sub>3</sub> is limited. The biological mechanisms underlying an O3-stillbirth association are not yet well understood, although animal studies report evidence of reduced birth weight (35) and reduced postnatal weight gain (36) in offspring following gestational O<sub>3</sub> exposure. The O<sub>3</sub>-stillbirth association is likely mediated by maternal inflammatory responses, which affect fetal growth, and pregnant women are more likely to have a higher internal dose than nonpregnant women due to their high alveolar ventilation (37). We evaluated the association between O<sub>3</sub> and stillbirth in a racially and ethnically diverse urban area (Harris County, Texas, where Houston is located) with historic nonattainment O<sub>3</sub> levels. We first used survival analysis, which allowed us to evaluate the same exposure windows at different gestational ages that might result in a stillbirth, and then considered short-term exposures over lag day periods in a case-crossover analysis.

We found a 9% increased risk of stillbirth per 3.6-ppb increase in O<sub>3</sub> exposure. For ease of comparison with previous findings, this represents a hazard ratio of 1.28 (95% CI: 1.04, 1.57) per 10-ppb increase in  $O_3$  exposure. Previous studies are mixed; 3 studies, conducted in Taiwan in 2011 (16), California in 2015 (15), and Wuhan, China, in 2018 (22), reported null findings for entire pregnancy exposure. Our findings confirm the strong associations reported in a US-wide study for exposure over the entire pregnancy (relative risk = 1.39, 95% CI: 1.05, 1.84, per 7.8-ppb IQR increase) (21). However, we found no evidence of an association between short-term O<sub>3</sub> exposure and risk of stillbirth, whereas Mendola et al. (21) reported risk ratios that ranged from 1.09 to 1.22 for associations on the day of delivery as well as on each of the preceding seven days.

In stratified analysis, we found that the risk of stillbirth increased by 13% per interquartile-range increase in O<sub>3</sub> exposure over the entire pregnancy for women with pregnancies shorter than 37 weeks and by 6% among longer term pregnancies. Hwang et al. (16) previously reported null estimates for the association with pregnancy-long O<sub>3</sub> exposure (per 10 ppb among preterm births, odds ratio = 1.00, 95% CI: 0.91, 1.09, and among term births, odds ratio = 0.93, 95% CI: 0.85, 1.03).

Racial and ethnic disparities in the risk of stillbirth are welldocumented (38-40) and previous studies have reported that associations between ambient air pollution and adverse birth outcomes are modified by maternal race/ethnicity (41-43). The only previous study, to our knowledge, to examine race/ethnicity as an effect measure modifier for the O<sub>3</sub>-stillbirth association found little evidence in support of this hypothesis (15). In contrast, while we cannot rule out the role of chance, the association between O<sub>3</sub> and stillbirth in our population was considerably

Table 1. Selected Sociodemographic Characteristics and Pregnancy Conditions of Women With Stillbirths or Livebirths in Harris County, Texas, 2008–2013.

	Pregnancy Outcome					
Characteristic	Stillbirths (n =	1,599)	Livebirths (n = 3	356,767)		
	No. of Women	%	No. of Women	%		
Maternal age group, years						
<20	179	11.2	38,918	10.9		
20–24	363	22.7	86,520	24.3		
25–29	390	24.4	98,786	27.7		
30–34	309	19.3	83,094	23.3		
35–39	191	11.9	40,155	11.3		
≥40	68	4.3	9,291	2.6		
Missing	99	6.2	3	<0.1		
Maternal race/ethnicity						
Non-Hispanic white	269	16.8	83,143	23.3		
Non-Hispanic black	529	33.1	63,980	17.9		
Hispanic	725	45.3	184,117	51.6		
Other/unknown	76	4.8	25,527	7.2		
Maternal education						
High school or less	987	61.7	192,599	54.0		
Some college	370	23.1	85,703	24.0		
College or beyond	224	14.0	77,963	21.9		
Missing	18	1.1	502	0.1		
No. of prenatal care visits						
0	43	2.7	14,730	4.1		
<10	1,026	64.2	191,524	53.7		
≥10	204	12.8	146,545	41.1		
Missing	326	20.4	3,968	1.1		
Smoking						
No smoking before or during pregnancy	1,519	95.0	343,662	96.3		
Smoked 3 months before and during pregnancy	79	4.9	13,003	3.6		
Missing	1	0.1	102	<0.1		
Fetal sex						
Male	855	53.5	181,756	51.0		
Female	742	46.4	175,011	49.1		
Missing	2	0.1				
Prepregnancy BMI <sup>a</sup>						
<18.5	36	2.3	14,640	4.1		
18.5–24.9	491	30.7	163,355	45.8		
25.0–29.9	397	24.8	94,180	26.4		
30.0–34.9	224	14.0	47,306	13.3		
≥35.0	224	14.0	33,408	9.4		
Missing	227	14.2	3,878	1.1		

Abbreviation: BMI, body mass index.

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<sub>3</sub> (mean = 37.65 (SD, 2.67) ppb) compared with non-Hispanic

<sup>&</sup>lt;sup>a</sup> Weight (kg)/height (m)<sup>2</sup>.

Table 2. Estimated Average Air Pollutant Exposures Across Pregnancy Among Women With Stillbirths or Livebirths in Harris County, Texas, 2008-2013

Pollutant	Pregnancy Outcome									
	Stillbirths (n = 1,599)					Livebirths (n = 356,767)				
	Minimum	25th Percentile	50th Percentile	75th Percentile	Maximum	Minimum	25th Percentile	50th Percentile	75th Percentile	Maximum
O <sub>3</sub> , 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 <sub>2</sub> , 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

Abbreviations:  $NO_2$ , nitrogen dioxide;  $O_3$ , ozone;  $PM_{2.5}$ , particulate matter with an aerodynamic diameter  $\leq 2.5 \,\mu\text{m}$ ; ppb, parts per billion.

black (37.80 (SD, 2.77) ppb) and non-Hispanic white women (38.52 (SD, 2.76) ppb). Further, while the majority of Hispanic women (58.5%) were foreign-born, there was little difference in risk estimates between this group and Hispanic women born in the United States (foreign-born, HR = 1.12 (95% CI: 0.96, 1.31) per IQR increase; US-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<sub>3</sub> exposures, which 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 (including maternal smoking) as potential confounders in a racially and ethnically diverse population. However, we were unable to account for occupational or leisure-time exposures, although there is evidence to suggest that adjustment for these factors might not influence the effect estimate (44). Our study location, Harris County, was uniquely suited for studying O<sub>3</sub> exposure, given its nonattainment status and the higher density of ambient air monitors (48 monitors in total, over a study area of 1,777 square miles) compared with previous studies (15, 16). Characterized by heavy traffic pollution and emissions from many petrochemical manufacturing sites (45, 46), the county has been designated as a nonattainment area for O<sub>3</sub> since 1992 (47) because it has failed to meet subsequent National Ambient Air Quality Standards for O<sub>3</sub>, which stipulate that an area will

meet the standard for  $O_3$  if the 3-year average of the annual fourth-highest daily maximum 8-hour average at every O<sub>3</sub> monitor is less than or equal to the level of the standard (48). The area has been designated as being in moderate nonattainment for O<sub>3</sub> based on the 2008 8-hour O<sub>3</sub> standard of 0.075 parts per million (ppm) (25) and in marginal nonattainment based on the 2015 8-hour  $O_3$  standard of 0.070 ppm (26). Our results are likely generalizable to other US populations with similar exposure levels (i.e., counties currently designated as nonattainment areas for either the 2008 (n = 160) (25) or 2015 (n = 201) (26) 8-hour O<sub>3</sub> standard).

We used inverse-distance weighting to assign exposures. O<sub>3</sub> 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 (49). 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. (50) found the likelihood of misclassification of air pollution exposure due to maternal residential mobility in a Texas population to be small—they found no significant differences in exposure assessment between address at delivery and address at conception. To the extent that the proportion of women who moved during pregnancy was similar between mothers with stillbirths and mothers with livebirths, it is possible our study underestimated

Table 3. Crude and Adjusted Hazard Ratios for the Association Between O<sub>3</sub> Exposure and Stillbirth Among Women in Harris County, Texas, 2008-2013

Pollutant		Risk of Stillbirth								
		Crude		Adjusted <sup>a</sup>						
				All Deliveries		Preterm Deliveries		Term Deliveries		
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI		
O <sub>3</sub> , 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 <sub>3</sub> , 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		

Abbreviations: CI, confidence interval; HR, hazard ratio; O<sub>3</sub>, ozone; ppb, parts per billion.

<sup>&</sup>lt;sup>a</sup> Adjusted for apparent temperature, maternal age, race/ethnicity, education, smoking, prepregnancy body mass index, and number of prenatal care visits.

the association between  $O_3$  exposure and risk of stillbirth due to nondifferential exposure misclassification. This is, to our knowledge, the first study to account for differences in time-varying  $O_3$  exposures over different gestational lengths between stillbirths and livebirths, 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.

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