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A Nationwide Study of Maternal Exposure To Ambient Ozone and Term Birth Weight In the United States

Shengzhi Sun

Capital Medical University, shengzhisun@ccmu.edu.cn

Jiajia Wang

Capital Medical University

Wangnan Cao

Peking University, wangnancao@bjmu.edu.cn

Lizhi Wu

Zhejiang Provincial Center for Disease Control and Prevention

Yu Tian

Capital Medical University

See next page for additional authors

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Authors

Shengzhi Sun, Jiajia Wang, Wangnan Cao, Lizhi Wu, Yu Tian, Feng Sun, Zhenyu Zhang, Yang Ge, Jianqiang Du, Xiaobo Li, and Rui Chen



Full length article

A nationwide study of maternal exposure to ambient ozone and term birth weight in the United States

Shengzhi Sun^{a,1,*}, Jiajia Wang^{a,1}, Wangnan Cao^{b,*}, Lizhi Wu^c, Yu Tian^a, Feng Sun^d, Zhenyu Zhang^e, Yang Ge^f, Jianqiang Du^g, Xiaobo Li^a, Rui Chen^a

^a School of Public Health, Capital Medical University, Beijing 100069, China

^b Department of Social Medicine and Health Education, School of Public Health, Peking University, Beijing 100191, China

^c Zhejiang Provincial Center for Disease Control and Prevention, 3399 Bin Sheng Road Binjiang District, Hangzhou 310051, China

^d Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China

^e Department of Global Health, Peking University School of Public Health, Beijing 100191, China

^f School of Health Professions, University of Southern Mississippi, Hattiesburg 39406, MS, USA

^g The Key Laboratory of Biomedical Information Engineering of Ministry of Education, School of Life Science and Technology, Xi'an Jiaotong University, Xi'an 710049, Shaanxi, China

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ABSTRACT

Background: Maternal exposure to ozone (O₃) may cause systemic inflammation and oxidative stress and contribute to fetal growth restriction. We sought to estimate the association between maternal exposure to O₃ and term birth weight and term small for gestational age (SGA) in the United States (US).

Methods: We conducted a nationwide study including 2,179,040 live term singleton births that occurred across 453 populous counties in the contiguous US in 2002. Daily county-level concentrations of O₃ data were estimated using a Bayesian fusion model. We used linear regression to estimate the association between O₃ exposure and term birth weight and logistic regression to estimate the association between O₃ exposure and term SGA during each trimester of the pregnancy and the entire pregnancy after adjusting for maternal characteristics, infant sex, season of conception, ambient temperature, county poverty rate, and census region. We additionally used distributed lag models to identify the critical exposure windows by estimating the monthly and weekly associations.

Results: A 10 parts per billion (ppb) increase in O₃ over the entire pregnancy was associated with a lower term birth weight (-7.6 g; 95 % CI: -8.8 g, -6.4 g) and increased risk of SGA (odds ratio = 1.030; 95 % CI: 1.020, 1.040). The identified critical exposure windows were the 13th- 25th and 32nd -37th gestational weeks for term birth weight and 13th- 25th for term SGA.

We found the association was more pronounced among mothers who were non-Hispanic Black, unmarried, or had lower education level.

Conclusions: Among US singleton term births, maternal exposure to O₃ was associated with lower rates of fetal growth, and the 13th- 25th gestational weeks were the identified critical exposure windows.

1. Introduction

Birth weight is a good proxy for infant morbidity and mortality and may also influence the health status in adulthood (Horikoshi et al. 2016; Zhang et al. 2014). Known risk factors for fetal growth restriction include genetic makeup, placental insufficiency, poor nutrition, and

maternal morbidities, such as chronic hypertension and gestational diabetes (Malhotra et al. 2019).

Previous studies suggested that environmental risk factors might adversely affect fetal growth, such as ambient heat (Sun et al. 2019a) and ambient air pollution (Bekkar et al. 2020; Li et al. 2017). For example, synthesizing evidence from 32 studies, a recent meta-analysis

* Corresponding authors at: School of Public Health, Capital Medical University, Beijing 100069, China (S. Sun) Department of Social Medicine and Health Education, School of Public Health, Peking University, Beijing 100191, China (W. Cao).

E-mail addresses: shengzhisun@ccmu.edu.cn (S. Sun), wangancao@bjmu.edu.cn (W. Cao).

¹ Shengzhi Sun and Jiajia Wang contributed equally to this work.

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reported that each $10 \mu\text{g}/\text{m}^3$ increase in full pregnancy fine particulate matter ($\text{PM}_{2.5}$) exposure led to a reduction in birth weight by -15.9 g (95 % CI: -26.8 g , -5.0 g) (Sun et al. 2016). Ozone (O_3) is one of the criteria air pollutants and is associated with a broad range of health outcomes, such as asthma (Dai et al. 2018) and cardiovascular diseases (Niu et al. 2022). Maternal exposure to O_3 could trigger preterm births (Rappazzo et al. 2021), but the evidence for birth weight is limited (Chen et al. 2002; Gouveia et al. 2004; Lamichhane et al. 2020; Morello-Frosch et al. 2010; Niu et al. 2020; Stieb et al. 2012; Wang et al. 2021). Fetal growth requires adequate oxygen and nutrient; exposure to O_3 may affect placental functions by inducing inflammation and oxidative stress, leading to reduced birth weight (EPA 2020).

Leveraging a nationwide study of ~ 2.2 million US live term births, we aimed to estimate the association of maternal exposure to O_3 with term birth weight and term small for gestational age (SGA). We also sought to identify susceptible exposure windows and to examine whether the associations varied by maternal characteristics.

2. Methods

2.1. Study population

We obtained data on US live births from the CDC's National Center for Health Statistics (NCHS 2022). For each birth, we obtained data on county of maternal residence, gestational weeks, maternal age, maternal race/ethnicity, maternal educational attainment, marital status, parity, smoking and alcohol drinking during pregnancy, chronic hypertension, date of last menstrual period (LMP), and infant sex. Given the availability of air pollution data, county of maternal residence, and data-coding consistency between years, we used the 2002 birth data only. We included only singleton births (i.e., a child that is the only one born at birth) with gestational age between 37 and 44 weeks and birth weight between 1000 g and 5500 g born to mothers who resided in counties with populations of 100,000 or more in the contiguous US. We excluded births with implausible combinations of birth weight and gestational age based on the Alexander criteria (Alexander et al. 1996). We excluded births with missing values of race/ethnicity, parity, educational attainment, beginning month of prenatal care, and LMP (Fig S1). We did not exclude births with missing values of smoking, alcohol drinking, or chronic hypertension, as a large proportion of these variables were recorded as unknown or not stated. We finally included 2,179,040 term births in our analytical data set.

2.2. Birth outcome definition

The birth outcomes were term birth weight and term small for gestational age (SGA). We obtained birth weight in grams and gestational weeks based on LMP from the birth certificate. We chose term SGA as it takes gestational length into account. We used the sex- and gestational week-specific US national reference percentiles for birth weight to classify each birth into corresponding birth weight percentiles (Oken et al. 2003), and those births with birth weight less than the 10th percentile were classified as SGA.

2.3. Air pollution assessment

Daily concentrations of 8-hour maximum O_3 and 24-hour average $\text{PM}_{2.5}$ with spatial resolutions of $36 \text{ km} \times 36 \text{ km}$ and $12 \text{ km} \times 12 \text{ km}$ were obtained from the US Environmental Protection Agency (EPA) for the Tracking Network. These data were generated using hierarchical Bayesian space-time downscaling fusion models combining output from the Community Multi-scale Air Quality model with air quality monitoring data from US EPA's air quality system (Berrocal et al. 2012; Byun and Schere 2006). The daily county-level population-weighted O_3 and $\text{PM}_{2.5}$ data were then aggregated by summing the predictions of air pollution concentrations falling within that census tract based on the

2000 US Census multiplying the corresponding proportion of the county population. Details about the theory and evaluation of the downscaler model have been published elsewhere (Berrocal et al. 2010; Berrocal et al. 2012). These data have been used to estimate the health effects of air pollution in the US (Mirabelli et al. 2016; Strosnider et al. 2019). Based on the LMP, we calculated weekly, monthly, and trimester average O_3 exposure for each birth and also calculated average $\text{PM}_{2.5}$ exposure during the full pregnancy for each pregnancy (eMethods).

2.4. Ambient temperature assessment

We obtained gridded daily ambient temperature estimates from the Parameter-elevation Relationships on Independent Slopes model and calculated daily population-weighted average of ambient temperature for each county (Spangler et al. 2019; Sun et al. 2019a; Sun et al. 2021; Sun et al. 2019b). We then calculated the average ambient temperature during the full pregnancy for each birth (eMethods).

2.5. Statistical analysis

We used linear regression to estimate the association between O_3 exposure and term birth weight and logistic regression to estimate the association between O_3 exposure and term SGA during each trimester and the full pregnancy. In the main models, we adjusted for maternal age (18–24, 25–29, 30–34, 35–40, 40–50 years), maternal race/ethnicity (non-Hispanic White, non-Hispanic Black, other), maternal educational attainment (below high school, high school, above high school), marital status (married versus not married), parity (0, 1, ≥ 2), infant sex (male versus female), chronic hypertension (yes, no, unknown), alcohol drinking during pregnancy (yes, no, unknown), smoking during pregnancy (yes, no, unknown), prenatal care initiation time (no prenatal care, 1st–3rd month, 4th–6th month, 7th month to final month), conception season (spring: March–May, summer: June–August, fall: September–November, winter: December–February), county poverty rate defined as the percentage of 2002 county residents below the federal poverty line ($<10\%$, 10% – 14.9% , 15% – 19.9% , $\geq 20\%$) (U. S. Census Bureau 2022), census regions (Northeast, Midwest, South, West), mean ambient temperature during the pregnancy using natural cubic splines with 3 degrees of freedom, and mutually adjusted for O_3 exposure in other trimesters. We adjusted maternal race/ethnicity and census regions in the main models as the level of air pollution exposure might vary by race/ethnicity and geographic regions (Jbaily et al. 2022). For term birth weight models, we additionally adjusted for gestational age (37–38, 39–40, 41–42, 43–44 weeks).

We conducted sensitivity analyses by additionally adjusting for $\text{PM}_{2.5}$ to assess potential confounding by other air pollutants. As the causal relationships between ambient temperature, O_3 , and disease outcomes are complex (Buckley et al. 2014), we conducted sensitivity analyses without adjustment for ambient temperature during the entire pregnancy. We reported changes in birth weight (g) for term birth weight and odds ratios (ORs) for term SGA per 10 parts per billion (ppb) increase in O_3 concentration.

To identify potential susceptible subgroups, we conducted subgroup analysis to assess whether the associations between full pregnancy O_3 exposure and term birth weight or term SGA varied by maternal age, maternal race/ethnicity, maternal educational attainment, marital status, and infant sex. We performed a Wald statistic to assess the heterogeneity across subgroups (Rothman et al. 2008).

To identify the critical exposure window, we used distributed lag models combined with linear regression or logistic regression to estimate the monthly and weekly associations for term birth weight or term SGA. We modeled the association between O_3 exposure and term birth weight or term SGA using a linear function and modeled the lag function using a natural cubic function with knots placed at equal intervals on the scale of lags up to 37 gestational weeks (Wilson et al. 2017). We set the maximum lag as 37 gestational weeks to ensure an equal length of

exposure among all pregnant women. The number of knots for the lag function was selected to minimize the Akaike Information Criterion (Table S1).

We carried out all statistical analyses with R software (version: 3.5.1) and fitted the distributed lag models using the “dlnm” package (version: 2.4.7).

3. Results

Our analysis included 2,179,040 singleton term births across 453 US counties in 2002, with an average birth weight of 3,423 g (Table 1 & Fig. 1). Among the population, 9.5 % of which were born SGA. The birth weight was lower among first live births or births born to mothers younger than 25 years, unmarried individuals, non-Hispanic Black individuals, individuals with a high school education, individuals who received no prenatal care, or smoked or consumed alcohol during pregnancy, or living in counties with higher level of poverty rate.

3.1. Trimester O₃ exposure and fetal growth

Maternal exposure to O₃ was associated with a lower term birth weight and a higher risk of term SGA (Table 2). In the main models after adjusting for individual-level covariates, county-level poverty rate and census region, mean ambient temperature during pregnancy, and mutually adjusted for O₃ exposure in the other trimesters, a 10 ppb increase in O₃ during the pregnancy was associated with a reduction in birth weight of −7.6 g (95 % CI: −8.8 g, −6.4 g) for term birth weight or an OR of 1.030 (95 % CI: 1.020, 1.040) for term SGA. The associations were also observed in all three trimesters for term birth weight and in the second and third trimesters for term SGA with the strongest association consistently observed in the second trimester. For example, the OR per 10 ppb increase in O₃ exposure for term SGA was 1.016 (95 % CI: 1.008, 1.024) during the second trimester, 1.006 (95 % CI: 1.000, 1.013) during the third trimester, and 1.005 (95 % CI: 0.998, 1.012) during the first trimester. Results were similar in sensitivity analyses with additionally adjusted for PM_{2.5} or without adjustment for the average ambient temperature during the entire pregnancy (Table 2).

3.2. Subgroup analysis

We conducted subgroup analyses to assess whether the association of term birth weight or term SGA with full pregnancy O₃ exposure varied by maternal age, maternal race/ethnicity, educational attainment, marital status, and infant sex. We found a statistically significant heterogeneity across race/ethnicity, educational attainment, and marital status (*p* for heterogeneity < 0.05) for both term birth weight and term SGA, with the strongest impact observed among non-Hispanic Black mothers, mothers with high school education, or unmarried mothers (Table 3). For example, the reduced birth weight per 10 ppb increase in O₃ during pregnancy was −13.8 g (95 % CI: −15.1 g, −12.0 g) among non-Hispanic Black mothers, −6.7 g (95 % CI: −10.8 g, −3.0 g) among non-Hispanic White mothers, and −9.5 g (95 % CI: −11.8 g, −7.0 g) among Hispanic mothers, and the corresponding estimate for term birth weight was −13.8 g (95 % CI: −15.6 g, −12.0 g), −6.7 g (95 % CI: −10.8 g, −3.0 g), and −9.5 g (95 % CI: −11.8 g, −1.0 g), respectively. We found the association was stronger among younger women for term birth weight but was not observed for term SGA. We found no evidence of any heterogeneity between male and female infants (*p* for heterogeneity > 0.05).

3.3. Critical exposure windows

To identify potential critical exposure windows, we fitted distributed lag models to estimate associations for O₃ exposure in each of the 9 months or 37 gestational weeks of pregnancy while including O₃ concentrations in the other months or gestational weeks of pregnancy in the

Table 1
Demographics of singleton term births in the United States in 2002.

Characteristics	Term births (%)	Term birth weight (g) mean (SD)	Term SGA (%) ^a
Total population	2,179,040 (100.0)	3423 (471)	208,064 (9.5)
Infant sex			
Male	1,108,434 (50.9)	3485 (476)	106,728 (9.6)
Female	1,070,606 (49.1)	3359 (458)	101,336 (9.5)
Parity			
0	863,624 (39.6)	3379 (467)	100,183 (11.6)
1	728,342 (33.4)	3449 (463)	57,984 (8.0)
≥2	587,074 (26.9)	3456 (482)	49,897 (8.5)
Gestational age (weeks)			
37–38	637,385 (29.3)	3266 (470)	57,549 (9.0)
39–40	1,138,418 (52.2)	3470 (450)	110,009 (9.7)
41–42	340,158 (15.6)	3550 (468)	34,222 (10.1)
43–44	63,079 (2.9)	3474 (475)	6284 (10.0)
Maternal age (years)			
18–24	666,400 (30.6)	3350 (460)	83,145 (12.5)
25–29	600,258 (27.5)	3431 (466)	54,070 (9.0)
30–34	576,647 (26.5)	3471 (470)	44,043 (7.6)
35–40	277,041 (12.7)	3477 (482)	21,558 (7.8)
40–50	58,694 (2.7)	3452 (499)	5248 (8.9)
Maternal race/ethnicity			
Non-Hispanic White	1,166,173 (53.5)	3481 (467)	85,987 (7.4)
Non-Hispanic Black	302,817 (13.9)	3280 (472)	47,814 (15.8)
Hispanic	553,674 (25.4)	3412 (461)	53,204 (9.6)
Other	156,376 (7.2)	3309 (447)	21,059 (13.5)
Marital status			
Married	1,521,456 (69.8)	3458 (466)	120,584 (7.9)
Not married	657,584 (30.2)	3341 (473)	87,480 (13.3)
Maternal educational attainment (years)			
Lower than high school	132,851 (6.1)	3414 (469)	13,441 (10.1)
High school	912,100 (41.9)	3378 (475)	106,091 (11.6)
Higher than high school	1,134,089 (52.0)	3460 (465)	88,532 (7.8)
Timing of initiation of prenatal care			
No prenatal care	13,400 (0.6)	3264 (517)	2600 (19.4)
1st-3rd month	1,866,327 (85.6)	3433 (469)	168,394 (9.0)
4th-6th month	247,416 (11.4)	3372 (476)	30,076 (12.2)
7th-final month	51,897 (2.4)	3353 (476)	6994 (13.5)
Smoking during pregnancy			
Yes	153,211 (7.0)	3252 (473)	27,517 (18.0)
No	1,652,027 (75.8)	3434 (468)	147,264 (8.9)
Unknown ^b	373,802 (17.2)	3445 (468)	33,283 (8.9)
Alcohol drinking during pregnancy			
Yes	14,178 (0.7)	3355 (503)	2014 (14.2)
No	1,788,486 (82.1)	3419 (471)	172,563 (9.6)
Unknown ^b	376,376 (17.3)	3446 (469)	33,487 (8.9)
Chronic hypertension			
Yes	14,517 (0.7)	3330 (546)	2140 (14.7)
No	2,151,932 (98.8)	3423 (470)	204,749 (9.5)
Unknown	12,591 (0.6)	3452 (484)	1175 (9.3)

(continued on next page)

Table 1 (continued)

Characteristics	Term births (%)	Term birth weight (g) mean (SD)	Term SGA (%) ^a
Season of conception ^c			
Spring	525,102 (24.1)	3420 (472)	51,321 (9.8)
Summer	537,690 (24.7)	3431 (472)	50,066 (9.3)
Fall	563,279 (25.8)	3423 (470)	53,721 (9.5)
Winter	552,969 (25.4)	3418 (469)	52,956 (9.6)
County poverty rate ^d			
<10 %	799,652 (36.7)	3456 (470)	66,666 (8.3)
10 %-14.9 %	886,297 (40.7)	3414 (470)	87,148 (9.8)
15 %-19.9 %	362,023 (16.6)	3394 (470)	38,493 (10.6)
≥20 %	131,068 (6.0)	3361 (470)	15,757 (12.0)
Census region			
Northeast	463,736 (21.3)	3437 (475)	43,976 (9.5)
Midwest	484,518 (22.2)	3440 (476)	44,550 (9.2)
South	637,221 (29.2)	3391 (468)	65,701 (10.3)
West	593,565 (27.2)	3433 (466)	53,837 (9.1)

^a The percentage of term small for gestational age was obtained by dividing the number of term small for gestational age by the number of term births in the corresponding category.

^b Smoking and drinking were not recorded on California birth certificates and we assigned an unknown category of smoking and alcohol status for all California births.

^c Season of conception: spring (March-May), summer (June-August), fall (September-November), and winter (December-February).

^d The percentage of people in a county below the federal poverty line. Abbreviations: SGA = small for gestational age; SD = standard deviation.

models (Fig. 2). For term birth weight, O₃ exposures during the 4th-6th, 8th, and 9th gestational months or the 13th-24th and 32nd-37th gestational weeks were associated with reduced birth weight. For term SGA, exposure to O₃ during the 5th-8th gestational months or the 14th-17th and 21st-26th gestational weeks was associated with an increased risk of term SGA. Although not statistically significant, the association

was marginally significant during the 18th-20th gestational weeks for term SGA.

4. Discussion

Leveraging this nationwide study of ~ 2.2 million singleton term birth across 453 populous US counties, we estimated the association between maternal exposure to O₃ and term birth weight and term SGA. We found that maternal exposure to O₃ was associated with lower term birth weight and higher risk of term SGA. The potential critical exposure windows were the 13th- 25th and 32nd –37th gestational weeks for term birth weight and the 13th- 25th for term SGA.

We found that maternal exposure to O₃ was associated with lower term birth weight or higher risk of term SGA, which is consistent with a systematic review summarizing six studies of O₃ and term birth weight (Klepac et al. 2018). The pooled meta-analytic estimates of reduced birth weight associated with 10 ppb increase in O₃ over the full pregnancy ranged from -4.6 g to -27.3 g (Klepac et al. 2018), which was comparable with our estimates of -7.6 g. Our findings are also in line with a recent multi-city study in China, which found a 5.7 g (95 % CI: -10.1 g, -1.3 g) reduction in birth weight per 10 ppb increase in O₃ over the full pregnancy (Guo et al. 2020). However, our findings are in contrast with a few previous studies, which found no evidence of any association between maternal exposure to O₃ and lower rates of fetal growth (Chen et al. 2002; Gouveia et al. 2004; Stieb et al. 2012).

Although the biological plausibility for the association between O₃ exposure and fetal growth is not clear yet, oxidative stress and systemic inflammation may play a role (Bignami et al. 1994; Gunnison and Hatch 1999; Larini and Bocci 2005; Schoots et al. 2018; Thibodeaux et al. 2003). Fetal weight grows dramatically from the second trimester and fetal growth requires adequate oxygen and nutrient. Exposure to O₃ triggers the release of lipid peroxidation products and inflammatory cytokines into circulation (Larini and Bocci 2005). These oxidative and inflammatory products could harm placental circulation and function, leading to placental insufficiency and therefore affecting fetal growth (Larini and Bocci 2005). The O₃ exposure induced birth weight

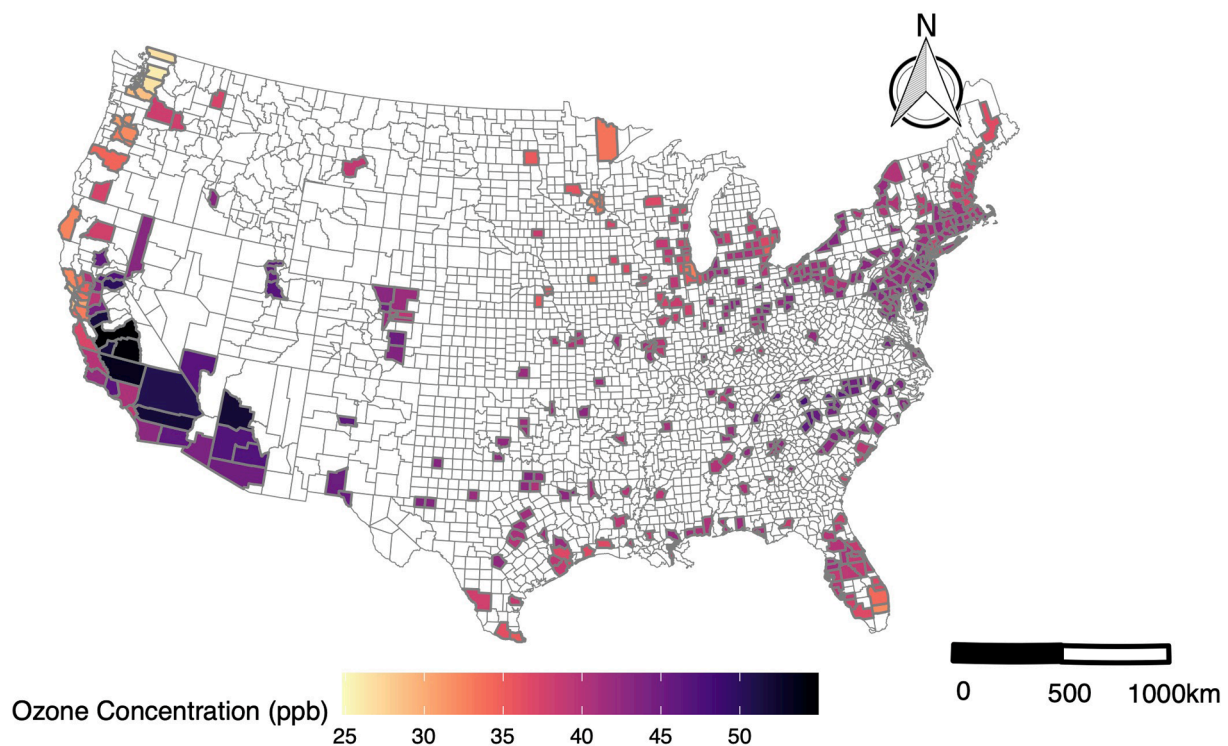


Fig. 1. Annual average ozone concentrations among 453 US counties in 2002.

Table 2

Changes in birth weight (grams) and odds ratio of term small for gestational age associated with 10 parts per billion (ppb) increase in ozone exposure in the United States.

Model	Trimester	Term birth weight [change (g) (95 % CI)]	Term SGA [OR (95 % CI)]
Main model ^a	Entire pregnancy	-7.6 (-8.8, -6.4)	1.030 (1.020, 1.040)
	First trimester	-1.3 (-2.2, -0.4)	1.005 (0.998, 1.012)
	Second trimester	-3.3 (-4.3, -2.3)	1.016 (1.008, 1.024)
Main model + PM _{2.5} ^b	Entire pregnancy	-7.3 (-8.6, -6.0)	1.030 (1.020, 1.040)
	First trimester	-1.1 (-2.0, -0.2)	1.005 (0.998, 1.012)
	Second trimester	-3.3 (-4.3, -2.3)	1.016 (1.008, 1.024)
Main model - Temperature ^c	Entire pregnancy	-7.8 (-8.9, -6.6)	1.029 (1.020, 1.038)
	First trimester	-1.4 (-2.3, -0.4)	1.005 (0.997, 1.012)
	Second trimester	-3.4 (-4.3, -2.5)	1.014 (1.007, 1.021)
	Third trimester	-2.6 (-3.4, -1.7)	1.007 (1.001, 1.014)

^a Models were adjusted for maternal age, maternal race/ethnicity, maternal educational attainment, marital status, chronic hypertension, infant sex, parity, alcohol drinking during pregnancy, smoking during pregnancy, timing of initiation of prenatal care, season of conception, mean ambient temperature during the entire pregnancy using natural cubic splines with 3 degrees of freedom, county poverty rate, census region, and mutually adjusted for ozone exposure in other trimesters. Term birth weight models were also adjusted for gestational length.

^b Main models with additionally adjusted for PM_{2.5}.

^c Main models without adjustment for mean ambient temperature during the entire pregnancy using natural cubic splines with 3 degrees of freedom. Abbreviations: OR = odds ratio; CI = confidence interval; SGA = small for gestational age; PM_{2.5} = fine particulate matter.

reduction was observed in animal studies (Bignami et al. 1994; Gunnison and Hatch 1999; Thibodeaux et al. 2003). Mid and late pregnancy exposure to O₃ reduced mice weight gain (Bignami et al. 1994; Thibodeaux et al. 2003).

We found that the association was stronger among non-Hispanic Black, unmarried mothers, or mothers with a lower school education, which could be due to those mothers being more likely to be exposed to a higher level of air pollution (Jbaily et al. 2022; Lamichhane et al. 2020). For example, in a descriptive analysis linking demographic data and PM_{2.5} data among 32,000 US zip codes, the non-Hispanic population was exposed to ~ 14 % higher level of PM_{2.5} concentration than those of the white population in 2016 (Jbaily et al. 2022). The more pronounced associations among pregnant women with lower socioeconomic status might also due to a lack of awareness or access to maternal health care services (Lamichhane et al. 2020; Shah and Births 2010). Our finding of no heterogeneity between male and female infants is consistent with the previous study (Guo et al. 2020).

To identify critical exposure windows, most prior studies (Gouveia et al. 2004; Lamichhane et al. 2020; Olsson et al. 2020) ignore O₃ exposure in other exposure windows, which might lead to identify inaccurate critical windows (Wilson et al. 2017). To our knowledge, we only found two studies that modelled monthly or weekly O₃ exposure using distributed lag models to identify critical exposure windows for O₃ and term birth weight (Darrow et al. 2011; Wang et al. 2021). Our findings are in agreement with the Chinese study conducted in

Table 3

Stratified analysis for changes in birth weight (grams) and odds ratio of term small for gestational age associated with 10 parts per billion (ppb) increase in ambient ozone during the entire pregnancy.

Variables	Term birth weight		Term SGA	
	Change in birth weight (g) (95 % CI)	P ^a _{Heterogeneity}	OR	P ^a _{Heterogeneity}
Maternal age (years)		<0.001		0.353
18–24	-12.9 (-15.1, -11.0)		1.046 (1.030, 1.063)	
25–29	-9.9 (-12.3, -8.0)		1.031 (1.012, 1.051)	
30–34	-5.7 (-8.2, -3.0)		1.020 (0.999, 1.042)	
35–39	-3.1 (-6.7, 1.0)		1.025 (0.995, 1.056)	
≥40	1.4 (-6.5, 9.0)		1.032 (0.972, 1.095)	
Maternal race/ethnicity		<0.001		<0.001
Hispanic	-9.5 (-11.8, -7.0)		1.035 (1.017, 1.054)	
Non-Hispanic White	-6.7 (-10.8, -3.0)		1.045 (1.019, 1.072)	
Non-Hispanic Black	-13.8 (-15.6, -12.0)		1.060 (1.043, 1.076)	
Other	8.1 (3.9, 12.0)		0.977 (0.948, 1.006)	
Educational attainment		<0.001		<0.001
Lower than high school	-6.1 (-10.8, -1.0)		1.030 (0.994, 1.066)	
High school	-13.2 (-15.1, -11.0)		1.055 (1.040, 1.070)	
Higher than high school	-5.1 (-6.8, -3.0)		1.008 (0.993, 1.023)	
Marital status		<0.001		0.006
Married	-6.3 (-7.8, -5.0)		1.021 (1.008, 1.034)	
Unmarried	-11.6 (-13.9, -9.0)		1.050 (1.034, 1.067)	
Infant sex		0.305		0.273
Male	-8.3 (-10.0, -6.0)		1.025 (1.012, 1.039)	
Female	-6.9 (-8.6, -5.0)		1.036 (1.022, 1.051)	

Abbreviations: SGA = small for gestational age; OR = odds ratio.

Models were adjusted for maternal age, maternal race/ethnicity, maternal educational attainment, marital status, chronic hypertension, infant sex, parity, alcohol drinking during pregnancy, smoking during pregnancy, timing of initiation of prenatal care, season of conception, mean ambient temperature during the entire pregnancy using natural cubic splines with 3 degrees of freedom, county poverty rate, and census region. Term birth weight models were also adjusted for gestational length.

^aWe used a Wald statistic to test the heterogeneity across subgroups.

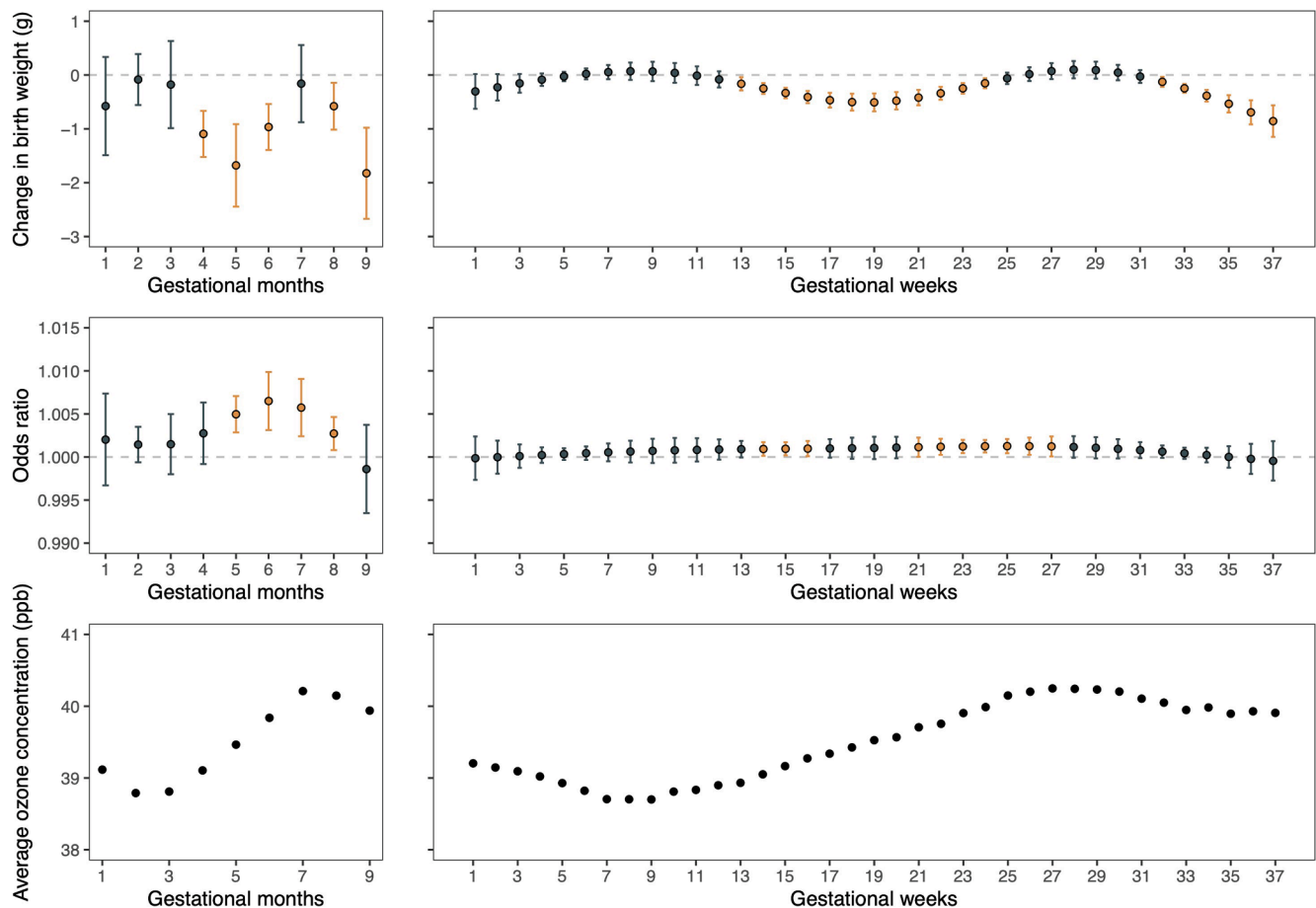


Fig. 2. Changes in birth weight (top panel) and odds ratio of term small for gestational age (middle panel) associated with 10 parts per billion (ppb) increase in monthly and weekly ozone exposure and the average ozone concentration across gestational months and weeks (bottom panel) during the pregnancy among term singleton births in the United States, 2002. Models were adjusted for maternal age, maternal race/ethnicity, maternal educational attainment, marital status, chronic hypertension, infant sex, parity, alcohol drinking during pregnancy, smoking during pregnancy, timing of initiation of prenatal care, season of conception, mean ambient temperature during the entire pregnancy using natural cubic splines with 3 degrees of freedom, county poverty rate, and census region. Term birth weight models were also adjusted for gestational length.

Guangzhou, which identified the critical exposure window for O_3 and low birth weight during the 15th-26th gestational weeks (Wang et al. 2021).

Our study has several limitations. First, we used the population-weighted average of county-level O_3 exposure instead of personal O_3 exposure, which might lead to exposure misclassification. However, this potential exposure misclassification is more likely to be nondifferential and lead to underestimation of the associations (Kioumourtzoglou et al. 2014). Second, we did not consider residential mobility in our exposure assessment due to a lack of data, which might introduce another source of exposure misclassification. However, previous studies (Chen et al. 2010; Pennington et al. 2017) suggested that only a small proportion of pregnant women relocated during their pregnancies and much less moved to another county, suggesting that bias from this source of exposure misclassification should be limited. Third, compared to particulate matter, the spatial resolution of O_3 is relatively low. The low spatial resolution of exposure estimates may result in increased bias and confounding (McIsaac et al. 2021), leading to underestimate the associations. Fourth, although we adjusted for maternal characteristics, infant sex, season of conception, county-level factors, and meteorological factors, residual confounding is still possible, such as traffic noise (Smith et al. 2017). Fifth, we included only 453 US counties with the availability of both O_3 and the births data, and our findings may not be generalizable to the remaining counties. We only used the 2002 birth data, and our results may not be generalizable to other years. Also, early

delivery mediates the effects of O_3 on birth weight. To evaluate the direct effects of O_3 on birth weight, we restricted to term births, and findings of our study cannot be generalizable to all births.

One strength of our study is the large sample size, including ~ 2.2 million US singleton births across different geographic regressions in the US. Also, we used distributed lag models fitting monthly and weekly O_3 exposure during pregnancy to identify potential critical exposure windows. The consistency in identified critical windows using different temporal scales confirmed the robustness of our findings.

5. Conclusions

In summary, among ~ 2.2 million singleton live births across 453 US counties, we found that maternal exposure to O_3 was associated with lower birth weight and a higher risk of small for gestational age, and the critical exposure windows were the 13th- 25th gestational weeks. Our findings might be useful to prevention of fetal growth restriction.

CRedit authorship contribution statement

Shengzhi Sun: Conceptualization, Writing – original draft, Formal analysis, Data curation, Investigation. **Jiajia Wang:** Formal analysis, Methodology, Writing – review & editing. **Wangnan Cao:** Conceptualization, Writing – original draft, Data curation, Investigation. **Lizhi Wu:** Writing – review & editing. **Yu Tian:** Writing – review & editing. **Feng**

Sun: Writing – review & editing. **Zhenyu Zhang:** Writing – review & editing. **Yang Ge:** Writing – review & editing. **Jianqiang Du:** Writing – review & editing. **Xiaobo Li:** Writing – review & editing. **Rui Chen:** Conceptualization, Resources, Writing – review & editing.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary material

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2022.107554>.

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