Science of the Total Environment 872 (2023) 162292

Contents lists available at ScienceDirect

Science of the Total Environment

journal homepage: www.elsevier.com/locate/scitotenv

# Maternal exposure to ozone and risk of gestational hypertension and eclampsia in the United States

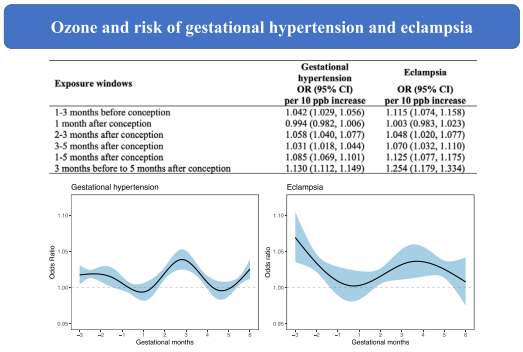
Kun Yuan [a,b,1], Feng Sun [c,1], Yangchang Zhang [a,b], Ying Du [a,b], Lizhi Wu [d], Yang Ge [e], Zhenyu Zhang [f,g], Wangnan Cao [h,*], Shengzhi Sun [a,b,**]

[a] School of Public Health, Capital Medical University, Beijing 100069, China
[b] Beijing Municipal Key Laboratory of Clinical Epidemiology, Capital Medical University, Beijing 100069, China
[c] Department of Epidemiology and Biostatistics, School of Public Health, Peking University, Beijing 100191, China
[d] Zhejiang Provincial Center for Disease Control and Prevention, 3399 Bin Sheng Road, Binjiang District, Hangzhou 310051, China
[e] School of Health Professions, University of Southern Mississippi, Hattiesburg, 39402, MS, USA
[f] Department of Global Health, School of Public Health, Peking University, Beijing 100191, China
[g] Institute for Global Health and Development, Peking University, Beijing, China
[h] Department of Social Medicine and Health Education, School of Public Health, Peking University, Beijing 100191, China

## HIGHLIGHTS

- We estimated the association of $O_3$ exposure with HDPs across 454 US counties.
- Maternal exposure to $O_3$ was associated with higher risk of GH and eclampsia.
- The critical exposure windows were 2 to 4 months after conception.

## GRAPHICAL ABSTRACT




## ARTICLE INFO

Editor: Scott Sheridan

*Keywords:*
Hypertensive disorders in pregnancy
Ozone
Susceptible window
Gestational hypertension
Eclampsia

## ABSTRACT

*Background:* Exposure to ambient ozone during pregnancy may be linked with hypertensive disorders in pregnancy, but evidence is largely unknown. We aimed to estimate the association between maternal exposure to ozone and risk of gestational hypertension and eclampsia in the contiguous United States (US).

*Methods:* We included 2,393,346 normotensive mothers aged from 18 to 50 years old who had a live singleton birth documented in the National Vital Statistics system in the US in 2002. We obtained information on gestational hypertension and eclampsia from birth certificates. We estimated daily ozone concentrations from a spatiotemporal ensemble model. We used distributed lag model and logistic regression to estimate the association between monthly ozone exposure and risk of gestational hypertension or eclampsia after adjusting for individual-level covariates and county poverty rate.

*Results:* Of the 2,393,346 pregnant women, there were 79,174 women with gestational hypertension and 6034 with eclampsia. A 10 parts per billion (ppb) increase in ozone was associated with an increased risk of gestational hypertension over 1–3 months before conception (OR = 1.042, 95 % CI: 1.029, 1.056), 2–3 months after conception (OR =

* Corresponding author.
** Corresponding author at: School of Public Health, Capital Medical University, Beijing 100069, China.
*E-mail addresses:* wangnancao@bjmu.edu.cn (W. Cao), shengzhisun@ccmu.edu.cn (S. Sun).
[1] Kun Yuan and Feng Sun were joint first-author.

http://dx.doi.org/10.1016/j.scitotenv.2023.162292
Received 12 January 2023; Received in revised form 12 February 2023; Accepted 13 February 2023
Available online 17 February 2023

1.058, 95 % CI: 1.040, 1.077), and 3–5 months after conception (OR = 1.031, 95 % CI: 1.018, 1.044). The corresponding OR for eclampsia was 1.115 (95 % CI: 1.074, 1.158), 1.048 (95 % CI: 1.020, 1.077), and 1.070 (95 % CI: 1.032, 1.110), respectively.

*Conclusions:* Exposure to ozone was associated with an increased risk of gestational hypertension or eclampsia, especially during 2 to 4 months after conception.

## 1. Introduction

Hypertensive disorders in pregnancy (HDPs) are among the most serious pregnancy complications, affecting approximately 5–10 % of pregnant women worldwide (Sears et al., 2018; Shah, 2020). HDPs contribute to the leading morbidity and mortality for maternal and offspring health (Endeshaw and Berhan, 2015; Yoder et al., 2009). For example, HDPs are associated with an increased risk of cardiovascular diseases (Ying et al., 2018), liver and kidney diseases (Barrett et al., 2020), and diabetes for mothers (Jiang et al., 2022), and are also associated with a higher risk of adverse birth outcomes for offspring, including preterm birth and low birth weight (Liu et al., 2021). The risk factors for HDPs include a history of hypertension during pregnancy, a family history of hypertension, and old age (Hinkosa et al., 2020).

Air pollution was the fourth leading risk factor for global premature mortality and disease burden (Brauer et al., 2016). Exposure to air pollution increased the risk of mortality and morbidity from cardiovascular and respiratory disease (Brauer et al., 2021), adversely affected fetal growth (Sun et al., 2022), and triggered preterm birth (Ghosh et al., 2021). Exposure to air pollution may be associated with an increased risk of HDPs (Pedersen et al., 2014). Among air pollutants, ozone is closely related to anthropogenic emissions, and levels of ozone are expected to be increasing with global warming. A large amount of evidence suggested that exposure to ozone could induce systemic inflammation and oxidative stress (Brook et al., 2004; Jauniaux et al., 2006), causing placental malfunction, and thus leading to HDPs and preeclampsia/eclampsia. For example, a recent meta-analysis documented five studies that examined the association between ozone exposure and gestational hypertension and preeclampsia/eclampsia (Pedersen et al., 2014), and reported a marginally significant association between ozone exposure and gestational hypertension or preeclampsia/eclampsia. However, the results of the included five studies were heterogeneous, subjected to a small number of cities, or applied different model choices, making the generalizability of these findings uncertain.

Given the health consequences of HDPs and the projected increase in levels of ozone in the context of global warming, we sought to examine the association of maternal exposure to ozone with gestational hypertension and eclampsia among over 2.3 million mother-infant pairs in 2002 across 454 counties in the US.

## 2. Methods

### 2.1. Study population

We obtained data on US live singleton births from the US Centers for Disease Control and Prevention's National Centre for Health Statistics (NCHS, 2003). Given the availability of the county of maternal residence and data-coding consistency between years, we used the 2002 birth data only. Data were only available for pregnant women living in counties with a population of ≥100,000. We restricted our analysis to births at ≥20 weeks gestation and to births born to mothers aged between 20 and 50 years old. We excluded births with a missing value for maternal residence, last menstrual period, race/ethnicity, educational attainment, parity, and starting months of prenatal care. We further excluded births born to mothers with pre-existing hypertension, resulting in 2,393,346 mother-infant pairs in our analytical data set (Fig. S1).

### 2.2. Outcome definition

Gestational hypertension and eclampsia were reported on birth certificates, each with a checkbox (CDC, 2000). Gestational hypertension was defined as an increase in blood pressure of at least 30 mmHg systolic or 15 mmHg diastolic on two measurements taken 6 h apart after the 20th week of gestation. Eclampsia was defined as the occurrence of convulsions and/or coma unrelated to other cerebral conditions in women with signs and symptoms of preeclampsia.

### 2.3. Air pollution assessment

Daily concentrations of 8-hour maximum ozone and 24-hour average fine particulate matter ($PM_{2.5}$) were estimated from spatiotemporal ensemble models developed by Di et al. (2019) and Requia et al. (2020). The models incorporated three machine learning models, including neural network, random forest, and gradient boosting. The models combined ground monitoring data from the US Environmental Protection Agency air quality system, remote sensing data, meteorological conditions, such as ambient temperature, relative humidity, and wind speed, chemical transport model simulations, and land-use variables, such as road intensity. Based on the models, daily air pollutant concentrations were estimated at every 1 km × 1 km grid cell in the contiguous US. The model demonstrated good performance by comparing predicted values with monitored data, with a ten-fold cross-validated of 0.91 for ozone and 0.86 for $PM_{2.5}$. Daily county-level population-weighted ozone and $PM_{2.5}$ data were calculated by summing the predictions of air pollution concentrations falling within the 2002 US census tract by multiplying the corresponding proportion of the county population. Based on the last menstrual period, we calculated the monthly average ozone exposure for each birth and calculated the average $PM_{2.5}$ from 3 months before to 5 months after conception (Table S1).

### 2.4. Ambient temperature assessment

We obtained 4 km × 4 km gridded estimates of daily ambient temperature and relative humidity from the Parameter-elevation Relationships on Independent Slopes (PRISM) model (Spangler et al., 2019; Sun et al., 2019a, 2019b, 2021). We calculated daily population-weighted ambient temperature and relative humidity for each county as we did for the air pollution assessment. We calculated the average ambient temperature and relative humidity from 3 months before to 5 months after conception for each birth.

### 2.5. Statistical analysis

We used logistic regression to estimate the association between maternal exposure to monthly ozone and risk of gestational hypertension or eclampsia. In the models, we adjusted for maternal age (18–24, 25–29, 30–34, 35–50 years), race/ethnicity (Non-Hispanic White, Non-Hispanic Black, Hispanic, other), marital status (married versus not married), educational attainment (lower than high school, high school, higher than high school), prenatal care initiation time (no prenatal care, first trimester, second trimester, third trimester), infant sex (male versus female), parity (0, 1, ≥2), smoking during pregnancy (yes, no, unknown), alcohol drinking during pregnancy (yes, no, unknown), and county poverty rate defined as the percentage of 2002 county residents below the federal poverty line (<10 %, 10 %–14.9 %, ≥15 %) (Bureau, 2022). We applied a distributed lag model to fit the exposure-response and time-response functions for the

relationship between ozone exposure and gestational hypertension or eclampsia. We used a linear function to model the association between monthly ozone exposure and gestational hypertension or eclampsia. We modeled the lag function using a natural cubic function with knots placed at equal intervals on the scale of lags up to 5 gestational months after conception (Wilson et al., 2017). To ensure an equal length of ozone exposure among all women, we set the maximum lag as 5 gestational months after conception. We conducted sensitivity analyses by varying the key parameters for the time-response function (Figs. S2 & S3) and selected the number of knots for the lag function based on the minimum Akaike Information Criterion (Table S2). To explore nonlinearity, we used a natural cubic spline with 3 degrees of freedom to model the association between monthly ozone exposure and gestational hypertension or eclampsia.

Based on the biological rationale of critical windows for HDPs (Kroener et al., 2016), we selected the following four time windows: 3 months before conception, 1 month after conception (embryo implantation), 2–3 months after conception (vascularization and placentation), and 3–5 months of gestation (after placentation). We reported odds ratios (ORs) and 95 % confidence intervals of gestational hypertension or eclampsia per 10 parts per billion (ppb) increase in ozone concentration. We also performed sensitivity analyses by additionally adjusting for average $PM_{2.5}$, ambient temperature, or relative humidity from 3 months before to 5 months after conception to assess potential confounding by air pollution and meteorological factors.

We conducted subgroup analysis to identify potential susceptible subgroups. We assessed whether the associations varied by maternal age, maternal race/ethnicity, infant sex, and county poverty rate. A Wald statistic was used to test the heterogeneity across subgroups (Rothman et al., 2008).

We performed all statistical analyses with R software (version: 3.5.1). We used the "survival" package (version 2.42-6) for the logistic regression and the "dlnm" package (version: 2.4.7) for the distributed lag models.

## 3. Results

### 3.1. Participants characteristics

A total of 2,393,346 pregnant women across 454 US counties were included in the analysis (Table 1 & Fig. 1). Among them, 2,309,765 (96.5%) pregnant women were normotensive, 79,174 (3.3%) women had gestational hypertension, and 6034 (0.3%) had eclampsia. Most women with HDPs were Non-Hispanic White (59.0 %), married (67.9 %), had received higher education levels than high school (53.8 %), and started prenatal care in the first trimester (86.5 %). Women had gestational hypertension or eclampsia tended to be nulliparous, non-Hispanic Black, and unmarried (Table 1).

### 3.2. Ozone exposure and risk of gestational hypertension or eclampsia

We found a positive and nonlinear exposure-response relationship between ozone exposure and risk of gestational hypertension or eclampsia.

**Table 1**
Demographic characteristics of pregnant women in 454 US counties, 2002.

| Characteristics | Total | Normotensive women | Gestational hypertension | Eclampsia |
|---|---|---|---|---|
| Total population | 2,393,346 (100.0) | 2,309,765 (96.5) | 79,174 (3.3) | 6034 (0.3) |
| Infant sex | | | | |
| Male | 1,224,449 (51.2) | 1,181,080 (96.5) | 41,090 (3.4) | 3096 (0.3) |
| Female | 1,168,897 (48.8) | 1,128,685 (96.6) | 38,084 (3.3) | 2938 (0.3) |
| Parity | | | | |
| 0 | 946,919 (39.6) | 899,431 (95.0) | 44,927 (4.7) | 3539 (0.4) |
| 1 | 792,585 (33.1) | 772,451 (97.5) | 19,081 (2.4) | 1399 (0.2) |
| ≥2 | 653,842 (27.3) | 637,883 (97.6) | 15,166 (2.3) | 1096 (0.2) |
| Maternal age (years) | | | | |
| 18–24 | 745,344 (31.1) | 718,726 (96.4) | 24,923 (3.3) | 2277 (0.3) |
| 25–29 | 655,672 (27.4) | 632,742 (96.5) | 21,788 (3.3) | 1563 (0.2) |
| 30–34 | 624,947 (26.1) | 604,494 (96.7) | 19,488 (3.1) | 1334 (0.2) |
| 35–50 | 367,383 (15.4) | 353,803 (96.3) | 12,975 (3.5) | 860 (0.2) |
| Maternal race/ethnicity | | | | |
| Non-Hispanic White | 1,260,554 (52.7) | 1,211,205 (96.1) | 47,086 (3.7) | 3208 (0.3) |
| Non-Hispanic Black | 352,178 (14.7) | 337,154 (95.7) | 13,899 (3.9) | 1458 (0.4) |
| Hispanic | 617,624 (25.8) | 601,737 (97.4) | 15,039 (2.4) | 1137 (0.2) |
| Other | 162,990 (6.8) | 159,669 (98.0) | 3150 (1.9) | 231 (0.1) |
| Marital status | | | | |
| Married | 1,646,224 (68.8) | 1,589,471 (96.6) | 54,071 (3.3) | 3760 (0.2) |
| Not married | 747,122 (31.2) | 720,294 (96.4) | 25,103 (3.4) | 2274 (0.3) |
| Education level | | | | |
| Lower than high school | 150,018 (6.3) | 146,652 (97.8) | 3172 (2.1) | 249 (0.2) |
| High school | 1,020,365 (42.6) | 985,145 (96.5) | 33,077 (3.2) | 2875 (0.3) |
| Higher than high school | 1,222,963 (51.1) | 1,177,968 (96.3) | 42,925 (3.5) | 2910 (0.2) |
| Timing of initiation of prenatal care | | | | |
| No prenatal care | 17,499 (0.7) | 16,960 (96.9) | 495 (2.8) | 65 (0.4) |
| 1st–3rd month | 2,036,691 (85.1) | 1,964,382 (96.4) | 68,576 (3.4) | 5120 (0.3) |
| 4th–6th month | 280,933 (11.7) | 271,878 (96.8) | 8535 (3.0) | 709 (0.3) |
| 7th–final month | 58,223 (2.4) | 56,545 (97.1) | 1568 (2.7) | 140 (0.2) |
| Smoking during pregnancy | | | | |
| Yes | 174,980 (7.3) | 168,847 (96.5) | 5812 (3.3) | 443 (0.3) |
| No | 1,807,463 (75.5) | 1,737,909 (96.2) | 65,559 (3.6) | 5485 (0.3) |
| Unknown | 410,903 (17.2) | 403,009 (98.1) | 7803 (1.9) | 106 (0.0) |
| Alcohol drinking during pregnancy | | | | |
| Yes | 16,135 (0.7) | 15,488 (96.0) | 610 (3.8) | 50 (0.3) |
| No | 1,965,895 (82.1) | 1,890,872 (96.2) | 70,743 (3.6) | 5878 (0.3) |
| Unknown | 411,316 (17.2) | 403,405 (98.1) | 7821 (1.9) | 106 (0.0) |
| County poverty rate[a] | | | | |
| <10 % | 865,255 (36.2) | 833,523 (96.3) | 30,194 (3.5) | 2182 (0.3) |
| 10 %–14.9 % | 974,795 (40.7) | 939,439 (96.4) | 33,503 (3.4) | 2511 (0.3) |
| ≥15 % | 553,296 (23.1) | 536,803 (97.0) | 15,477 (2.8) | 1341 (0.2) |

[a] The percentage of people in a county below the federal poverty line.

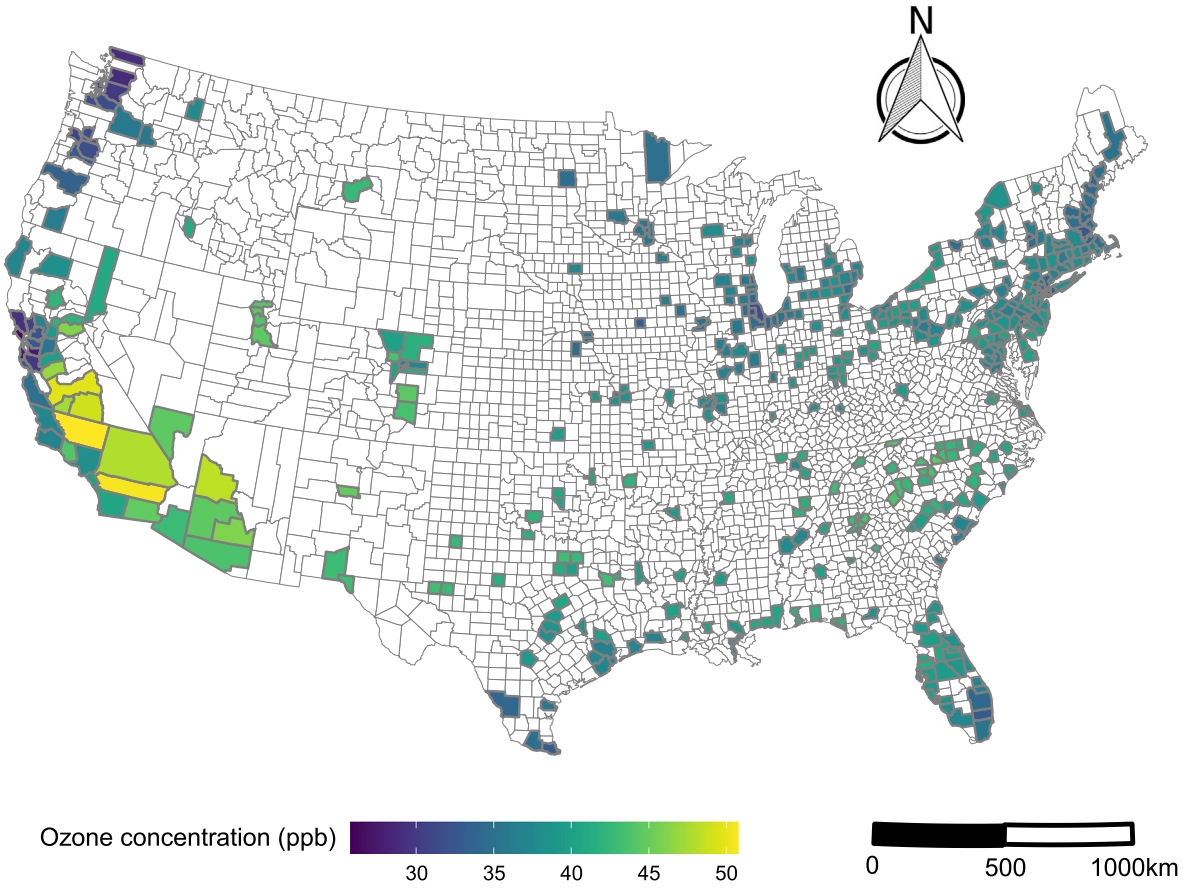



**Fig. 1.** Annual average concentration of ozone by US county in 2002.

When we applied a linear function for the exposure-response curves, we observed an elevated OR before conception and 2–4 months after conception for both gestational hypertension and eclampsia, with a peak identified in the 3rd month after conception (Fig. 2).

We next presented results for each critical exposure window (Table 2). In models after adjusting for individual-level covariates and county poverty rate, the OR of gestational hypertension per 10 ppb increase in ozone was 1.042 (95 % CI: 1.029, 1.056) for 3 months before conception, 0.994 (95 % CI: 0.982, 1.006) for 1 month after conception, 1.058 (95 % CI: 1.040, 1.077) for 2–3 months after conception, and 1.031 (95 % CI: 1.018, 1.044) for 3–5 months after conception. The corresponding OR for eclampsia was 1.115 (95 % CI: 1.074, 1.158) for 3 months before conception, 1.003 (95 % CI: 0.983, 1.023) for 1 month after conception, 1.048 (95 % CI:1.020, 1.077) for 2–3 months after conception, and 1.070 (95 % CI:1.032, 1.110) for 3–5 months after conception. Results were similar when additionally adjusted for $PM_{2.5}$, ambient temperature, or relative humidity (Table 2).

### 3.3. Subgroup analysis

We conducted subgroup analyses to assess whether the association of gestational hypertension or eclampsia with ozone exposure varied by maternal age, maternal race/ethnicity, infant sex, and county poverty rate (Table 3). We found that the association was more pronounced among

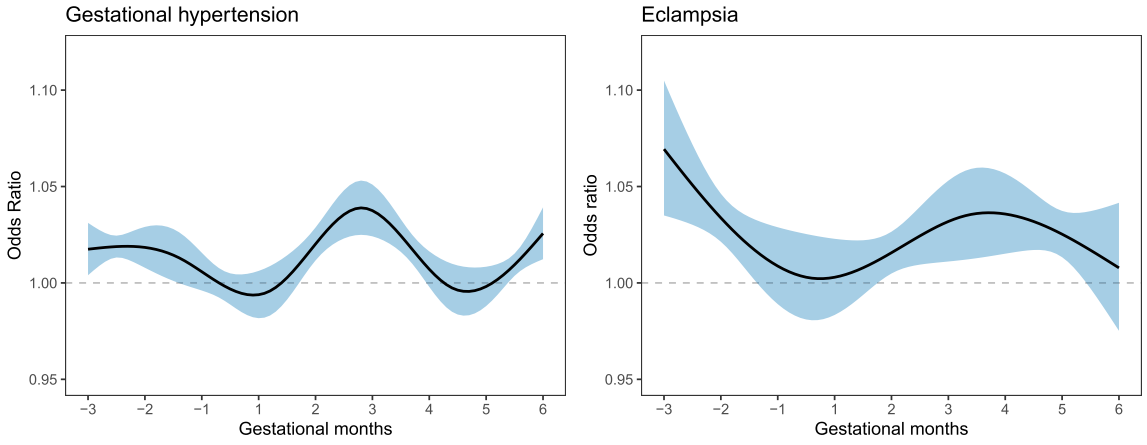



**Fig. 2.** The exposure-response curves for the association between maternal exposure to ozone and gestational hypertension and eclampsia in the United States, 2002.

**Table 2**
Odds ratios of gestational hypertension and eclampsia associated with 10 parts per billion increase in ozone exposure by exposure windows in the United States, 2002.

| Models | Exposure windows | Gestational hypertension | Eclampsia |
|---|---|---|---|
| | | OR (95 % CI) | OR (95 % CI) |
| Main model[a] | 1–3 months before conception | 1.042 (1.029, 1.056) | 1.115 (1.074, 1.158) |
| | 1 month after conception | 0.994 (0.982, 1.006) | 1.003 (0.983, 1.023) |
| | 2–3 months after conception | 1.058 (1.040, 1.077) | 1.048 (1.020, 1.077) |
| | 3–5 months after conception | 1.031 (1.018, 1.044) | 1.070 (1.032, 1.110) |
| | 1–5 months after conception | 1.085 (1.069, 1.101) | 1.125 (1.077, 1.175) |
| | 3 months before to 5 months after conception | 1.130 (1.112, 1.149) | 1.254 (1.179, 1.334) |
| Main model + $PM_{2.5}$[b] | 1–3 months before conception | 1.048 (1.035, 1.062) | 1.119 (1.078, 1.162) |
| | 1 month after conception | 0.999 (0.986, 1.011) | 1.011 (0.991, 1.031) |
| | 2–3 months after conception | 1.059 (1.041, 1.078) | 1.048 (1.020, 1.077) |
| | 3–5 months after conception | 1.038 (1.025, 1.051) | 1.076 (1.038, 1.116) |
| | 1–5 months after conception | 1.098 (1.081, 1.114) | 1.141 (1.092, 1.192) |
| | 3 months before to 5 months after conception | 1.151 (1.132, 1.170) | 1.277 (1.201, 1.358) |
| Main model + temperature[c] | 1–3 months before conception | 1.053 (1.040, 1.067) | 1.099 (1.057, 1.143) |
| | 1 month after conception | 1.000 (0.987, 1.012) | 0.991 (0.970, 1.011) |
| | 2–3 months after conception | 1.064 (1.045, 1.083) | 0.997 (0.968, 1.027) |
| | 3–5 months after conception | 1.035 (1.022, 1.048) | 1.070 (1.031, 1.110) |
| | 1–5 months after conception | 1.100 (1.083, 1.118) | 1.057 (1.007, 1.109) |
| | 3 months before to 5 months after conception | 1.159 (1.139, 1.179) | 1.162 (1.085, 1.243) |
| Main model + relative humidity[d] | 1–3 months before conception | 1.059 (1.046, 1.072) | 1.109 (1.068, 1.151) |
| | 1 month after conception | 0.994 (0.982, 1.006) | 0.999 (0.980, 1.018) |
| | 2–3 months after conception | 1.063 (1.045, 1.081) | 1.054 (1.027, 1.081) |
| | 3–5 months after conception | 1.046 (1.033, 1.059) | 1.072 (1.033, 1.113) |
| | 1–5 months after conception | 1.105 (1.088, 1.122) | 1.128 (1.078, 1.181) |
| | 3 months before to 5 months after conception | 1.170 (1.150, 1.191) | 1.251 (1.171, 1.337) |

Abbreviations: OR = odds ratio; CI = confidence interval; $PM_{2.5}$ = fine particulate matter.
[a] Models were adjusted for maternal age, race/ethnicity, marital status, education level, smoking during pregnancy, alcohol drinking during pregnancy, parity, timing of initiation of prenatal care, infant sex, and county poverty rate.
[b] Main models with additionally adjusted for $PM_{2.5}$.
[c] Main models with additionally adjusted for mean ambient temperature from preconception to second trimester using natural cubic splines with 3 degrees of freedom.
[d] Main models with additionally adjusted for mean relative humidity from preconception to second trimester using natural cubic splines with 3 degrees of freedom.

women living in counties with a higher poverty rate. For example, a 10 ppb increase in ozone was associated with an OR of 0.933 (95 % CI: 0.829, 1.050) among women living in counties with a poverty rate <10 % compared with 1.724 (95 % CI: 1.527, 1.946) among women living in counties with a poverty rate ≥15 % for eclampsia.

## 4. Discussion

Leveraging a nationwide study of 2,393,346 mother-infant pairs, we estimated the association between maternal exposure to ozone and risk of gestational hypertension or eclampsia. We found that exposure to ozone during pregnancy was associated with an increased risk of gestational hypertension or eclampsia, especially during 2 to 4 months after conception. The association was more pronounced among women residing in counties with a higher poverty rate.

Our findings of a significant association between ozone exposure and risk of gestational hypertension or eclampsia were consistent with the previous literature (Michikawa et al., 2015; Michikawa et al., 2022; Pedersen et al., 2014; Yan et al., 2022). For example, synthesizing five studies among 258,985 pregnancies, the systematic review and meta-analysis reported a marginally significant association between ozone exposure and HDPs (OR = 1.06; 95 % CI: 0.99, 1.14 per 10 ppb increase in ozone) or preeclampsia (RR = 1.09; 95 % CI: 0.98, 1.21 per 10 ppb increase in ozone). In an analysis of 36,620 singleton pregnant women from Japan between 2005

**Table 3**
Odds ratios of gestational hypertension and eclampsia associated with 10 parts per billion increase in ozone exposure during three months before to five months after conception by personal characteristics in the United States, 2002.

| Characteristics | Gestational hypertension | | Eclampsia | |
|---|---|---|---|---|
| | Odds ratio (95 % CI) | P for heterogeneity | Odds ratio (95 % CI) | P for heterogeneity |
| Maternal age (years) | | | | |
| 18–24 | 1.073 (1.042, 1.104) | [Reference] | 1.146 (1.037, 1.267) | [Reference] |
| 25–29 | 1.162 (1.126, 1.199) | <0.001 | 1.418 (1.256, 1.602) | 0.008 |
| 30–34 | 1.131 (1.094, 1.169) | 0.019 | 1.246 (1.092, 1.422) | 0.322 |
| 35–50 | 1.152 (1.107, 1.198) | 0.004 | 1.236 (1.050, 1.456) | 0.440 |
| Maternal race/ethnicity | | | | |
| Non-Hispanic White | 1.136 (1.110, 1.162) | [Reference] | 1.298 (1.187, 1.420) | [Reference] |
| Non-Hispanic Black | 1.165 (1.119, 1.213) | 0.287 | 1.105 (0.974, 1.255) | 0.042 |
| Hispanic | 1.099 (1.064, 1.134) | 0.098 | 1.284 (1.130, 1.458) | 0.891 |
| Other | 1.047 (0.975, 1.124) | 0.032 | 1.394 (1.049, 1.852) | 0.639 |
| Infant sex | | | | |
| Male | 1.127 (1.102, 1.153) | [Reference] | 1.274 (1.169, 1.389) | [Reference] |
| Female | 1.134 (1.108, 1.161) | 0.709 | 1.234 (1.130, 1.348) | 0.612 |
| County poverty rate | | | | |
| <10 % | 0.956 (0.926, 0.986) | [Reference] | 0.933 (0.829, 1.050) | [Reference] |
| 10 %–14.9 % | 1.236 (1.206, 1.268) | <0.001 | 1.234 (1.125, 1.352) | <0.001 |
| ≥15 % | 1.227 (1.187, 1.269) | <0.001 | 1.724 (1.527, 1.946) | <0.001 |

and 2010, Michikawa et al. (2015) found that exposure to ozone was associated with an increased risk of hypertensive disorders (highest quintile vs. lowest: OR = 1.20; 95 % CI:1.01, 1.42) during the first trimester (Michikawa et al., 2015).

The potential biological mechanisms of gestational hypertension and eclampsia caused by ozone remain unclear, but some plausible pathways have been proposed in previous studies, such as systematic inflammation, oxidative stress and vasoconstriction (Sanidas et al., 2017; Wong et al., 2014). Exposure to ozone might induce systemic oxidative stress, promote the release of inflammatory factors, and lead to vascular endothelial dysfunction, imbalance of the autonomic nervous system and vasoconstriction (Sanidas et al., 2017). In addition, oxidative stress and inflammation may cause vascular remodeling, raise blood pressure, and increase sympathetic activity (Wong et al., 2014), all of which may increase the risk of gestational hypertension or eclampsia.

To identify critical exposure windows, we examined the time course of the association between ozone exposure and risk of gestational hypertension or eclampsia. We also estimated the association for four-time windows: 3 months before conception, 1 month after conception (embryo implantation), 2–3 months after conception (vascularization and placentation), and 3–5 months of gestation (after placentation). We found that the impacts of ozone on gestational hypertension or eclampsia were more pronounced during 2–3 months after conception (vascularization and placentation) and 3–5 months of gestation (after placentation) than that during 1 month after conception (embryo implantation), which indicates that placental dysfunction may play a key role in the pathogenesis of HDPs. Exposure to ozone might induce placental inflammation and oxidative stress, causing abnormal placentation (Kroener et al., 2016), and thus leading to gestational hypertension or eclampsia. We found that exposure to ozone before conception was also associated with gestational hypertension or eclampsia, which was consistent with studies that reported that ozone exposure was associated with increased hypertension and blood pressure in the general population (Coogan et al., 2017; Niu et al., 2022).

We found that the association was more pronounced among women living in counties with a lower socioeconomic condition. To our knowledge, we found no published studies to identify susceptible subpopulations for ozone exposure and HDPs, and thus we cannot compare our findings with others. Although the exact reasons explaining the identified susceptible subgroups are unknown, we speculated that exposure to higher ozone concentrations and tendencies to experience poor health are the potential reasons. Previous studies suggested that individuals living in areas with lower socioeconomic conditions faced more physical and psychosocial stressors and were consistently exposed to higher levels of air pollution than those living in areas with higher socioeconomic conditions (Jbaily et al., 2022; Morello-Frosch and Shenassa, 2006).

Our study has several potential limitations. First, we obtained information on gestational hypertension and eclampsia from birth certificates, and the accuracy of the outcome assessment is unclear. The assessment of gestational hypertension and eclampsia was through regular prenatal care. In the studied population, over 99 % of pregnant women received prenatal care, and thus we expect the sensitivity of gestational hypertension and eclampsia ascertainment to be high. Second, over 50 % of pregnancies in the US are unplanned, and therefore screening for hypertension before conception may not be done regularly. Although we excluded women with pre-existing hypertension, it is still possible that some women with pre-existing hypertension were undiagnosed and thus retained in the analysis. Third, we adjusted for a wide range of potential confounders; however, we cannot exclude the possibility of residual confounding from unmeasured factors, such as medication use. Fourth, we used ambient air pollution as a proxy for personal exposure, which might introduce exposure misclassification. We did not have information on residential mobility during pregnancy, which might also introduce another source of exposure misclassification. However, these two sources of exposure misclassification would be nondifferential and tend to bias estimates toward the non-association (Kioumourtzoglou et al., 2014). Fifth, pregnant women are exposed to multiple air pollutants simultaneously. We only included $PM_{2.5}$ in the sensitivity analysis. We cannot rule out the possibility of confounding effects of other pollutants. Nevertheless, to our knowledge, our study is one of the first nationwide studies to examine the association between maternal exposure to ozone and risk of gestational hypertension and eclampsia.

## 5. Conclusions

In summary, in this nationwide study of over 2.3 million mother-infant pairs, we found that exposure to ozone was associated with a higher risk of gestational hypertension or eclampsia, especially during 2 to 4 months after conception. Our findings suggest that ozone is a potential novel risk factor for hypertensive disorders in pregnancy. Women during pregnancy should be aware of the potential risk of exposure to ozone and seek to reduce exposure to ozone.

## Funding

This study was funded by Capital Medical University Startup (3100/12200140).

## CRediT authorship contribution statement

**Kun Yuan:** Writing – original draft, Methodology, Data curation, Investigation. **Feng Sun:** Writing – review & editing. **Yangchang Zhang:** Writing – review & editing. **Ying Du:** Writing – review & editing. **Lizhi Wu:** Writing – review & editing. **Yang Ge:** Writing – review & editing. **Zhenyu Zhang:** Writing – review & editing. **Wangnan Cao:** Conceptualization, Writing – review & editing, Data curation, Investigation. **Shengzhi Sun:** Conceptualization, Writing – original draft, Formal analysis, Resources, Writing – review & editing.

## Data availability

Data will be made available on request.

## 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.

## Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.scitotenv.2023.162292.

## References

Barrett, P.M., McCarthy, F.P., Evans, M., Kublickas, M., Perry, I.J., Stenvinkel, P., Khashan, A.S., Kublickiene, K., 2020. Hypertensive disorders of pregnancy and the risk of chronic kidney disease: a Swedish registry-based cohort study. PLoS Med. 17, e1003255. https://doi.org/10.1371/journal.pmed.1003255.

Brauer, M., Freedman, G., Frostad, J., van Donkelaar, A., Martin, R.V., Dentener, F., van Dingenen, R., Estep, K., Amini, H., Apte, J.S., Balakrishnan, K., Barregard, L., Broday, D., Feigin, V., Ghosh, S., Hopke, P.K., Knibbs, L.D., Kokubo, Y., Liu, Y., Ma, S., Morawska, L., Sangrador, J.L., Shaddick, G., Anderson, H.R., Vos, T., Forouzanfar, M.H., Burnett, R.T., Cohen, A., 2016. Ambient air pollution exposure estimation for the Global Burden of Disease 2013. Environ. Sci. Technol. 50, 79–88. https://doi.org/10.1021/acs.est.5b03709.

Brauer, M., Casadei, B., Harrington, R.A., Kovacs, R., Sliwa, K., Group, W.A.P.E., 2021. Taking a stand against air pollution—The impact on cardiovascular disease: a joint opinion from the world heart federation, American College of Cardiology, American Heart Association, and the European Society of Cardiology. Circulation 143, e800–e804. https://doi.org/10.1161/CIRCULATIONAHA.120.052666.

Brook, R.D., Franklin, B., Cascio, W., Hong, Y., Howard, G., Lipsett, M., Luepker, R., Mittleman, M., Samet, J., Smith Jr., S.C., Tager, I., 2004. Air pollution and cardiovascular disease: a statement for healthcare professionals from the expert panel on population and prevention science of the American Heart Association. Circulation 109, 2655–2671. https://doi.org/10.1161/01.CIR.0000128587.30041.C8.

Bureau, U.S.C., 2022. Small Area Income and Poverty Estimates.

CDC, 2000. Documentation of the detail natality tape file for 2000 data.

Coogan, P.F., White, L.F., Yu, J., Brook, R.D., Burnett, R.T., Marshall, J.D., Bethea, T.N., Rosenberg, L., Jerrett, M., 2017. Long-term exposure to $NO_2$ and ozone and hypertension incidence in the black women's health study. Am. J. Hypertens. 30, 367–372. https://doi.org/10.1093/ajh/hpw168.

Di, Q., Amini, H., Shi, L., Kloog, I., Silvern, R., Kelly, J., Sabath, M.B., Choirat, C., Koutrakis, P., Lyapustin, A., 2019. An ensemble-based model of $PM_{2.5}$ concentration across the contiguous United States with high spatiotemporal resolution. Environ. Int. 130, 104909. https://doi.org/10.1016/j.envint.2019.104909.

Endeshaw, G., Berhan, Y., 2015. Perinatal outcome in women with hypertensive disorders of pregnancy: a retrospective cohort study. Int. Sch. Res. Not. 2015, 208043. https://doi.org/10.1155/2015/208043.

Ghosh, R., Causey, K., Burkart, K., Wozniak, S., Cohen, A., Brauer, M., 2021. Ambient and household $PM_{2.5}$ pollution and adverse perinatal outcomes: a meta-regression and analysis of attributable global burden for 204 countries and territories. PLoS Med. 18, e1003718. https://doi.org/10.1371/journal.pmed.1003718.

Hinkosa, L., Tamene, A., Gebeyehu, N., 2020. Risk factors associated with hypertensive disorders in pregnancy in Nekemte referral hospital, from July 2015 to June 2017, Ethiopia: case-control study. BMC Pregnancy Childbirth 20, 1–9. https://doi.org/10.1016/s12884-019-2693-9.

Jauniaux, E., Poston, L., Burton, G.J., 2006. Placental-related diseases of pregnancy: involvement of oxidative stress and implications in human evolution. Hum. Reprod. Update 12, 747–755. https://doi.org/10.1093/humupd/dml016.

Jbaily, A., Zhou, X., Liu, J., Lee, T.H., Kamareddine, L., Verguet, S., Dominici, F., 2022. Air pollution exposure disparities across US population and income groups. Nature 601, 228–233. https://doi.org/10.1038/s41586-021-04190-y.

Jiang, L., Tang, K., Magee, L.A., von Dadelszen, P., Ekeroma, A., Li, X., Zhang, E., Bhutta, Z.A., 2022. A global view of hypertensive disorders and diabetes mellitus during pregnancy. Nat. Rev. Endocrinol., 1–16 https://doi.org/10.1038/s41574-022-00734-y.

Kioumourtzoglou, M.-A., Spiegelman, D., Szpiro, A.A., Sheppard, L., Kaufman, J.D., Yanosky, J.D., Williams, R., Laden, F., Hong, B., Suh, H., 2014. Exposure measurement error in $PM_{2.5}$ health effects studies: a pooled analysis of eight personal exposure validation studies. Environ. Health 13, 1–11. https://doi.org/10.1186/1476-069X-13-2.

Kroener, L., Wang, E.T., Pisarska, M.D., 2016. Predisposing factors to abnormal first trimester placentation and the impact on fetal outcomes. Seminars in Reproductive Medicine. Thieme Medical Publishers https://doi.org/10.1055/s-0035-1570029.

Liu, Y., Li, N., An, H., Li, Z., Zhang, L., Li, H., Zhang, Y., Ye, R., 2021. Impact of gestational hypertension and preeclampsia on low birthweight and small-for-gestational-age infants in China: a large prospective cohort study. J. Clin. Hypertens. 23, 835–842. https://doi.org/10.1111/jch.14176.

Michikawa, T., Morokuma, S., Fukushima, K., Ueda, K., Takeuchi, A., Kato, K., Nitta, H., 2015. A register-based study of the association between air pollutants and hypertensive disorders in pregnancy among the Japanese population. Environ. Res. 142, 644–650. https://doi.org/10.1016/j.envres.2015.08.024.

Michikawa, T., Morokuma, S., Yamazaki, S., Takami, A., Sugata, S., Yoshino, A., Takeda, Y., Nakahara, K., Saito, S., Hoshi, J., Kato, K., Nitta, H., Nishiwaki, Y., 2022. Exposure to chemical components of fine particulate matter and ozone, and placenta-mediated pregnancy complications in Tokyo: a register-based study. J. Expo. Sci. Environ. Epidemiol. 32, 135–145. https://doi.org/10.1038/s41370-021-00299-4.

Morello-Frosch, R., Shenassa, E.D., 2006. The environmental "riskscape" and social inequality: implications for explaining maternal and child health disparities. Environ. Health Perspect. 114, 1150–1153. https://doi.org/10.1289/ehp.8930.

NCHS, 2003. National Vital Statistics Reports. National Center for Health Statistics.

Niu, Z., Duan, Z., Wei, J., Wang, F., Han, D., Zhang, K., Jing, Y., Wen, W., Qin, W., Yang, X., 2022. Associations of long-term exposure to ambient ozone with hypertension, blood pressure, and the mediation effects of body mass index: a national cross-sectional study of middle-aged and older adults in China. Ecotoxicol. Environ. Saf. 242, 113901. https://doi.org/10.1016/j.ecoenv.2022.113901.

Pedersen, M., Stayner, L., Slama, R., Sørensen, M., Figueras, F., Nieuwenhuijsen, M.J., Raaschou-Nielsen, O., Dadvand, P., 2014. Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review and meta-analysis. Hypertension (Dallas, Tex : 1979) 64, 494–500. https://doi.org/10.1161/HYPERTENSIONAHA.114.03545.

Requia, W.J., Di, Q., Silvern, R., Kelly, J.T., Koutrakis, P., Mickley, L.J., Sulprizio, M.P., Amini, H., Shi, L., Schwartz, J., 2020. An ensemble learning approach for estimating high spatiotemporal resolution of ground-level ozone in the contiguous U.S. Environ Sci Technol 54, 11037–11047. https://doi.org/10.1021/acs.est.0c01791.

Rothman, K.J., Greenland, S., Lash, T.L., 2008. Modern Epidemiology. Wolters Kluwer Health/Lippincott Williams & Wilkins Philadelphia.

Sanidas, E., Papadopoulos, D.P., Grassos, H., Velliou, M., Tsioufis, K., Barbetseas, J., Papademetriou, V., 2017. Air pollution and arterial hypertension. A new risk factor is in the air. J. Am. Soc. Hypertens. 11, 709–715. https://doi.org/10.1016/j.jash.2017.09.008.

Sears, C.G., Braun, J.M., Ryan, P.H., Xu, Y., Werner, E.F., Lanphear, B.P., Wellenius, G.A., 2018. The association of traffic-related air and noise pollution with maternal blood pressure and hypertensive disorders of pregnancy in the HOME study cohort. Environ. Int. 121, 574–581. https://doi.org/10.1016/j.envint.2018.09.049.

Shah, S., 2020. Hypertensive disorders in pregnancy. Obstetric and Gynecologic Nephrology, pp. 11–23 https://doi.org/10.1007/978-3-030-25324-0_2.

Spangler, K.R., Weinberger, K.R., Wellenius, G.A., 2019. Suitability of gridded climate datasets for use in environmental epidemiology. J. Expo. Sci. Environ. Epidemiol. 29, 777–789. https://doi.org/10.1038/s41370-018-0105-2.

Sun, S., Spangler, K.R., Weinberger, K.R., Yanosky, J.D., Braun, J.M., Wellenius, G.A., 2019a. Ambient temperature and markers of fetal growth: a retrospective observational study of 29 million U.S. Singleton births. Environ. Health Perspect. 127, 67005. https://doi.org/10.1289/EHP4648.

Sun, S., Weinberger, K.R., Spangler, K.R., Eliot, M.N., Braun, J.M., Wellenius, G.A., 2019b. Ambient temperature and preterm birth: a retrospective study of 32 million US singleton births. Environ. Int. 126, 7–13. https://doi.org/10.1016/j.envint.2019.02.023.

Sun, S., Wang, J., Cao, W., Wu, L., Tian, Y., Sun, F., Zhang, Z., Ge, Y., Du, J., Li, X., 2022. A nationwide study of maternal exposure to ambient ozone and term birth weight in the United States. Environ. Int. 170, 107554. https://doi.org/10.1016/j.envint.2022.107554.

Sun, S., Weinberger, K.R., Nori-Sarma, A., Spangler, K.R., Sun, Y., Dominici, F., Wellenius, G.A., 2021. Ambient heat and risks of emergency department visits among adults in the United States: time stratified case crossover study. BMJ 375, e065653. https://doi.org/10.1136/bmj-2021-065653.

Wilson, A., Chiu, Y.M., Hsu, H.L., Wright, R.O., Wright, R.J., Coull, B.A., 2017. Potential for bias when estimating critical windows for air pollution in Children's health. Am. J. Epidemiol. 186, 1281–1289. https://doi.org/10.1093/aje/kwx184.

Wong, M.C., Tam, W.W., Wang, H.H., Lao, X.Q., Zhang, D.D., Chan, S.W., Kwan, M.W., Fan, C.K., Cheung, C.S., Tong, E.L., Cheung, N.T., Tse, L.A., Yu, I.T., 2014. Exposure to air pollutants and mortality in hypertensive patients according to demography: a 10 year case-crossover study. Environ. Pollut. 192, 179–185. https://doi.org/10.1016/j.envpol.2014.05.025.

Yan, M., Liu, N., Fan, Y., Ma, L., Guan, T., 2022. Associations of pregnancy complications with ambient air pollution in China. Ecotoxicol. Environ. Saf. 241, 113727. https://doi.org/10.1016/j.ecoenv.2022.113727.

Ying, W., Catov, J.M., Ouyang, P., 2018. Hypertensive disorders of pregnancy and future maternal cardiovascular risk. J. Am. Heart Assoc. 7, e009382. https://doi.org/10.1161/JAHA.118.009382.

Yoder, S.R., Thornburg, L.L., Bisognano, J.D., 2009. Hypertension in pregnancy and women of childbearing age. Am. J. Med. 122, 890–895. https://doi.org/10.1016/j.amjmed.2009.03.036.