Adverse Effects of Exposure to Fine Particulate Matters and Ozone on Gestational Hypertension*

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Summary: Gestational hypertension (GH) is a common complication during pregnancy. GH is regarded as a potential public health challenge for pregnant women and infants. Limited evidence has linked ambient air pollution to an increased GH risk. However, most of the studies were conducted in developed countries, with inconsistent results obtained. The present study was performed to explore whether exposure to particulate matters with an aerodynamic diameter ≤ 2.5 ($PM_{2.5}$) and ozone (O_3) was related to elevated odds of GH in a Chinese population. This population-based cohort study involved 38 115 pregnant women in Wuhan, China. All information was collected from the Wuhan Maternal and Child Health Management Information System, using standardized quality control. The daily air pollutant data for $PM_{2.5}$ and O_3 were obtained from the 20 monitoring stations of the Wuhan Environmental Monitoring Center during 2014. The nearest monitor approach was applied to individual exposure assessment of $PM_{2.5}$ and O_3 for each participant. After adjusting for major confounders and other air pollutants, a 10 μg/m^3 increase in $PM_{2.5}$ and O_3 concentrations was found to correlate to a 1.14-fold [95% confidence interval (95% CI): 1.09, 1.20] and a 1.05-fold (95% CI: 1.02, 1.07) increase in GH risk, respectively. Additionally, stronger relationships between GH risk and $PM_{2.5}$ and O_3 exposure were observed in women who conceived in winter and summer, respectively. These findings suggest that air pollutants may contribute to the development of GH.
Key words: air pollution; fine particulate matter; ozone; hypertensive disorders of pregnancy; gestational hypertension

Hypertensive disorders of pregnancy (HDP) are a group of the most common obstetric diseases characterized by elevated blood pressure (BP) during pregnancy, affecting about 6%–10% of all pregnancies[1]. Pregnancy is a relatively sensitive period in the life. The changes in intravascular plasma volume and other physiological characteristics during pregnancy can increase the cardiovascular burden in pregnant women and lead to cardiovascular diseases, including HDP[2]. According to the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy, HDP are divided into four categories: a) chronic hypertension, b) preeclampsia-eclampsia, c) preeclampsia superimposed on chronic hypertension, and d) gestational hypertension (GH)[3]. HDP can exert adverse effects on both mothers and their babies. The World Health Organization (WHO) estimates that approximately 1 in 10 maternal deaths in Africa and Asia are related to HDP, and a quarter of maternal deaths in Latin America can be attributed to hypertensive complications during pregnancy[4]. In addition, there is evidence that HDP might increase the risks of cardiovascular diseases, liver and kidney diseases, and diabetes mellitus for mothers later in life[5–7]. Newborns of women with HDP have been

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found to possess an increased risk of adverse birth outcomes (i.e., stillbirth, small for gestational age and low birth weight), neurodevelopmental disorders, type 2 diabetes, and elevated BP[8–12]. However, the underlying etiology of HDP is not yet fully understood.

In recent decades, emerging evidence has linked ambient air pollution to the elevation of BP levels during pregnancy, as well as the risk of GH or HDP[13–19]. For example, Lee *et al*[15] and van den Hooven *et al*[17] concluded that air pollutant exposure during pregnancy was significantly associated with elevated BP during pregnancy. A cohort study of 34 705 participants using birth records from 1997 to 2002 in Allegheny County observed that exposure to particulate matters with an aerodynamic diameter ≤2.5 ($PM_{2.5}$) could increase GH risk, while ozone (O_3) exposure showed no significant association with GH risk[14]. Another study investigating the relationship between ambient air pollution and the risk of GH found that exposure to $PM_{2.5}$, particulate matters with an aerodynamic diameter ≤10 (PM_{10}), and sulfur dioxide (SO_2) were significantly associated with increased risk of GH, but the association between O_3 exposure and GH risk was not significant[19]. Findings from the Florida birth record showed significantly positive associations between exposure to five criteria air pollutants [$PM_{2.5}$, nitrogen dioxide (NO_2), SO_2, carbon monoxide (CO), and O_3] and increased risk of HDP[13, 18]. Additional findings from a case-control study conducted in the U.S. and a register-based study conducted in Japan were in accordance with the above results[16, 20]. However, null or even inverse associations have also been reported in previous literature[21, 22]. Recently, two similar meta-analyses summarized the ambient air pollution effects on HDP, and obtained conflicting conclusions about the associations of HDP with $PM_{2.5}$ and O_3[23, 24]. Of the included studies, only three of them have investigated the relationship between air pollution and GH risk. Several underlying biological mechanisms have been proposed for the association, including oxidative stress, endothelial dysfunction, systemic inflammation and autonomic nervous system imbalance, which might be plausible mechanisms of GH commonly shared[25, 26].

Most of the previous studies have been carried out in developed countries with limited and inconsistent findings. The outcomes of interest were restricted to preeclampsia, eclampsia or HDP. However, air pollution in developing countries is more severe than in developed countries. Based on the inconsistent conclusions of previous studies and given the lack of evidence in Asian populations, relevant studies are urgently needed to examine the relationships of air pollutants with GH. In order to fill these gaps, this cohort study in Wuhan, China was conducted to explore the two concern-specific pollutants, $PM_{2.5}$ and O_3, with the risk of GH.

1 MATERIALS AND METHODS

1.1 Study Population and Outcome Assessment

This population-based cohort study consisted of 38 115 participants identified from the Wuhan Maternal and Child Health Management Information System (WMCHMIS) throughout 2014. The aim was to examine the relationships between air pollution and the risk of GH in Wuhan, China. As the capital city of Hubei Province, Wuhan is one of the largest cities in the central part of China with a high population density and severe air pollution problems. The WMCHMIS is a comprehensive health care system across Wuhan established by the Wuhan Medical and Health Center for Women and Children in 2003. Its goal is to improve the quality of perinatal care and reduce adverse pregnancy outcomes. The standardized, computer-based database from the WMCHMIS collected critical information on demographic characteristics [i.e., maternal age, education level, gestational age at the diagnosis of hypertensive conditions, body mass index (BMI) before pregnancy, and season of conception], medical and reproductive history at baseline (parity, gravidity), pregnancy tests, deliveries, and postnatal follow-up of pregnant women and infants. Pregnant women were considered to be enrolled in this study using the following inclusion criteria: (1) participants were permanent residents in Wuhan; (2) participants who had their last menstrual period between December 1, 2013 and November 30, 2014 underwent prenatal examinations in the obstetrics departments of Wuhan by December 31, 2014; (3) participants had no history of hypertension, diabetes, cardiovascular disease, any other disease, or abnormal pregnancy (i.e., abortion, ectopic pregnancy, stillbirth, etc.); (4) participants delivered singleton live births without birth defects; (5) the participants had residential addresses marked with latitude and longitude using Baidu Maps in Wuhan. Furthermore, pregnant women who had missing or incomplete information on air pollutant exposure, BP measurements, or demographic data were excluded. Available data from all participants were extracted from the WMCHMIS during each prenatal care visit.

During routine pregnancy tests for all pregnant women, standardized BP measurements were obtained using an electronic sphygmomanometer at least twice on the same arm after 5 min of rest in sitting position. The average values of repeated BP measurements were assigned to systolic blood pressure (SBP) and diastolic blood pressure (DBP). HDP was mainly composed of preeclampsia-eclampsia, preeclampsia superimposed on chronic hypertension, and GH, with elevated BP during pregnancy. In the present study, only GH was included. GH was defined as SBP of ≥140 mmHg and/or DBP of ≥90 mmHg, without proteinuria during pregnancy. All participants with GH, as diagnosed

by clinicians, were identified from electronic medical records of the WMCHMIS using the International Classification of Diseases, Tenth Revision (ICD–10). The study protocol was reviewed and approved by the Ethics Committee of the Wuhan Women and Children Health Care Center.

1.2 Exposure Assessment

With air pollution becoming an increasingly serious problem, the Wuhan Environmental Monitoring Center, since 2013, has established 20 automatic air quality monitoring stations (10 national and 10 urban) across most of the districts of Wuhan. The objective is to obtain the distribution of background air pollution levels. In strict accordance with the ambient air quality monitoring standards of China, these air quality monitoring stations are located away from traffic roads, industrial emission sources, residential area emission sources, and electromagnetic interference sources.

Daily air pollutant concentrations of PM_{10} and O_3 were obtained from the 20 environmental monitoring stations during 2014. These measurements were performed using standardized air pollutant analysis methods and quality assurance by the Wuhan Environmental Monitoring Center, as described elsewhere[27]. The study excluded the abnormal hourly values, and calculated the 24-h average concentrations of $PM_{2.5}$. The average concentrations of O_3 were assessed for 8-h intervals (between 10:00 a.m. and 6:00 p.m.) at each monitoring station. The exposure levels of $PM_{2.5}$ and O_3 for each study participant were assessed using the nearest monitor approach. The nearest monitoring station to the pregnant woman's home address was identified using spherical distance, calculated by latitude and longitude. Then, available data from the nearest monitoring station was applied to estimate the concentrations of air pollutants for individual participants during the study period. The diagnostic dates for GH in participants were extracted from the WMCHMIS database and the exposure assessments of air pollutants were conducted for a one-month period before diagnosis. One-month average concentrations of air pollutants for each participant were calculated from the daily average concentrations of $PM_{2.5}$ and the 8-h average concentrations of O_3.

1.3 Statistical Analysis

Descriptive analyses were conducted to summarize the demographic characteristics of pregnant women and the concentration distributions of air pollutants in this study. Differences in the demographic characteristics of pregnant women were analyzed based on the status of GH (normotensive or GH) using the student's *t*-test and the chi-square test. The potential associations of $PM_{2.5}$ and O_3 with GH risk were examined using several multivariate logistic regression models. The concentrations of $PM_{2.5}$ and O_3 were used as both continuous and categorical variables in these models. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated per 10 $\mu g/m^3$ increase in average $PM_{2.5}$ and O_3 concentrations. The average values of these air pollutants were also categorized into quartiles. First, $PM_{2.5}$ and O_3 were assigned as independent variables to enter into single-pollutant logistic regression models, without adjustments for any confounders. Then, some confounders were introduced to the first multivariable logistic regression model to consider their potential effects on BP. Based on previous evidence and the characteristics of the study population, the following variables were considered as potential confounders: maternal age, pre-pregnancy body mass index (BMI), gestational age at diagnosis, maternal education level (middle school or below, high school, college, bachelor's or higher degree), parity (1, ≥2), gravidity (1, ≥2), season of conception (spring: March–May; summer: June–August; autumn: September–November; and winter: December–February)[13, 19]. Age, pre-pregnancy BMI, and gestational age at diagnosis were treated as continuous variables; maternal education level was regarded as an ordinal category variable; parity and gravidity were assigned to be dichotomous variables; and season of conception was considered for entering into the final models as a dummy variable. Though smoking and drinking have important impacts on BP, this study did not adjust for maternal smoking and drinking during pregnancy due to the low smoking and drinking rates shown in previous data[28]. $PM_{2.5}$ and O_3 were also added to the second multivariable logistic regression model simultaneously to adjust for each other, as well as other confounders mentioned above. Lastly, these analyses were extended to the third multivariable logistic regression model by additionally controlling for the potential confounding effects of other air pollutants (PM_{10}, NO_2, SO_2, and CO), based on the second model, in order to determine an independent effect assessment of $PM_{2.5}$ and O_3 on GH. In addition, a subgroup analysis stratified by season of conception was conducted to estimate the associations of $PM_{2.5}$ and O_3 exposure with GH. Sensitivity analyses were also applied to test the robustness of the findings by excluding pregnant women of age >40 years and <18 years (n=283) and pregnant women with pre-pregnancy BMI ≥ 28 kg/m^2 (n=450), as these groups are known to have a higher GH risk.

All data analyses were conducted using SAS, version 9.4 (SAS Institute, Inc., USA), with a two-sided P<0.05 of statistical significance.

2 RESULTS

2.1 Characteristics of the Study Population

The participants' characteristics by status of GH are summarized in table 1. There were 38115 pregnant women enrolled in this study and, of these,

Table 1 Maternal characteristics by gestational hypertension status in Wuhan, China, during 2014 (*n*=38 115)

Variables	Normotensive (*n*=36 339)	Gestational hypertension (*n*=1776)	*P*
Maternal age (years), mean (±SD)	26.9 (±4.2)	26.9 (±4.3)	0.997
Pre-pregnancy BMI (kg/m^2), mean (±SD)	20.6 (±2.3)	21.3 (±3.0)	< 0.001
Gestational age (weeks) at diagnosis, mean (±SD)	29.7 (±9.4)	31.1 (±8.2)	< 0.001
Maternal education level (%)			0.085
Middle school or below	12 648 (34.8)	640 (36.0)	
High school	7513 (20.7)	395 (22.2)	
College	7129 (19.6)	313 (17.6)	
Bachelor's or higher degree	9049 (24.9)	428 (24.1)	
Parity (%)			< 0.001
1	27 067 (74.5)	1395 (78.5)	
≥2	9272 (25.5)	381 (21.5)	
Gravidity (%)			< 0.001
1	18 700 (51.5)	1000 (56.3)	
≥2	17 639 (48.5)	776 (43.7)	
Season of conception (%)			< 0.001
Winter (December–February)	10 497 (28.9)	613 (34.5)	
Spring (March–May)	13 361 (36.8)	895 (50.4)	
Summer (June–August)	7425 (20.4)	220 (12.4)	
Autumn (September–November)	5056 (13.9)	48 (2.7)	

SD, standard deviation; BMI, body mass index

1776 participants were identified to have GH. The incidence of GH during pregnancy was 4.7% in this study. Maternal age in the normotensive group and the GH group was consistent, with mean values of 26.9 years [standard deviation (SD)=4.2 years] and 26.9 years (SD=4.3 years), respectively. Compared with the normotensive group, pregnant women with GH tended to have higher pre-pregnancy BMIs (mean=21.3 kg/m^2; SD=3.0 kg/m^2, P<0.001), as well as longer gestational age at diagnosis of GH (mean=31.1 weeks; SD=8.2 weeks, P<0.001). The similar distributions of maternal education level in both the normotensive and the GH groups were observed with no significant difference noted. The GH group was more likely to be nulliparous (P<0.001) and to conceive in winter and spring than the normotensive participants (P<0.001).

2.2 Distribution of Air Pollutant Levels

Table 2 presents the distribution of air pollutant levels for a one-month period at the 20 monitoring stations in Wuhan during 2014. The mean (±SD) concentrations of $PM_{2.5}$ and O_3 were 83.4 (±28.6) μg/m^3 and 72.2 (±32.0) μg/m^3, respectively, with wide ranges ($PM_{2.5}$: 33.0–202.6 μg/m^3; O_3: 25.5–183.9 μg/m^3). According to China's national ambient air quality standard (GB 3095–2012) and the WHO guidelines, the average concentrations of $PM_{2.5}$ significantly exceeded the reference value. This highlights the serious $PM_{2.5}$ pollution in Wuhan. However, O_3 average levels met the recommended value.

2.3 Association of Exposure to Fine Particulate Matters and Ozone with GH

Table 3 exhibits the crude and adjusted ORs for GH per 10 μg/m^3 increase in both $PM_{2.5}$ and O_3 levels in several multivariate logistic regression models. The negative association of $PM_{2.5}$ levels with the risk of GH was found in the crude model (OR=0.87, 95% CI: 0.85, 0.88), the first adjusted model (OR=0.93, 95% CI: 0.93, 0.97), and the second adjusted model (OR=0.96, 95% CI: 0.93, 0.98). However, this association became positive, with significant difference found, after adjusting for major confounders and other air pollutants (PM_{10}, NO_2, SO_2, CO, and O_3) in the third model (OR=1.14, 95% CI: 1.09, 1.20). Compared with the reference group, pregnant women with the highest quartile of $PM_{2.5}$ exposure had higher odds of GH (OR=1.59, 95% CI: 1.18, 2.14) in the third model. The exposure levels of O_3 were observed to have a positive correlation with the risk of GH in the crude model, with an OR of 1.11 (95% CI: 1.09, 1.12). The effect of O_3 on GH was weak, but the association was statistically significant, after adjustments for major confounders in the first model (OR=1.06, 95% CI: 1.03, 1.08) and

Table 2 Distribution of air pollutants levels during the study period in Wuhan, China, during 2014

Variables (μg/m^3)	Mean	SD	Minimum	P25	Median	P75	Maximum	NS*	WHO#
$PM_{2.5}$	83.4	28.6	33.0	64.6	79.5	98.3	202.6	75	25
O_3	72.2	32.0	25.5	45.5	61.8	98.0	183.9	160	100

SD: standard deviation; P25: the percentile of 25; P75: the percentile of 75.
*China national ambient air quality standard (GB 3095–2012).
#WHO 2005 air quality guidelines

additional adjustments for $PM_{2.5}$ in the second model (OR=1.05, 95% CI: 1.03, 1.07). Further adjustments for other air pollutants (PM_{10}, NO_2, SO_2, and CO) did not drastically change the results in the third model. An increase, per 10 μg/m^3, in O_3 was related to the increased risk of GH, with an OR of 1.05 (95% CI: 1.02, 1.07). Meanwhile, pregnant women in the 2nd, 3rd, and 4th quartile of O_3 levels possessed a significantly increased risk of GH in the third model, with ORs of 1.96 (95% CI: 1.63, 2.36), 1.71 (95% CI: 1.39, 2.11), and 1.94 (95% CI: 1.52, 2.49), respectively.

2.4 Association of Exposure to Fine Particulate Matters and Ozone with GH Stratified by Season of Conception

Table 4 shows the adjusted associations between $PM_{2.5}$ and O_3 levels and the risk of GH stratified by season of conception. For $PM_{2.5}$ exposure, the pregnant women with conception in spring, summer, autumn, and winter were found to have ORs for GH of 1.08 (95% CI: 1.01, 1.15), 1.14 (95% CI: 1.01, 1.29), 0.97 (95% CI: 0.78, 1.21), and 1.46 (95% CI: 1.28, 1.67), respectively. The OR of 1.46 for GH was significantly higher in participants with conception in winter than the overall estimate of 1.14 in all participants, as well as in these pregnant women with conception in other seasons. As for O_3 exposure, the ORs for GH for pregnant women with conception in spring, summer, autumn, and winter were 1.11 (95% CI: 1.06, 1.16), 1.13 (95% CI: 1.04, 1.24), 1.14 (95% CI: 0.86, 1.52), and 1.07 (95% CI: 1.03, 1.12), respectively. The increased GH risk for O_3 exposure in pregnant women with conception in spring, summer, and winter were slightly stronger than the estimated risk of GH in all participants, in which the association among women with conception in summer was the most obvious. No significant associations were found between $PM_{2.5}$

Table 3 Association between air pollution and the risk of gestational hypertension in the multivariable logistic regression models in Wuhan, China, during 2014 (*n*=38 115)

Variables	Crude Model	Adjusted model 1*	Adjusted model 2#	Adjusted model 3**
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
$PM_{2.5}$ (continuous)	0.87 (0.85, 0.88)	0.95 (0.93, 0.97)	0.96 (0.93, 0.98)	1.14 (1.09, 1.20)
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	0.75 (0.67, 0.85)	0.98 (0.86, 1.11)	1.02 (0.89, 1.16)	1.05 (0.90, 1.24)
Quartile 3	0.58 (0.51, 0.66)	0.77 (0.67, 0.88)	0.83 (0.72, 0.95)	1.12 (0.91, 1.38)
Quartile 4	0.36 (0.31, 0.42)	0.69 (0.58, 0.82)	0.81 (0.68, 0.96)	1.59 (1.18, 2.14)
O_3 (continuous)	1.11 (1.09, 1.12)	1.06 (1.03, 1.08)	1.05 (1.03, 1.07)	1.05 (1.02, 1.07)
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.97 (1.67, 2.31)	2.26 (1.91, 2.68)	2.16 (1.82, 2.56)	1.96 (1.63, 2.36)
Quartile 3	2.05 (1.74, 2.40)	1.94 (1.62, 2.31)	1.87 (1.56, 2.24)	1.71 (1.39, 2.11)
Quartile 4	2.96 (2.54, 3.45)	2.06 (1.69, 2.52)	1.98 (1.61, 2.43)	1.94 (1.52, 2.49)

*Adjusted for maternal age, pre-pregnancy BMI, gestational age at diagnosis, maternal education level, parity, gravidity, and season of conception

#Adjusted for maternal age, pre-pregnancy BMI, gestational age at diagnosis, maternal education level, parity, gravidity, season of conception, and O_3 or $PM_{2.5}$

**Adjusted for maternal age, pre-pregnancy BMI, gestational age at diagnosis, maternal education level, parity, gravidity, season of conception, PM_{10}, NO_2, SO_2, CO, and O_3 or $PM_{2.5}$

Table 4 Adjusted OR (95% CI) for the relationships between the risk of gestational hypertension and exposure to the air pollution stratified by season of conception

Variables	Spring	Summer	Autumn	Winter
	OR (95% CI)	OR (95% CI)	OR (95% CI)	OR (95% CI)
$PM_{2.5}$ (continuous)*	1.08 (1.01, 1.15)	1.14 (1.01, 1.29)	0.97 (0.78, 1.21)	1.46 (1.28, 1.67)
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	1.07 (0.87, 1.32)	1.44 (0.94, 2.23)	0.85 (0.36, 2.01)	0.97 (0.74, 1.26)
Quartile 3	0.87 (0.68, 1.12)	1.97 (1.01, 3.84)	0.70 (0.23, 2.13)	1.81 (1.21, 2.69)
Quartile 4	1.09 (0.76, 1.57)	1.71 (0.81, 3.60)	0.46 (0.08, 2.78)	0.98 (0.97, 0.99)
O_3 (continuous)#	1.11 (1.06, 1.16)	1.13 (1.04, 1.24)	1.14 (0.86, 1.52)	1.07 (1.03, 1.12)
Quartile 1	Reference	Reference	Reference	Reference
Quartile 2	2.01 (1.57, 2.57)	1.52 (0.92, 2.52)	3.09 (1.16, 8.23)	0.97 (0.74, 1.28)
Quartile 3	2.04 (1.56, 2.68)	2.22 (1.32, 3.73)	1.97 (0.67, 5.79)	1.07 (0.81, 1.42)
Quartile 4	2.94 (2.13, 4.04)	2.48 (1.34, 4.59)	1.50 (0.48, 4.63)	1.53 (1.18, 2.00)

*Adjusted for maternal age, pre-pregnancy BMI, gestational age at diagnosis, maternal education level, parity, gravidity, PM_{10}, NO_2, SO_2, CO, and O_3

#Adjusted for maternal age, pre-pregnancy BMI, gestational age at diagnosis, maternal education level, parity, gravidity, PM_{10}, NO_2, SO_2, CO, and $PM_{2.5}$

and O_3 exposure and GH risk in pregnant women with conception in autumn.

After excluding pregnant women of age >40 years and <18 years, and pregnant women with a pre-pregnancy BMI ≥28 kg/m^2, there were 37 832 and 37 665 participants included in the sensitivity analyses, respectively. The crude and adjusted results of the association in relation to O_3 exposure and GH were similar to those from the total population, all of which were statistically significant. The association between $PM_{2.5}$ exposure and GH risk in the third adjusted model was slightly attenuated, but it was not significantly changed.

3 DISCUSSION

As one of the most common hypertensive disorders during pregnancy, GH has been categorized as a potential public health challenge for pregnant women and their infants. This study used a cohort design to explore the associations of exposure to $PM_{2.5}$ and O_3 with GH risk in the Chinese population. Results indicated that exposure to $PM_{2.5}$ and O_3 during pregnancy was significantly associated with an elevated risk of GH, even after considering for basic confounders and other air pollutants. Additionally, stronger relationships of GH risk with $PM_{2.5}$ and O_3 exposure were observed in pregnant women with conception in winter and summer, respectively.

A growing body of literature has linked ambient air pollution to hypertension and elevated BP during pregnancy, although the findings have been inconsistent[13, 14, 16, 19–21, 29]. The positive correlation of $PM_{2.5}$ exposure with the risk of GH observed in this study was in accordance with the findings from a recent study investigating the associations between ambient air pollutants and GH risk by Zhu *et al*[19]. In further support of these results, Lee *et al*[14] conducted a cohort study of 34 705 participants relying on birth records from 1997 to 2002 in Allegheny County to determine the associations between air pollution and GH risk. They observed exposure to $PM_{2.5}$ was associated with increased GH risk. Similar findings were obtained from birth record data in North Carolina[29]. In addition, a case-control study from Los Angeles showed that a 7 μg/m^3 increase in $PM_{2.5}$ during the first trimester correlated to a nearly 4-fold risk of HDP[16]. Recently, a study from China examined the effect of air pollution on preeclampsia and observed prenatal exposure to PM_{10} and SO_2 increased preeclampsia risk, similar with our findings[30]. Unfortunately, they did not obtain monitoring data of $PM_{2.5}$ levels. Women with higher O_3 exposure in the second trimester were more likely to develop HDP[16]. Likewise, Savitz *et al*[21] used birth certificates and hospital discharges from New York City to assess the effects of $PM_{2.5}$ and NO_2 exposure on HDP. Elevated risk of HDP was found to be related to higher $PM_{2.5}$ exposure after standard adjustments for demographic and reproductive characteristics, socioeconomic deprivation, and BMI[21]. However, when additionally adjusted for delivery hospital, this association became insignificant[21]. Other studies have reported similar results about the relationships of $PM_{2.5}$ exposure with an elevated risk of preeclampsia[31, 32]. With regard to the effect of O_3 exposure on HDP risk, a large sample study of 36 620 pregnant women from Japan supported the results of this study by reporting that high O_3 exposure during the first trimester could cause increased odds of HDP[20]. Recently, the findings by Hu *et al*[13] suggested a significant and positive association between exposure to O_3 and the risk of HDP. Others also observed higher O_3 exposure might lead to an increase in the risk of preeclampsia[33, 34]. Nevertheless, it must be noted that some studies are inconsistent with the findings of our study and reported null relationships of air pollutants with GH or preeclampsia risk. For instance, according to the nationwide cohort study of labor and delivery, O_3 exposure during pregnancy showed no significant association with an increased GH risk, which was consistent with results from Lee *et al*[14, 19]. A large obstetric cohort from the U.S. found that increased risk of preeclampsia was not associated with $PM_{2.5}$ and O_3 exposure in any trimester among pregnant women with or without asthma[35]. Similar conclusions were also observed in other studies[36].

Despite some difficulties in comprehensively comparing different studies, the discrepancies found could be explained by the following reasons. First, different exposure assessment methods for individual exposure levels of air pollutants were used with respective advantages in these studies, which might give rise to exposure misclassification. These methods included the inverse distance weighted method, space-time ordinary kriging interpolation, and air quality monitoring station data. Next, the actual background exposure levels of air pollutants varied significantly among different regions or countries. This was especially true when comparing developing countries and developed countries. In this study, levels of $PM_{2.5}$ were much higher than those reported in the U.S. (median values, 79.5 μg/m^3 *vs.* 15.6 μg/m^3), while O_3 concentrations were comparable (28.8 ppb *vs.* 21.7 ppb)[14]. As a developing country, China has been faced with serious $PM_{2.5}$ pollution for many years, giving significant rise to its the background concentrations. Also, exposure assessments of air pollutants were carried out for different stages of pregnancy, resulting in inconsistent causal relationships. To date, it remains unclear which stage of pregnancy has the greatest susceptibility to the adverse effects induced by air pollution exposure. Further research is needed to identify window-specific exposure effects of air

pollution on GH or BP. In addition, the determination of outcomes was inconsistent when comparing the results of this study with others. The outcomes were defined as GH in this study, while others restricted their outcomes of interest to either GH, preeclampsia, and eclampsia or the total HDP. It should be recognized that the comparability among these findings was not well to some extent. Finally, there were a great number of unidentified and unknown confounding factors that might bias these associations towards different directions. Adjustment for covariates obviously varied among these studies. Therefore, it was difficult to distinguish the independent effect of each individual air pollutant.

Given the similarities between HDP and cardiovascular diseases, it is plausible that HDP may share common pathogenic pathways with cardiovascular diseases induced by air pollutants[37, 38]. Toxicological experiments have demonstrated that exposure to air pollutants could trigger severe oxidative effects, vascular endothelial dysfunction, system inflammation, and the imbalance of the autonomic nervous system in mice or Sprague Dawley rats[39–42]. All of these have been proposed as plausible mechanisms for the association of exposure to air pollutants with cardiovascular diseases[25, 38]. Of these biological mechanisms, systemic inflammation reaction and oxidative stress caused by air pollutants are suspected to increase sympathetic nerve tension and cause vascular remodeling[43]. The elevated levels of circulating inflammatory cytokines induced by oxidative stress can also lead to endothelial dysfunction. Subsequently, an imbalance of vascular homeostasis and total peripheral resistance occur, resulting in elevated levels of BP[43]. In addition, the autonomic imbalance and vasoconstriction directly induced by air pollutants may be responsible for increased BP[44]. Further experiments should be conducted to understand the potential mechanisms of the development of GH induced by air pollution.

Our study found there were stronger correlations of GH risk with the exposure to $PM_{2.5}$ and O_3 for pregnant women with conception in winter and summer, while no significant association was observed in autumn. Evidence from previous studies has indicated that seasonal variation of conception is associated with the risk of HDP. An investigation conducted in Hong Kong examined the potential relationship of seasonal variation with the incidence in preeclampsia, and found that women with summer conceptions tended to have a higher risk than women with autumn conceptions[45]. Another investigation also suggested that conceptions in summer had the highest risk of preeclampsia[46]. Recently, a report from Norway by Weinberg *et al*[47] found that higher preeclampsia risk occurred in spring conceptions and lower risk occurred in autumn conceptions, demonstrating that season of conception was a potential driver for preeclampsia. The inconsistencies across the above findings highlight the need for more studies with a large sample size and rigorous cohort design in the future. The results of elevated risk of GH in both winter conceptions and summer conceptions could be partially attributed to seasonal variation of BP, physiological responses to drastic temperature change, physical activity, seasonal infections, and dietary pattern changes[48]. For example, it has been observed that seasonal trends of BP during pregnancy reached its peak in winter and gradually dropped to the lowest point in summer[49]. Cold could cause arteriolar constriction, increase peripheral resistance and lead to apro-hypertensive status that may be more vulnerable to external stimuli such as air pollution[50]. With an increase of 10°C in daily temperature, SBP and DBP could decrease by the mean value of 2.5 mmHg[51]. However, high ambient temperatures have been suggested to result in skin blood flow increase and skin surface moistening, which might further exacerbate the toxicity of exposed chemicals from air pollutants[52, 53]. Additionally, the higher temperature and humidity during early pregnancy might affect placental vascular development and remodeling, which would produce a greater risk of preeclampsia in pregnant women[45]. Thus, we could observe elevated risk effects of air pollution in relatively low and high temperatures of conception season. Another alternative explanation suggested that dietary pattern during early pregnancy might vary seasonally. As a consequence, maternal nutrition status would be altered and immune function might be reduced[48].

There were several strengths of this study. First, all the pregnant women who met the inclusion criteria during the study period were recruited from a large, metropolitan area (Wuhan), using a population-based cohort design. The large sample size and decreased population variability (using a single city) provided higher statistical power and smaller possibility for information bias. Also, all critical information (i.e., demographic characteristics, medical history, and reproductive history) was obtained from the WMCHMIS, which provided more complete and accurate data than those provided by reliance on birth certificates. Additionally, the diagnosis date of GH in the pregnant women was available, which provided the possibility for this study to accurately evaluate the exposure levels of air pollutants prior to disease occurrence. Furthermore, other criteria pollutants, such as PM_{10}, SO_2, NO_2, and CO have been demonstrated to have detrimental effects on maternal BP during pregnancy. Daily average concentrations of these air pollutants, as well as $PM_{2.5}$ and O_3, could be obtained from the Wuhan Environmental Monitoring Center during the study period. This allowed for the

identification of the relatively independent effects of $PM_{2.5}$ and O_3 on GH risk after controlling for the impact of the other pollutants.

Although this study proposes new evidence on the relationships of air pollutants with GH risk, there are some limitations worth mentioning when making inferences. One of the main limitations was the potential for exposure misclassification due to the reliance on the data source of air quality monitoring stations. Direct individual exposure measurement methods are unlikely to be implemented for large-scale cohort studies because of the restrictions of the research conditions. Thus, the exposure levels of air pollutants for each pregnant woman were assessed using the nearest air monitor method, where daily air pollutants data were provided by the Wuhan Environmental Monitoring Center. This exposure assessment method might suffer from some misclassifications induced by information bias, individual daily mobility or behavior patterns, and residential mobility. The air quality monitoring stations could not capture the spatial heterogeneity of air pollutants adequately because the concentration distribution of atmospheric pollutants was easily affected by weather, vegetation, road traffic and other conditions. This increased the chance of information bias. Usually, the space-time ordinary kriging interpolation model provides better spatial coverage, but it still depends on air monitors and neglects atmospheric influences on the dispersion of air pollutants[14]. Although Gaussian dispersion model estimates local traffic-generated air pollutants with better spatiotemporal variability, the results are easily affected by residential mobility[32]. Recently, the land use regression (LUR) model is greatly developed and often used, since it can characterize the small-scale within-city variation of pollutant levels and has been suggested to be an effective tool in predicting long-term intra-urban variation of air pollution[31, 54]. However, the LUR model requires that variables included in models are temporally stable and are not transferable from one urban area to another, and the results may be influenced by the different buffering radius used in the model[55]. It should be noted that there were the comparable results between air pollution and preeclampsia when exposure was assessed using dispersion model, LUR model, or a more simplistic method such as nearest air monitor as we used[34]. Additionally, the actual air pollution exposure may be significantly affected by the fact that individual exposure might vary over time spent at different places and daily activity patterns during pregnancy. Unfortunately, like most similar studies, the data on daily activity patterns were not available for this present investigation. The fact that residential mobility might occur during pregnancy was not addressed, introducing the possibility of exposure misclassification. However, residential mobility during pregnancy was reportedly lower in China than in the U.S., suggesting the possibility of a non-differential bias[27]. In this case, most of the effect estimates were likely to attenuate and trend towards conservative conclusions. Another limitation was that the synergistic or cumulative effects of the simultaneous exposure to other unknown environment pollutants might interfere with these associations, leading to the increased chance of false positive results. Humans are constantly exposed to known or unknown environmental pollutants, which restricts the generalization of this study' conclusions. Finally, although major covariates had been controlled in the final models, there were still important confounders that were inaccessible or unidentified due to limited research conditions, such as socioeconomic status and secondhand smoke.

In conclusion, this study examined the association between exposure to $PM_{2.5}$ and O_3 and risk of GH with a large sample size in the Chinese population. Exposure to $PM_{2.5}$ and O_3 during pregnancy was found to be significantly associated with an elevated GH risk after controlling for confounders and other air pollutants. The relationships for $PM_{2.5}$ and O_3 exposure were observed to be stronger in winter conception and summer conception, respectively. Given the public health challenge of air pollution in China, these findings could serve as a platform for the establishment of future policies aimed at addressing the impact of air pollution on pregnancy. Further research is warranted to confirm these findings and elucidate biologically plausible mechanisms.

Conflict of Interest Statement

The authors of this study declare no conflict of interest.

REFERENCES

1 Kintiraki E, Papakatsika S, Kotronis G, *et al*. Pregnancy-Induced hypertension. Hormones (Athens), 2015,14(2): 211-223

2 Yoder SR, Thornburg LL, Bisognano JD. Hypertension in Pregnancy and Women of Childbearing Age. Am J Med, 2009,122(10):890-895

3 Report of the National High Blood Pressure Education Program Working Group on High Blood Pressure in Pregnancy. Am J Obstet Gynecol, 2000,183(1):s1-s22

4 Wu W, Zhou F, Wang Y, *et al*. Phthalate levels and related factors in children aged 6-12 years. Environ Pollut, 2017,220(Pt B):990-996

5 Duley L. The global impact of pre-eclampsia and eclampsia. Semin Perinatol, 2009,33(3):130-137

6 Feig DS, Shah BR, Lipscombe LL, *et al*. Preeclampsia as a risk factor for diabetes: a population-based cohort study. PLoS Med, 2013,10(4):e1001425

7 Tooher J, Thornton C, Makris A, *et al*. All Hypertensive Disorders of Pregnancy Increase the Risk of Future Cardiovascular Disease. Hypertension, 2017,70(4):798-803

8 Curran EA, O'keeffe GW, Looney AM, *et al*. Exposure

to Hypertensive Disorders of Pregnancy Increases the Risk of Autism Spectrum Disorder in Affected Offspring. Mol Neurobiol, 2018,55(7):5557-5564
9 Johnson KM, Zash R, Haviland MJ, *et al*. Hypertensive disease in pregnancy in Botswana: Prevalence and impact on perinatal outcomes. Pregnancy Hypertens, 2016,6(4):418-422
10 Kajantie E, Osmond C, Eriksson JG. Gestational hypertension is associated with increased risk of type 2 diabetes in adult offspring: the Helsinki Birth Cohort Study. Am J Obstet Gynecol, 2017,216(3):281.e281-281.e287
11 Shen M, Smith GN, Rodger M, *et al*. Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia. PLoS One, 2017,12(4):e0175914
12 Tenhola S, Rahiala E, Halonen P, *et al*. Maternal preeclampsia predicts elevated blood pressure in 12-year-old children: evaluation by ambulatory blood pressure monitoring. Pediatr Res, 2006,59(2):320-324
13 Hu H, Ha S, Xu X. Ozone and hypertensive disorders of pregnancy in Florida: Identifying critical windows of exposure. Environ Res, 2017,153:120-125
14 Lee PC, Roberts JM, Catov JM, *et al*. First trimester exposure to ambient air pollution, pregnancy complications and adverse birth outcomes in Allegheny County, PA. Matern Child Health J, 2013,17(3):545-555
15 Lee PC, Talbott EO, Roberts JM, *et al*. Ambient air pollution exposure and blood pressure changes during pregnancy. Environ Res, 2012,117(6):46-53
16 Mobasher Z, Salam MT, Goodwin TM, *et al*. Associations between ambient air pollution and Hypertensive Disorders of Pregnancy. Environ Res, 2013,123:9-16
17 Van Den Hooven EH, De Kluizenaar Y, Pierik FH, *et al*. Air pollution, blood pressure, and the risk of hypertensive complications during pregnancy: the generation R study. Hypertension, 2011,57(3):406-412
18 Xu X, Hu H, Ha S, *et al*. Ambient air pollution and hypertensive disorder of pregnancy. J Epidemiol Community Health, 2014,68(1):13-20
19 Zhu Y, Zhang C, Liu D, *et al*. Ambient Air Pollution and Risk of Gestational Hypertension. Am J Epidemiol, 2017,186(3):334-343
20 Michikawa T, Morokuma S, Fukushima K, *et al*. A register-based study of the association between air pollutants and hypertensive disorders in pregnancy among the Japanese population. Environ Res, 2015,142:644-650
21 Savitz DA, Elston B, Bobb JF, *et al*. Ambient fine particulate matter, nitrogen dioxide, and hypertensive disorders of pregnancy in New York City. Epidemiology, 2015,26(5):748-757
22 Zhai D, Guo Y, Smith G, *et al*. Maternal exposure to moderate ambient carbon monoxide is associated with decreased risk of preeclampsia. Am J Obstet Gynecol, 2012,207(1):57.e51-59
23 Hu H, Ha S, Roth J, *et al*. Ambient Air Pollution and Hypertensive Disorders of Pregnancy: A Systematic Review and Meta-analysis. Atmos Environ, 2014,97(3):336-345
24 Pedersen M, Stayner L, Slama R, *et al*. Ambient air pollution and pregnancy-induced hypertensive disorders: a systematic review and meta-analysis. Hypertension, 2014,64(3):494-500
25 Brook RD, Rajagopalan S, Pope CA, 3rd, *et al*. Particulate matter air pollution and cardiovascular disease: An update to the scientific statement from the American Heart Association. Circulation, 2010,121(21):2331-2378
26 Cai Y, Zhang B, Ke W, *et al*. Associations of Short-Term and Long-Term Exposure to Ambient Air Pollutants With Hypertension: A Systematic Review and Meta-Analysis. Hypertension, 2016,68(1):62-70
27 Qian Z, Liang S, Yang S, *et al*. Ambient air pollution and preterm birth: A prospective birth cohort study in Wuhan, China. Int J Hyg Environ Health, 2016,219(2):195-203
28 Zhang B, Liang S, Zhao J, *et al*. Maternal exposure to air pollutant $PM_{2.5}$ and PM_{10} during pregnancy and risk of congenital heart defects. J Expo Sci Environ Epidemiol, 2016,26(4):422-427
29 Vinikoor-Imler LC, Gray SC, Edwards SE, *et al*. The effects of exposure to particulate matter and neighbourhood deprivation on gestational hypertension. Paediatr Perinat Epidemiol, 2012,26(2):91-100
30 Wang Q, Zhang H, Liang Q, *et al*. Effects of prenatal exposure to air pollution on preeclampsia in Shenzhen, China. Environ Pollut, 2018,237:18-27
31 Dadvand P, Figueras F, Basagana X, *et al*. Ambient air pollution and preeclampsia: a spatiotemporal analysis. Environ Health Perspect, 2013,121(11-12):1365-1371
32 Wu J, Ren C, Delfino RJ, *et al*. Association between local traffic-generated air pollution and preeclampsia and preterm delivery in the south coast air basin of California. Environ Health Perspect, 2009,117(11):1773-1779
33 Olsson D, Mogren I, Forsberg B. Air pollution exposure in early pregnancy and adverse pregnancy outcomes: a register-based cohort study. BMJ Open, 2013,3(2)
34 Wu J, Wilhelm M, Chung J, *et al*. Comparing exposure assessment methods for traffic-related air pollution in an adverse pregnancy outcome study. Environ Res, 2011,111(5):685-692
35 Mendola P, Wallace M, Liu D, *et al*. Air pollution exposure and preeclampsia among US women with and without asthma. Environ Res, 2016,148:248-255
36 Rudra CB, Williams MA, Sheppard L, *et al*. Ambient carbon monoxide and fine particulate matter in relation to preeclampsia and preterm delivery in western Washington State. Environ Health Perspect, 2011,119(6):886-892
37 Kaaja RJ, Greer IA. Manifestations of chronic disease during pregnancy. JAMA, 2005,294(21):2751
38 Cai Y, Zhang B, Ke W, *et al*. Associations of Short-Term and Long-Term Exposure to Ambient Air Pollutants With Hypertension: A Systematic Review and Meta-Analysis. Hypertension, 2016,68(1):62-70
39 Dai J, Chen W, Lin Y, *et al*. Exposure to Concentrated Ambient Fine Particulate Matter Induces Vascular Endothelial Dysfunction via miR-21. Int J Biol Sci, 2017,13(7):868-877
40 Elder A, Couderc JP, Gelein R, *et al*. Effects of on-road highway aerosol exposures on autonomic responses in aged, spontaneously hypertensive rats. Inhal Toxicol, 2007,19(1):1-12
41 Pei Y, Jiang R, Zou Y, *et al* Effects of Fine Particulate

Matter (PM2.5) on Systemic Oxidative Stress and Cardiac Function in ApoE(-/-) Mice. Int J Environ Res Public Health, 2016,13(5)
42 Wang G, Jiang R, Zhao Z, *et al*. Effects of ozone and fine particulate matter (PM(2.5)) on rat system inflammation and cardiac function. Toxicol Lett, 2013,217(1):23-33
43 Brook RD, Rajagopalan S. Particulate matter, air pollution, and blood pressure. J Am Soc Hypertens, 2009,3(5):332
44 Coogan PF, White LF, Jerrett M, *et al*. Air pollution and incidence of hypertension and diabetes mellitus in black women living in Los Angeles. Circulation, 2012,125(6):767-772
45 Tam WH, Sahota DS, Lau TK, *et al*. Seasonal variation in pre-eclamptic rate and its association with the ambient temperature and humidity in early pregnancy. Gynecol Obstet Invest, 2008,66(1):22-26
46 Phillips JK, Bernstein IM, Mongeon JA, *et al*. Seasonal variation in preeclampsia based on timing of conception. Obstet Gynecol, 2004,104(5 Pt 1):1015-1020
47 Weinberg CR, Shi M, Basso O, *et al*. Season of Conception, Smoking, and Preeclampsia in Norway. Environ Health Perspect, 2017,125(6):067022
48 Tepoel MR, Saftlas AF, Wallis AB. Association of seasonality with hypertension in pregnancy: a systematic review. J Reprod Immunol, 2011,89(2):140-152
49 Bodnar LM, Daftary A, Markovic N, *et al*. Seasonal variation in gestational blood pressure. Hypertens Pregnancy, 2006,25(3):271-283
50 Shaowei W, Furong D, Jing H, *et al*. Does ambient temperature interact with air pollution to alter blood pressure? A repeated-measure study in healthy adults. J Hypertens, 2015,33(12):2414-2421
51 Metoki H, Ohkubo T, Watanabe Y, *et al*. Seasonal trends of blood pressure during pregnancy in Japan: the babies and their parents' longitudinal observation in Suzuki Memorial Hospital in Intrauterine Period study. J Hypertens, 2008,26(12):2406-2413
52 Gordon CJ, Johnstone AF, Aydin C. Thermal stress and toxicity. Compreh Physiol, 2014,4(3):995
53 Leon LR. Thermoregulatory responses to environmental toxicants: the interaction of thermal stress and toxicant exposure. Toxicol Appl Pharmacol, 2008,233(1):146-161
54 Pereira G, Haggar F, Shand AW, *et al*. Association between pre-eclampsia and locally derived traffic-related air pollution: a retrospective cohort study. J Epidemiol Community Health, 2013,67(2):147-152
55 Isakov V, Johnson M, Touma J, *et al*. Development and Evaluation of Land-Use Regression Models Using Modeled Air Quality Concentrations. Nato Science for Peace & Security, 2011:717-722

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