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Combined effects of ambient temperature and ozone exposure before and during pregnancy on hypertensive disorders of pregnancy in 568 Chinese healthcare facilities

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ABSTRACT

Hypertensive disorders in pregnancy (HDP) are a major contributor of maternal and perinatal mortality and morbidity. Although ambient ozone (O_3) and temperature have been individually associated with increased HDP risk, their combined effects remain unclear. In this multicenter retrospective cohort study involving 173,644 women, we assessed the independent and interactive relationships of O_3 and temperature on HDP risk using logistic regression and distributed lag non-linear models (DLNM). Temperature was categorized by percentiles as extreme cold ($\leq 5^{th}$), moderate cold ($>5^{th}$ to $\leq 10^{th}$), moderate ($>10^{th}$ to $\leq 90^{th}$), moderate hot ($>90^{th}$ to $\leq 95^{th}$), and extreme hot ($>95^{th}$). For DLNM analyses, the 10^{th} and 90^{th} percentiles of temperature were used to represent low and high temperature, respectively. Compared with moderate temperatures, preconception exposure to extreme cold conditions (OR: 1.37, 95 % CI: 1.21–1.54) and moderate hot during the first 20 weeks of pregnancy (OR: 1.14, 95 % CI: 1.01–1.29) were associated with higher HDP risk. Each 10 $\mu g/m^3$ increase in O_3 concentration elevated HDP risk during the 13 weeks before pregnancy (OR: 1.10, 95 % CI: 1.08–1.12) and the first 20 weeks of pregnancy (OR: 1.04, 95 % CI: 1.01–1.07). Temperature-related HDP risk increased significantly at O_3 concentrations above 60 $\mu g/m^3$ and was markedly amplified beyond 110 $\mu g/m^3$, where extreme temperatures nearly doubled the risk (OR: 2.00, 95 % CI: 1.35–2.96). Critical susceptibility windows were identified at weeks 9–12 before pregnancy for O_3 exposure and gestational weeks 13–20 for high temperature. These findings provide novel evidence of pre-pregnancy O_3-sensitivity windows, stage-specific bidirectional temperature associations, and significant O_3–temperature interactions, underscoring the need for targeted environmental interventions during preconception and early pregnancy.

1. Introduction

Hypertensive disorders of pregnancy (HDP) are the most prevalent pregnancy complications worldwide and represent a substantial global public health concern. HDP encompasses a spectrum of conditions, including chronic hypertension, gestational hypertension, preeclampsia-eclampsia, and chronic hypertension with superimposed preeclampsia (Sinkey et al., 2020; Wu et al., 2023a). Globally, approximately 5 %–10 % of pregnancies are affected by HDP (Li et al., 2021a), with reported incidence rates in China ranging from 4.5 % to 10 % (Chen et al., 2025; Li et al., 2021b). HDP substantially increases maternal mortality and morbidity (Sinkey et al., 2020) and poses serious risks to fetal outcomes, including intrauterine growth restriction, preterm birth, low birth weight, and stillbirth (Nawsherwan et al., 2023; Fu et al., 2023). Moreover, women affected by HDP are at heightened long-term risks of persistent hypertension, cardiovascular disease, and

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renal dysfunction later in life (Kristensen et al., 2019; Oliver-Williams et al., 2022).

While established risk factors for HDP include advanced maternal age, obesity, multifetal gestation, and a family history of hypertension (Umesawa and Kobashi, 2017), mounting evidence has drawn attention to environmental exposures—particularly air pollution and temperature extremes—as potential contributors to HDP risk (Part et al., 2022; Hu et al., 2017). Among air pollutants, ozone (O_3), a secondary pollutant resulting from industrial activities and meteorological conditions, has emerged as one of the most concerning environmental pollutants worldwide, second only to particulate matter (Tang et al., 2021). Epidemiological studies have consistently linked O_3 exposure to respiratory and cardiovascular diseases, as well as adverse pregnancy outcomes (Zhang et al., 2024a; Xu et al., 2024). Additionally, pregnancy induces profound physiological changes—such as increased cardiac output, blood volume expansion, and altered respiratory patterns—that may heighten maternal vulnerability to environmental stressors (Hu et al., 2014). Although several studies have explored the relationship between O_3 exposure and HDP, findings remain inconsistent: some report an elevated HDP risk associated with first-trimester O_3 exposure (Cai et al., 2016; Pedersen et al., 2014), whereas others observe no significant association (Yan et al., 2022). These discrepancies may be attributable to differences in population characteristics, exposure assessment methodologies, and regional climatic conditions, highlighting the need for more systematic and region-specific investigations.

In parallel, ambient temperature has recently emerged as another significant environmental risk factor for HDP. Exposure to extreme cold and hot may elevate HDP risk by triggering sympathetic nervous system activation, oxidative stress, and subsequent exacerbation of maternal hypertension (Stewart et al., 2017; Bennett, 2010). With global climate change leading to increased frequency and intensity of extreme temperature events, understanding the temperature-related HDP risk has become increasingly urgent (Sun et al., 2023a). Furthermore, according to Rothman's pie model, an interaction between two risk factors may occur when their pathogenic pathways converge (Rothman, 1995), suggesting potential synergistic relationships between temperature and O_3 on HDP risk. Given the well-established environmental correlation between O_3 and ambient temperature, as well as their potential synergistic relationships on pregnancy outcomes (Chen et al., 2023a; Pan et al., 2023), it is plausible that concurrent exposure to these two factors could jointly amplify HDP risk. However, existing evidence remains fragmented, with most studies focusing on the independent effects of either temperature or O_3. Therefore, a notable research gap persists regarding the systematic evaluation of their joint impacts on HDP development, necessitating further comprehensive investigations.

To address these knowledge gaps, the present study aimed to systematically evaluate both the independent and synergistic associations of ambient O_3 and temperature exposure on HDP risk during specific windows before and during early pregnancy. In addition, we sought to identify critical periods of heightened susceptibility to these environmental exposures and characterize high-risk subpopulations, thereby providing robust scientific evidence to support targeted environmental interventions and public health strategies aimed at mitigating environmental impacts on maternal-fetal health.

2. Methods

2.1. Study population

This multicenter retrospective cohort study utilized medical records from 568 healthcare facilities across Sichuan Province, China, covering the period from April 2013 to December 2022. Eligible participants included pregnant women with singleton gestations receiving antenatal care between April 2013 and December 2018. We excluded participants meeting the following criteria: maternal age <18 years, gestational age >42 weeks, multiple pregnancies, absence of a valid residential address, residence outside Sichuan Province, and documented histories of infectious diseases or chronic non-communicable diseases (e.g., HIV, diabetes mellitus, chronic hypertension). After applying these criteria, 173,644 pregnant women were included in the final analysis.

2.2. Outcome definition

HDP were defined according to the International Society for the Study of Hypertension in Pregnancy guidelines (Wu et al., 2023b). Specifically, HDP was defined as new-onset hypertension after 20 weeks of gestation in women without preexisting chronic hypertension, characterized by systolic blood pressure $\geq$140 mmHg and/or diastolic blood pressure $\geq$90 mmHg. Blood pressure measurements and HDP diagnoses at various gestational stages were retrieved from standardized obstetric examination records in hospital electronic medical record systems. All clinical diagnoses were confirmed by board-certified obstetricians with extensive clinical experience.

2.3. Exposure assessment

2.3.1. Exposure time window

To account for the timing of HDP onset, which typically occurs after 20 weeks of gestation, exposure windows were defined based on the last menstrual period. The following exposure periods were evaluated: the 13 weeks preceding pregnancy (pre-pregnancy exposure) and the first 20 gestational weeks, further divided into three physiologically relevant phases: weeks 1–4 (embryo implantation and placental development), weeks 5–12 (vascularization and placentation), and weeks 13–20 (post-placentation) (Aplin et al., 2020). For each window, average exposure levels of ambient temperature and air pollutants were calculated.

2.3.2. Ambient temperature and O_3 exposure assessment

Daily ground-level maximum 8-h average O_3 concentrations, average ambient temperatures, and particulate matter ($PM_{2.5}$ and PM_{10}) at a 1 km $\times$ 1 km spatial resolution were obtained from the China High Air Pollutant (CHAP) dataset (Wang et al., 2024a; Wei et al., 2022; Yang et al., 2025). This dataset integrates ground-based monitoring, satellite remote sensing, atmospheric reanalysis, and artificial intelligence modeling to capture spatiotemporal variations in air pollution. Additionally, daily concentrations of sulfur dioxide (SO_2), nitrogen dioxide (NO_2), and carbon monoxide (CO) at a 10 km $\times$ 10 km resolution were also obtained from the CHAP dataset (2013–2019) for use in sensitivity analyses, and relative humidity data were extracted from the 1 km High-resolution Atmospheric Moisture Index Collection over China dataset (Zhang et al., 2024b). Exposure assignments for each participant were based on residential addresses, enabling spatially precise exposure estimates for each defined exposure window (Liu et al., 2024).

To reflect local acclimation patterns, ambient temperature was categorized into five groups based on percentile cut-offs specific to the study population (Yu et al., 2023): extreme cold ($\leq$5th percentile, $\leq$6.0 °C), moderate cold ($>5^{th}$ to $\leq10^{th}$ percentile, 6.0–6.9 °C), moderate ($>10^{th}$ to $\leq90^{th}$ percentile, 6.9–25.9 °C), moderate hot ($>90^{th}$ to $\leq95^{th}$ percentile, 25.9–27.1 °C), and extreme hot ($>95^{th}$ percentile, $>$27.1 °C).

2.4. Statistical analysis

We first summarized participant demographics and environmental exposures using descriptive statistics. Multivariable logistic regression models were then employed to evaluate the associations between HDP risk and exposures to ambient O_3, average temperature, and categorized extreme temperatures across predefined exposure windows (13-weeks preceding pregnancy and gestational weeks 1–4, 5–12, 13–20 and 1–20).

For categorized temperature exposures (extreme cold, moderate cold, moderate, moderate hot, extreme hot), moderate temperature

served as the reference group. Odds ratios (ORs) and 95 % confidence intervals (CIs) were calculated to quantify associations. All regression models were adjusted for the following potential confounders: maternal age (<25, 25–34, ≥35 years), pre-pregnancy body mass index (BMI: <18.5, 18.5–24.9, 25.0–29.9, ≥30 kg/m^2), maternal ethnicity (Han, others), educational level (primary or middle school, high school, Bachelor's degree and above, others), folic acid supplementation (none, initiated during pregnancy, initiated before pregnancy), season of conception (warm season: May–October; cold season: November–April), and relative humidity. O_3 models were additionally adjusted for temperature. Multicollinearity was evaluated using variance inflation factors (VIFs), with all covariates demonstrating acceptable collinearity (VIF <5).

To explore potential nonlinear exposure–response relationships between O_3, ambient temperature, and HDP risk, logistic regression models incorporated restricted cubic splines (RCS) with three knots placed at the 25th, 50th, and 75th percentiles of each exposure distribution.

To investigate time-resolved exposure-lag-response relationships, distributed lag non-linear models (DLNMs) were constructed to evaluate weekly associations of O_3 and ambient temperature with HDP risk. Exposure–lag–response relationships were estimated continuously from 13 weeks pre-pregnancy to gestational week 20 using natural cubic splines with three degrees of freedom for both exposure and lag dimensions (Wang et al., 2020, 2021). For DLNM interpretation, the 90th percentile of O_3 concentrations (134.1 μg/m^3) represented high O_3 exposure, whereas the 10th (6.9 °C) and 90th (25.9 °C) percentiles of ambient temperature represented low and high temperature exposures, respectively.

We further evaluated potential interactions between O_3 and temperature on HDP risk by introducing an interaction term in generalized linear models. O_3 was modeled linearly, and temperature was modeled nonlinearly using natural cubic splines (three degrees of freedom), with exposures considered over a short-term lag of 0–1 week (de Bont et al., 2025). This lag period was selected based on evidence from previous literature highlighting short-term lag effects of environmental exposures on health outcomes (Lin et al., 2019; Chen et al., 2023b).

Based on these modeling frameworks, we estimated HDP risk per 10 μg/m^3 increase in O_3 across temperature percentiles and examined how HDP risk associated with an increase in temperature (from the 50th to 90th percentile) varied by O_3 concentration (range: 40–160 μg/m^3; based on data distribution, Fig. S1). Wald tests evaluated the statistical significance of interaction terms (de Bont et al., 2025). Statistical significance defined as a two-sided p-value <0.05.

Subgroup analyses were conducted to evaluate whether maternal characteristics (age and pre-pregnancy BMI categories) modified associations between exposures (ambient temperature and O_3) and HDP risk.

Sensitivity analyses were performed to verify robustness. First, two-pollutant models were constructed by individually adjusting for $PM_{2.5}$, PM_{10}, SO_2, NO_2, and CO. Second, we further adjusted O_3 and temperature models for the year of conception, and re-examined temperature associations after removing relative humidity from the models. Third, alternative lag structures covering the entire exposure window (13 weeks pre-pregnancy through gestational week 20) were evaluated, recalculating effect estimates for the O_3–temperature interactions. Finally, we further explored interactions between low temperature and O_3 exposure on HDP risk across different lag periods.

Statistical analyses were performed using R software (version 4.4.2). Major packages included mgcv (version 1.8-1.9.1), dlnm (version 2.4.7), splines (version 4.4.2), and ggplot2 (version 3.5.1).

3. Results

3.1. Characteristics of study participants and exposure

The baseline characteristics of the 173,644 pregnant women included in the analysis are summarized in Table 1. The mean (SD) maternal age was 27.09 (4.86) years, and the mean (SD) maternal pre-pregnancy BMI was 22.18 (3.53) kg/m^2. Most participants were between 25 and 34 years old (60.1 %), had a normal pre-pregnancy BMI (69.0 %), took folic acid during pregnancy (65.8 %), and were of Han ethnicity (96.5 %). Descriptive statistics for ambient O_3 and temperature across different exposure windows are provided in Table S1. During the 13-week pre-pregnancy period, the mean O_3 exposure was 85.46 μg/m^3, with the average temperature was 16.69 °C. In the first 20 weeks of pregnancy, the mean O_3 exposure was 90.55 μg/m^3, with an average temperature of 17.44 °C. We observed negative correlations between exposures to O_3, temperature, and other air pollutants within the defined exposure windows, with Pearson correlation coefficients ranging from −0.36 to −0.74 for O_3, and from −0.26 to −0.84 for temperature (Table S2–S3).

3.2. Associations between O_3 and ambient temperature and risk of hypertensive disorders of pregnancy

Exposure to both O_3 and ambient temperature was significantly linked to HDP risk (Fig. 1). Each 10 μg/m^3 increase in O_3 concentration was associated with higher HDP risk during the preconception period (OR: 1.10, 95 % CI: 1.08–1.12) and the first 20 weeks of pregnancy (OR: 1.04, 95 % CI: 1.01–1.07). Ambient temperature during the preconception period was inversely associated with HDP risk (OR: 0.96, 95 % CI: 0.95–0.97), whereas elevated temperatures during the first 20 weeks of pregnancy were linked to increased risk (OR: 1.04, 95 % CI: 1.03–1.05). This positive association between higher temperatures and HDP risk persisted across gestational weeks 1–4, 5–12, and 13–20.

Analyses of extreme temperature exposures revealed consistent patterns (Fig. 2). Compared with moderate temperatures, exposure to extreme cold during the preconception period increased HDP risk (OR: 1.37, 95 % CI: 1.21–1.54). In contrast, during the first 20 weeks of pregnancy, extreme cold (OR: 0.69, 95 % CI: 0.59–0.80) and moderate cold (OR: 0.66, 95 % CI: 0.57–0.77) exposures were associated with reduced HDP risk, while moderate hot exposure elevated the risk (OR: 1.14, 95 % CI: 1.01–1.29); extreme hot exposure may have also increased the risk, but the association was not statistically significant (Fig. 2).

Table 1
Characteristics of study participants (n = 173,644).

Characteristics	HDP	Non HDP	Total
	n = 5023	n = 168,621	n = 173,644
Maternal age, years			
<25	1337 (26.6)	53908 (32.0)	55245 (31.8)
25-34	2885 (57.4)	101546 (60.2)	104431 (60.1)
≥35	801 (15.9)	13167 (7.8)	13968 (8.0)
Pre-pregnancy BMI, kg/m^2			
<18.5	346 (6.9)	19947 (11.8)	20293 (11.7)
18.5–24.9	2858 (56.9)	116941 (69.4)	119799 (69.0)
25.0–29.9	1371 (27.3)	27244 (16.2)	28615 (16.5)
≥30.0	448 (8.9)	4489 (2.7)	4937 (2.8)
Folic acid			
Not taken	522 (10.4)	15746 (9.3)	16268 (9.4)
During pregnancy	3388 (67.4)	110824 (65.7)	114212 (65.8)
Before pregnancy	1113 (22.2)	42051 (24.9)	43164 (24.9)
Race			
Han nationality	4874 (97.0)	162779 (96.5)	167653 (96.5)
Minority nationality	149 (3.0)	5842 (3.5)	5991 (3.5)
Education			
Junior or primary school	1473 (29.3)	46600 (27.6)	48073 (27.7)
High school	2280 (45.4)	76117 (45.1)	78397 (45.1)
Bachelor's degree and above	1241 (24.7)	45005 (26.7)	46246 (26.6)
Other	29 (0.6)	899 (0.5)	928 (0.5)
Season of conception			
Cold (Nov–Apr)	2730 (54.3)	92510 (54.9)	95240 (54.8)
Warm (Mar–Oct)	2293 (45.7)	76111 (45.1)	78404 (45.2)

Abbreviation: HDP, Hypertensive disorders of pregnancy; BMI, Body mass index.

Exposure	Window	OR (95% CI)	P
Ozone	P13	1.10 (1.08–1.12)	<0.001
	W1−4	1.08 (1.06–1.10)	<0.001
	W5−12	1.06 (1.05–1.08)	<0.001
	W13−20	0.97 (0.95–0.99)	0.012
	W1−20	1.04 (1.01–1.07)	0.014
Temperature	P13	0.96 (0.95–0.97)	<0.001
	W1−4	1.03 (1.02–1.03)	<0.001
	W5−12	1.03 (1.03–1.04)	<0.001
	W13−20	1.03 (1.03–1.04)	<0.001
	W1−20	1.04 (1.03–1.05)	<0.001

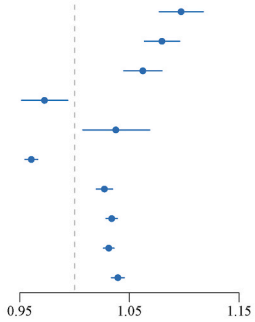

Fig. 1. Odds ratio (95 % CI) for HDP for associated with ozone and ambient temperature exposure during pre-pregnancy and pregnancy.
Note: ORs (95 % CIs) were calculated per 10-μg/m^3 increase in ozone concentration or 1 °C increment in ambient temperature across specified exposure windows. The models were adjusted for maternal age, pre-pregnancy body mass index, maternal educational level, maternal race, season of conception, folic acid supplementation, and relative humidity. Ozone models were additionally adjusted for temperature.Exposure windows were illustrated as follows: (1) P13: 13 weeks before pregnancy; (2) W1–4: Gestational weeks 1–4; (3) W5–12: Gestational weeks 5–12; (4) W13–20: Gestational weeks 13–20; (5) W1–20: Gestational weeks 1–20.

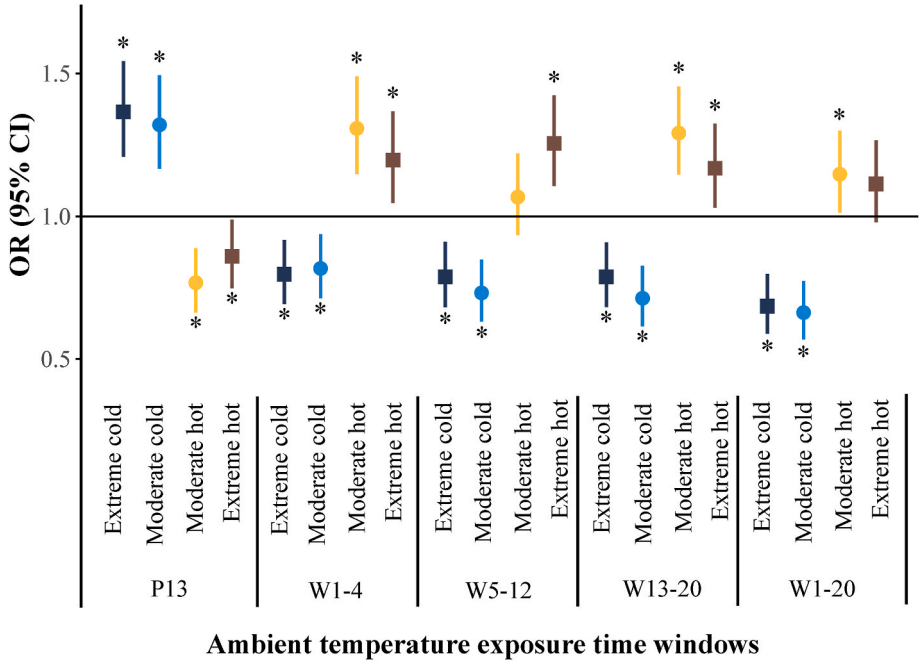

Fig. 2. Odds ratio (95 % CI) for HDP for associated with extreme temperatures exposure during pre-pregnancy and pregnancy.
Note: The models were adjusted for maternal age, pre-pregnancy body mass index, maternal educational level, maternal race, season of conception, folic acid supplementation, and relative humidity. Error bars correspond to 95 % confidence intervals, center for the error bars correspond to points estimate of ORs. Black stars denote $p < 0.05$. ORs and 95 % CIs for extreme cold, moderate cold, moderate hot, and extreme hot exposures, each compared with moderate temperature (reference category). Since moderate temperature was used as the reference group in all models, no ORs are displayed for this category. Exposure windows were illustrated as follows: (1) P13: 13 weeks before pregnancy; (2) W1–4: Gestational weeks 1–4; (3) W5–12: Gestational weeks 5–12; (4) W13–20: Gestational weeks 13–20; (5) W1–20: Gestational weeks 1–20.

3.3. Exposure-response relationship between O_3 and ambient temperature and hypertensive disorders of pregnancy

Higher O_3 concentrations were associated with increased HDP risk during both the preconception period and the first 20 weeks of pregnancy, with particularly strong associations observed during three critical windows: the 13-week pre-pregnancy period, gestational weeks 1–4, and gestational weeks 5–12 (Fig. 3A). The DLNMs further revealed that O_3 exposure from 12 weeks before pregnancy through 17 weeks gestation was significantly associated with HDP risk, with the strongest associations occurring at 9–12 weeks before pregnancy (Fig. S2).

For ambient temperature, HDP risk decreased with rising temperatures during the 13-week preconception period; however, this relationship reversed during pregnancy (Fig. 3B). Exposure to low temperatures was associated with a progressively higher HDP risk during the 13th week before pregnancy, weeks 5–9, and gestational weeks 13–20, with the most pronounced relationships occurring at the 13th preconception week (Fig. S3A). Notably, during the first eight weeks of pregnancy, low temperature exposure appeared protective. In contrast, ORs for high temperatures exposure increased steadily throughout pregnancy, peaking during gestational weeks 13–20 (Fig. S3B), although heat-related associations were generally weaker than those observed for cold exposure (Fig. S3).

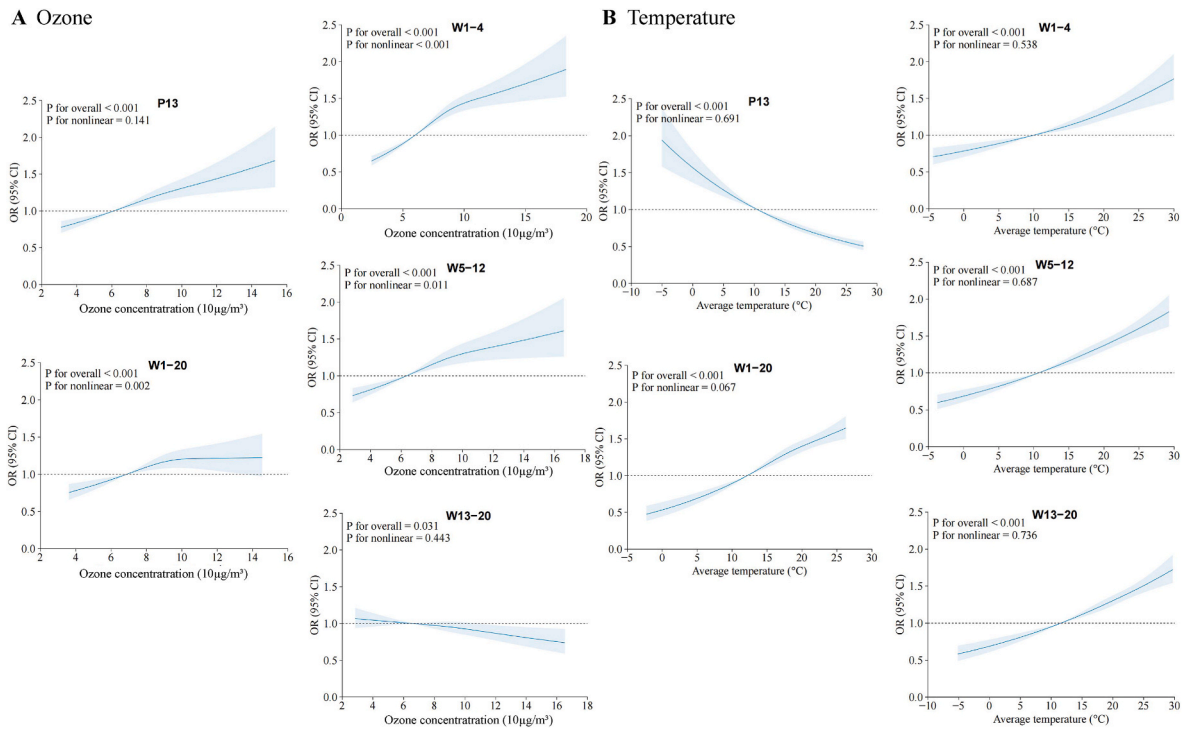

Fig. 3. Curves of the associations between (A) ozone, (B) temperature and HDP during pre-pregnancy and pregnancy.
Note: Solid blue lines correspond to points estimate of ORs of HDP; light blue shades correspond to 95 % confidence intervals. The models were adjusted for maternal age, pre-pregnancy body mass index, maternal educational level, maternal race, season of conception, folic acid and relative humidity. Ozone models were additionally adjusted for temperature. Exposure windows were illustrated as follows: (1) P13: 13 weeks before pregnancy; (2) W1–4: Gestational weeks 1–4; (3) W5–12: Gestational weeks 5–12; (4) W13–20: Gestational weeks 13–20; (5) W1–20: Gestational weeks 1–20. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

3.4. Interaction of O_3 and ambient temperature on hypertensive disorders of pregnancy

A significant interaction between ambient O_3 and temperature exposures was observed in relation to HDP risk ($p < 0.001$, Fig. 4). The modifying effect of ambient temperature on the O_3–HDP association exhibited a nonlinear pattern (Fig. 4A). The ORs for each 10 μg/m^3 increase in O_3 remained consistently above 1.015 across the entire temperature distribution, exhibiting a slight reduction around the 50th percentile and increasing slightly but statistically significantly at both lower and higher temperature ranges (p for interaction <0.001). Further analysis revealed that the risk associated with increasing temperature (from the 50th to the 90th percentile) rose progressively as O_3 concentrations increased (Fig. 4B). This trend indicates a synergistic interaction, with the combined effect of temperature and O_3 becoming particularly prominent when O_3 levels exceeded 110 μg/m^3.

3.5. Subgroup analysis

During the preconception period, the strongest associations between O_3 exposure and HDP risk were observed among women aged 25–34 years (OR: 1.10, 95 % CI: 1.08–1.13) and those with underweight (OR: 1.15, 95 % CI: 1.07–1.24) (Table S4). During the first 20 weeks of pregnancy, higher sensitivity to O_3 exposure was noted among women aged ≥35 years (OR: 1.12, 95 % CI: 1.04–1.20) and among those who were overweight (OR: 1.12, 95 % CI: 1.06–1.19) or obese (OR: 1.11, 95 % CI: 1.01–1.22) (Table S5). Regarding temperature exposures, increased vulnerability to non-optimal temperatures was evident among

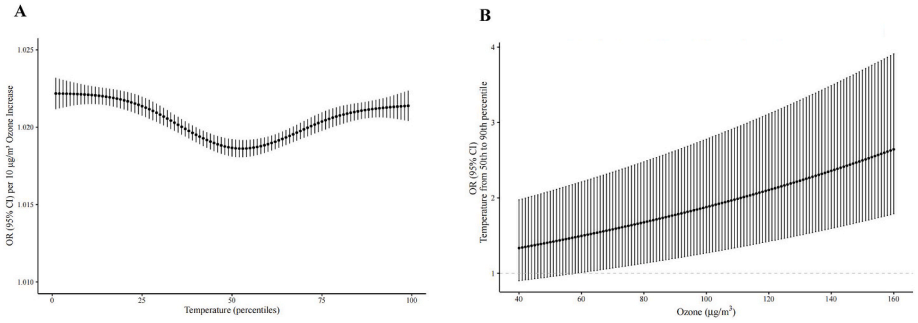

Fig. 4. Odds ratio (95 % CI) of HDP for interactions between ozone and ambient temperature exposure.
Note: Fig. 4A: Association between O_3 (per 10 μg/m^3) and HDP risk across temperature percentiles. Fig. 4B: Association between air temperature (an increment from 50th to the 90th percentile distribution) and HDP risk at different O_3 levels. Different y-axis ranges were used across panels to optimize visual clarity, given the subtle but statistically significant trends in Panel A and distinct modeling strategies across panels.The models were adjusted for maternal age, pre-pregnancy body mass index, maternal educational level, maternal race, season of conception, folic acid supplementation, and relative humidity. *p for interaction* <0.001.

younger women (<25 years) and those with underweight or overweight BMI (Table S4–5). Particularly, underweight women exhibited the greatest susceptibility, with ORs of 2.31 (95 % CI: 1.60–3.35) during the preconception period and 1.50 (95 % CI: 1.01–2.21) during pregnancy. All subgroup-specific ORs were estimated independently within each subgroup, as detailed in Table S4 and S5.

3.6. Sensitivity analysis

Sensitivity analyses confirmed the robustness of the main findings. Adjustment for individual air pollutants (SO_2, CO, NO_2, $PM_{2.5}$, and PM_{10}) in two-pollutant models did not materially alter the associations between O_3, temperature, and HDP risk (Fig. S4–5). After additionally adjusting the O_3 and temperature models for the year of conception, and removing relative humidity from the temperature models, our findings remained robust (Fig. S6–S9). Moreover, effect estimates for the O_3–temperature interaction remained consistent when applying alternative lag structures covering the entire exposure window from 13 weeks before conception to 20 gestational weeks, with slightly stronger associations observed under lower temperature conditions (Fig. S10A). Additional analyses further exploring the risks associated with low temperature and O_3–HDP indicated that HDP risk related to a temperature decrease from the 50^{th} to the 10^{th} percentile also increased significantly with rising O_3 concentrations, consistent with the pattern observed under rising temperatures (Fig. S11).

4. Discussion

To the best of our knowledge, this study represents the first comprehensive investigation of both the independent and joint associations of O_3 and ambient temperature exposures during the preconception and early pregnancy periods on the risk of HDP. In this large multicenter retrospective cohort study conducted in Sichuan Province, China, involving 173,644 pregnant women, we provide robust evidence that higher O_3 exposure, preconception cold exposure, and early gestational hot exposure were each independently associated with an increased risk of HDP. Furthermore, we identified significant interactions between O_3 and ambient temperature, suggesting that non-optimal temperature conditions may amplify the adverse effects of O_3 on HDP, and conversely, higher O_3 concentrations may also enhance the adverse effects of temperature extremes.

We observed that O_3 exposure during both the preconception period and the first half of pregnancy was associated with an increased risk of HDP, consistent with several previous studies (Hu et al., 2017; Michikawa et al., 2015; Cheng et al., 2023). For example, Michikawa et al. reported a significant association between early-pregnancy O_3 exposure and HDP among Japanese women (OR: 1.20, 95 % CI: 1.01–1.42) (Michikawa et al., 2015). Likewise, Cheng et al. found that each 10 $\mu g/m^3$ increase in early gestational O_3 was associated with a higher risk of gestational hypertension in Shanghai (RR: 1.28, 95 % CI: 1.04–1.57) (Cheng et al., 2023). Our findings further extend the current evidence by highlighting a more pronounced association during the preconception period—a critical window that has rarely been evaluated in prior research. Nonetheless, some studies conducted in China have reported no significant associations between O_3 exposure during early or mid-pregnancy and HDP (Zhang et al., 2024c; Jiang et al., 2023). Similarly, a study in the United States identified conception months 2–4 as the critical exposure window for O_3-associated HDP risk (Yuan et al., 2023). These discrepancies may be attributable to differences in population characteristics, ambient O_3 levels, exposure assessment methodologies, and regional climatic conditions.

The biological plausibility of the observed associations between O_3 and HDP is supported by multiple mechanistic pathways. O_3 inhalation induces systemic oxidative stress and inflammatory responses, which are well-established contributors to endothelial dysfunction and hypertensive pathogenesis (Sanidas et al., 2017). These processes may impair endothelial function, disrupt autonomic nervous regulation, and promote vasoconstriction—processes that are closely linked to the pathophysiology of HDP (Yuan et al., 2023). Notably, early pregnancy marks a critical period for trophoblast invasion and the establishment of maternal-fetal circulation (Abumaree et al., 2014), during which elevated exposure to air pollutants may hinder placental development and contribute to the onset of HDP (Ghazi et al., 2021). Experimental and animal studies further support these findings, demonstrating that O_3 can elevate maternal blood pressure by amplifying sympathetic tone and reducing vascular elasticity (Hunter et al., 2024), particularly during early gestation—a key period for placental vascular remodeling and cardiovascular adaptation (Aplin et al., 2020).

We observed a temporally distinct pattern in the association between temperature and HDP. Specifically, cold exposure prior to pregnancy and hot exposure during early gestation were associated with increased HDP risk. This bidirectional effect aligns with findings from a large Chinese cohort by Xiong et al., which reported increased HDP risk with preconception cold and early-pregnancy heat exposure (Xiong et al., 2020). A meta-analysis also suggested that hot and cold exposures exert time-specific effects on HDP risk, with low temperatures being harmful before conception and protective during early gestation (Mao et al., 2023). However, not all studies have reported such associations. Evidence from a United States cohort found no significant relationship between ambient temperature and HDP across pregnancy stages (Howe et al., 2024). Similarly, a study based on a Chinese birth cohort reported that cold exposure during mid-to-late pregnancy was positively associated with elevated maternal blood pressure and a higher prevalence of HDP (Sun et al., 2023b). These inconsistencies may be attributed to regional differences in temperature ranges, exposure assessment methods, study populations, climatic zones, and analytical approaches (Part et al., 2022).

We further observed that gestational weeks 13–20 may represent a period of increased sensitivity to cold exposure (Fig. 2, Fig. S3). This finding highlights the potential importance of exposure timing and accumulation patterns in shaping temperature-related health risks. While early pregnancy cold exposure may transiently support vascular adaptation, prolonged cold conditions beyond week 13 could exceed maternal compensatory capacity, potentially contributing to HDP development. Several plausible mechanisms may explain this pattern, such as reduced placental perfusion, suboptimal uterine artery remodeling, and heightened maternal pressor responses to sustained cold (Aplin et al., 2020; Wang et al., 2020; James et al., 2010). Moreover, in the study region (Sichuan Province, China), centralized heating is generally unavailable, and indoor heating remains limited, which may increase vulnerability to cold exposure. Although air conditioning use during hot seasons has become more common, coverage varies across settings, especially in rural areas. These contextual factors could partially influence the magnitude and direction of temperature-related associations observed in this study.

Previous studies suggest that cold exposure may increase cardiovascular burden through activation of the sympathetic nervous system and the renin–angiotensin system, subsequently increasing peripheral vascular resistance and blood pressure (De Vita et al., 2024). Cold-induced systemic inflammation and endothelial dysfunction may further impair placental development and increase HDP risk (Sun et al., 2023a). Conversely, while heat exposure is often associated with vasodilation and reduced peripheral resistance, during pregnancy, the capacity to dissipate heat is compromised. Elevated metabolic demand and impaired thermoregulation in early gestation may exacerbate maternal heat stress, triggering compensatory cardiovascular responses and promoting HDP development (Xiong et al., 2020). Animal studies support this hypothesis, showing that heat exposure during pregnancy reduces placental size and transport capacity, potentially disrupting maternal–fetal hemodynamics (Qiu et al., 2020).

Importantly, we found that O_3 and ambient temperature exerted synergistic relationships on HDP risk. The magnitude of O_3-related HDP

risk increased at both low and high temperature percentiles, with the stronger interactions occurring at O_3 concentrations exceeding 110 μg/m^3. These results suggest that thermal extremes may amplify the cardiovascular toxicity of O_3—a finding with serious implications in the context of climate change, where concurrent exposure to high O_3 and temperature extremes is increasingly common (Wang et al., 2024b). Despite its importance, limited research has focused on temperature–O_3 interactions in relation to HDP, with most studies emphasizing heat-related risks, while evidence on cold exposure remains scarce. One Chinese cohort reported significant O_3–temperature interactions affecting adverse birth outcomes (Chen et al., 2023c), while another found that cold exposure amplified PM_1-related HDP risk (Sun et al., 2023c). Synergism between temperature and O_3 has been more extensively documented for cardiovascular mortality, with meta-analyses and cohort studies demonstrating consistent interactions (Kazi et al., 2024; Xu et al., 2024).

The interaction between O_3 and ambient temperature may influence HDP development via shared mechanisms, including oxidative stress, vasoconstriction, and endocrine dysregulation (Wang et al., 2020; Tomimatsu et al., 2019). Our percentile-based analysis suggests that ambient temperature influences HDP risk via two pathways: first, through direct physiological impacts (e.g., sympathetic activation, endothelial dysfunction); and second, by modifying the effects of O_3. Experimental research supports this dual mechanism: animal and toxicological studies have shown that co-exposure to heat and O_3 induces stronger oxidative stress and impairs cardiac autonomic function compared to either exposure alone (Sanidas et al., 2017; Liang et al., 2020). In addition, biological plausibility supports a synergistic effect between cold and O_3 exposure. Extremely cold temperatures may alter pollutant concentrations and their chemical mixtures in ambient air (Wine et al., 2022). Environmental physiology studies suggest that marked changes in ambient temperature can modify individual physiological responses to toxicants (Gordon, 2003). Epidemiological evidence further indicates that prolonged cold exposure may elevate blood viscosity and inflammatory markers (e.g., C-reactive protein), promoting coronary thrombosis and increasing cardiovascular mortality risk (Cheng and Kan, 2012; Halonen et al., 2010). Furthermore, toxicological studies have reported enhanced cardiovascular responses to O_3 exposure under colder conditions, such as reductions in core body temperature and heart rate (Watkinson et al., 2003). Thus, extreme temperatures may plausibly amplify the cardiovascular impacts of O_3 exposure, contributing to elevated HDP risk through similar pathophysiological pathways, including impaired placental perfusion and vascular instability.

This study has several notable strengths. First, the large-scale, multicenter retrospective cohort design (n = 173,644) provides robust evidence regarding the associations between ambient temperature, O_3 exposure, and HDP risk. Second, to our knowledge, this is the first comprehensive investigation of joint associations of preconception and prenatal O_3–temperature effects on HDP. Third, diverging from conventional trimester-based approaches, we adopted physiologically informed exposure assessments specifically aligned with critical phases of placental vascular development and maternal hemodynamic adaptation. Moreover, the availability of weekly-resolution exposure data enabled precise identification of vulnerable windows.

Several limitations should be acknowledged. First, although we utilized high-resolution exposure estimates, the absence of direct personal exposure measurements or residential mobility information may introduce some degree of exposure misclassification. However, this potential bias is likely minimal, given the relatively low rates of residential mobility during pregnancy (Warren et al., 2017). Second, although we adjusted for multiple established confounders, residual confounding from unmeasured factors (e.g., individual socioeconomic status, physical activity patterns, traffic noise exposure, smoking status and parity) cannot be entirely ruled out. Third, antenatal records lacked information on prior HDP diagnoses, limiting our ability to exclude women with previous HDP; nonetheless, given the generally low prevalence of HDP and our large sample size, this limitation may minimally affect observed associations. Finally, the generalizability of our findings may be limited by the regional nature of the study population (Sichuan Province, China), and caution is warranted when extrapolating these results to other settings.

5. Conclusion

This study identified significant independent and synergistic associations of ambient temperature and O_3 exposure on the risk of HDP during both the preconception and early gestational periods. Our findings underscore pregnancy as a critical window of environmental vulnerability and highlight the compounded risks posed by concurrent climatic and pollution stressors. In light of the escalating impacts of climate change and persistent air pollution, further research is needed to replicate and extend these findings across diverse populations and settings, with the aim of informing effective prevention strategies and protecting maternal-fetal health.

CRediT authorship contribution statement

Ning Ma: Writing – original draft, Visualization, Software, Methodology, Investigation, Formal analysis. **Jie Yin:** Writing – review & editing. **Yangchang Zhang:** Writing – review & editing, Methodology. **Wangnan Cao:** Writing – review & editing. **Chunrong Li:** Writing – review & editing, Data curation. **Shengzhi Sun:** Writing – review & editing, Supervision, Conceptualization.

Declaration of generative AI and AI-assisted technologies in the writing process

None

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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.envres.2025.122668.

Data availability

The authors do not have permission to share data.

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