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Evidence of interactive effects of late-pregnancy exposure to air pollution and extreme temperature on preterm birth in China: a nationwide study

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Keywords: preterm birth, birth outcomes, air pollution, temperature extremes, threshold effect

Supplementary material for this article is available online

Abstract

Perinatal exposure to heat and air pollution has been shown to affect the risk of preterm birth (PTB). However, limited evidence exists regarding their joint effects, particularly in heavily polluted regions like China. This study utilized data from the ongoing China Birth Cohort Study, including 103 040 birth records up to December 2020, and hourly measurements of air pollution ($PM_{2.5}$, NO_2, and O_3) and temperature. We assessed the nonlinear associations between air pollution and temperature extereme exposures and PTB by employing generalized additive models with restricted cubic slines. Air pollution and temperature thresholds (corresponding to minimum PTB risks) were determined by the lowest Akaike Information Criterion. We found that maternal exposures to $PM_{2.5}$, NO_2, O_3, and both low and high temperature during the third trimester of pregnancy were independently associated with increased risk of PTB. The adjusted risk ratios for PTB of $PM_{2.5}$, O_3, NO_2, and temperature at the 95th percentile against thresholds were 1.32 (95% CI: 1.23, 1.42), 1.33 (95% CI: 1.18, 1.50), 1.44 (95% CI: 1.33, 1.56) and 1.70 (95% CI: 1.56, 1.85), respectively. Positive additive interactions [relative excess risk due to interaction (RERI) > 0] of $PM_{2.5}$–high temperature (HT), O_3–HT, O_3–low temperature (LT) are identified, but the interactive effects of $PM_{2.5}$ and LT were negative (RERI < 0). These observed independent effects of air pollution and temperature, along with their potential joint effects, have important implications for future studies and the development of public health policies aimed at improving perinatal health outcomes.

Abbreviations

ADH	Antidiuretic hormone
AIC	Akaike Information Criterion
API	Application programming interface
BMI	Body mass index
CI	Confidence interval
GAM	Generalized additive model
HIV	Human immunodeficiency virus
NO_2	Nitrogen dioxide
OT	Oxytocin
O_3	Ozone
$PM_{2.5}$	Particulate matter $\leqslant$2.5 μm in diameter
PTB	Preterm births
RCS	Restricted cubic spline
RR	Risk ratio
SDG	Sustainable Development Goal
SES	Socioeconomic status.

1. Introduction

PTBs, defined as birth before 37 completed gestational weeks [1], accounts for 75% of perinatal mortality and more than half the long-term morbidity in both developed and developing countries [1, 2]. China has the second highest number of PTBs in the world (>1 million per year), increasing by 1.1% per year [3]. Better understanding of risk factors and implementation of preventive interventions to reduce PTB and associated adverse outcomes play a critical role in both achieving the health aspects of the SDGs and alleviate disease burden [4].

Previous studies have shown that perinatal exposure to environmental factors, such as heat stress and air pollution, can affect risk of PTB [5–7]. These associations are biologically plausible as PTB has been suggested to be a syndrome initiated by multiple mechanisms. For example, particulate matter $\leqslant$2.5 μm in diameter ($PM_{2.5}$), through the maternal circulation, could trigger systemic inflammation and oxidative stress, or induce alterations of maternal cardiac, pulmonary, and autonomic nervous system functions [8, 9]. As a result, fetal-maternal circulation can be affected and fetus growth interrupted [10], leading to PTB. Exposure to heat during pregnancy can promote secretion of ADH and OT and trigger contractions and PTB [11].

Under a warming climate, the intensity, frequency, and duration of heatwave will enhance over many regions, and this trend is anticipated to persist in the coming decades [12]. Global climate change is also likely to exacerbate air pollution and thus poses greater threats to human health, referred to as 'climate penalty' [13]. It was also projected that more regions, especially highly polluted Asia, would be exposed to prolonged joint heatwave and high aerosol related extremes [14, 15].

A few studies [16–18] have emphasized that exposure to joint occurrences of weather and air pollution extremes could exert larger health effects than that associated with each of the individual factors. These studies have focused mainly on mortality, with very few studies exploring the interaction between temperature and air pollution on PTB [19, 20]. However, these studies were limited to a local or regional scale, and where air pollution is less serious (i.e., Guangdong province in China and California in the US). In the context of both wider ranges of exposure and geographical regions, the effect of air pollution and temperature on PTB remains unexplored.

Given the wide range of exposure to both air pollution and temperature across China, the associated effects on PTB could vary across the country. Here we provide a comprehensive analysis, with a focus on investigating the independent and potential interactive effects of exposure to temperature and multiple air pollutants on PTB using data from a nationwide birth cohort study in China.

2. Materials and methods

2.1. Study population and design

The study population consisted of participants from the China Birth Cohort Study, which is a national-based, prospective longitudinal mega-cohort study aimed at investigating risk factors for birth defects and developing strategies for their reduction. To be eligible for participation, pregnant women had to meet the following criteria: (1) Chinese nationality; (2) gestational age between 6 and 13 complete weeks at recruitment, including both naturally conceived pregnancies and those conceived using assisted reproductive technologies; (3) intention to attend routine antenatal examinations and deliver at the study site, with plans to continue residing locally for at least one year; (4) absence of notifiable infectious diseases such as hepatitis B, syphilis, and HIV; and (5) ability to comprehend the study and provide informed, written consent. Participants had the option to withdraw from the study at any stage. The recruitment process was conducted at 38 research sites located in 17 provinces, cities, autonomous regions, and municipalities, covering a wide geographical representation across China. The detailed information has been published elsewhere [21]. For this analysis, we utilized the cohort dataset that was updated as of December 2020. Detailed information on recruitment and data collection are presented in figure 1. The study was conducted in accordance with the Declaration of Helsinki and in accordance with local statutory requirements. The cohort study protocol was approved by the Ethics Committee of Beijing Obstetrics and Gynecology Hospital, Capital Medical University (Approval No.: 2018-KY-003-02).

2.2. PTB outcomes, air pollutants and ambient temperature

Gestational age was measured in days, based on the date of the last menstrual period in combination with confirmatory ultrasound examinations. PTB was defined as delivery prior to 37 completed weeks of gestation [1]. We also further defined three trimesters of pregnancy based on the complete weeks of gestation (1st trimester, ~13 complete weeks; 2nd trimester, 14–27 complete weeks and 3rd trimester, 28 complete weeks to birth) [22].

Hourly data on air pollutants, namely $PM_{2.5}$, NO_2, and O_3, were obtained from the China National Environmental Monitoring Center (CNEMC) network. To fully cover our study period, we used hourly data from 2017 to 2020. Hourly O_3 were further calculated as daily maximum 8 h average (MDA8) O_3. We used hourly ground-level temperature from the ERA5-land reanalysis dataset from the European Centre for Medium-Range Weather Forecasts at $0.1° \times 0.1°$ grids [23]. We also conducted validation analyses with ground observations to show the accuracy of the ERA5 dataset (supplementary files, figures S1–S3). We matched each participant's residential and work address with concentrations of air pollutants from the closest monitoring site and with temperature from the nearest grid and used time-weighted exposure based on working time patterns reported in the questionnaire. Each participant' trimester-specific average exposures (mean values) to air pollution and temperature were further calculated according to the trimester timeframe above.

2.3. Statistical analyses

To test whether the associations of daily air pollutants and temperature levels (continuous variables) on PTB were linear or nonlinear, as well as for potential threshold effects (if any), a RCS function was applied to each exposure variable in the GAMs, in line with previous studies [24–26]. GAM is a flexible regression modeling approach that allows for non-linear relationships between the predictor variables and the outcome.

In this study, the general formula of GAM with adjustment for covariates can be expressed as: $\mathrm{logit}(p) = \beta_0 + S_i(x) + \beta_1 C_1 + \beta_2 C_2 + \cdots + \beta_m C_m + \delta + \varepsilon$, where logit($p$) is the log-odds link function to the binary outcome Y($Y = 1$, if PTB or $\mathrm{Y} = 0$, if term birth), β_0 is the intercept term, $\mathrm{S_i}$ is the non-linear spline function, β_1, β_2,..., β_m are the regression coefficients associated with the covariates C_1, C_2,..., C_m, respectively, δ represents the random effect term and ε represents the error term, accounting for unexplained variability in the outcome variable.

The RCS function, with three knots was set at the 10th, 50th, 90th percentile. The selection of these knots was based on previous literature, and exploratory analyses of the data. By using these knot locations, we aimed to ensures that the RCS function is able to capture non-linear patterns that may exist across the entire exposure distribution. Details about the RCS function are also presented in the Supplementary Methods.

We followed the method used in previous studies [24–26] to determine the threshold value of each exposure variable. In brief, we first visually estimated preliminary intervals of possible thresholds. Subsequently, we iteratively fitted and obtained the effect estimates and AIC of the model in each iteration, by 0.1-unit increments in exposure variable within the preliminary intervals. The concentrations of air pollutants and temperature values corresponding to the lowest AIC values were chosen as the thresholds (minimum PTB concentrations of air pollutants/temperature. We calculated and reported the RRs and 95% CIs of PTB at 75th, 80th, 85th, 90th and 95th percentiles of exposure against the threshold concentration.

To investigate the interactive effects of air pollution and temperature, we calculated the relative excess risk due to interaction (RERI) [27], with an RERI > 0 indicating the combined effects were greater than that of each exposure alone (i.e., additive interaction), and an RERI < 0 indicating negative additive joint effects.

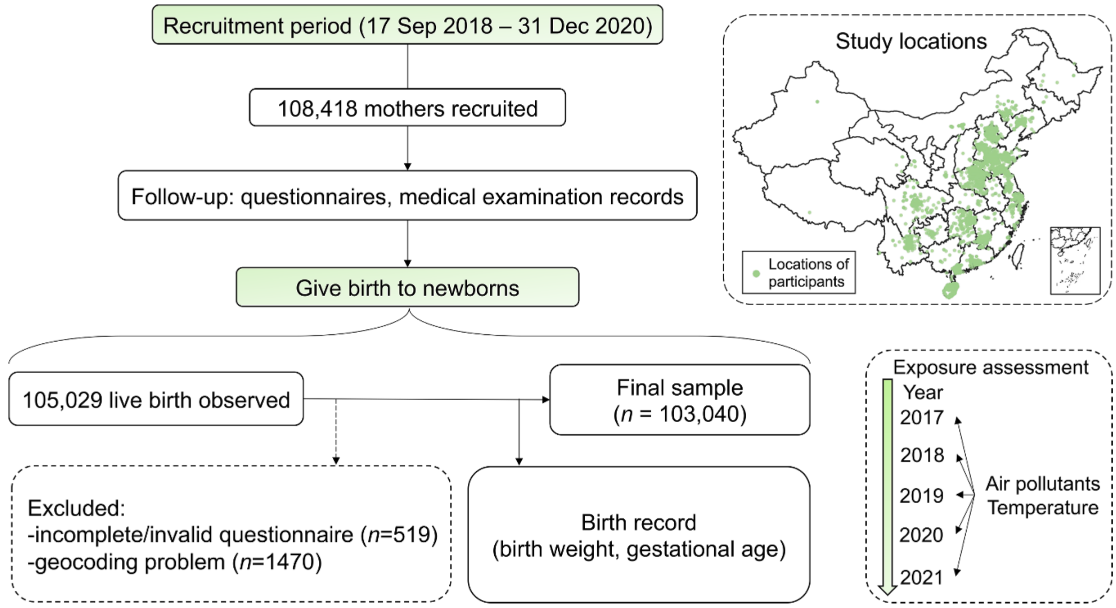

Figure 1. Flow chart of participant recruitment in the China Birth Cohort Study.

Attributable proportion (AP) of additive effects to the total observed effects were calculated by RERI divided by total effects, with 0 indicating the absence of interactions. To calculate RERI and AP, we classified the air pollutant variables into binary variables using the threshold value as the cut-off point, and we used lower than threshold value as the reference group. In light by other studies that showed both low and high temperature (HT) extremes may be associated with elevated risks of PTB [5, 28], we used tertiles to classify temperature into a ternary variable (i.e., low, medium, and high group based on tertiles), with medium group as the reference, in which two dummy variables were created, namely variable low temperature (LT) = 1, if temperature falls in the first tertiles and LT = 0, if temperature falls in the second tertiles (representing medium level of temperature); and HT = 1, if temperature falls in the third tertiles and LT = 0, if temperature falls in the second tertiles. RERI can be calculated by creating an instrumental variable that corresponds to the combinations of the abovementioned binary/ternary variables. The RERI and 95% CI calculation was done by the R package 'interactionR' [29].

For all regression models, we considered several confounding factors based on the available literature [5, 6, 24, 28, 30, 31], and formed a directed acyclic graph (DAG) for the variables by using DAGitty [32]. The covariates included maternal age, ethnicity, education level, income level, pre-pregnancy BMI, sugar and alcohol consumption, noise, sex of newborn and environmental tobacco exposure status (supplementary figure S4). To adjust the models with a minimum yet sufficient set of covariates, the selection of covariates was based on the DAG diagram generated using DAGitty and supplemented by previous studies. The analyses were adjusted for sex of newborn, maternal age, ethnicity, education, income, environmental tobacco exposure, use of air purifier, proximity to main roads and noise disturbance.

To test the robustness of our results, two-pollutant models were additionally fitted to evaluate the potential confounding effects of the co-linearity among air pollutants and temperature. To test whether the effects were biased by the difference in pollutant levels in north/south China, we replicated our main analyses using data from north or south China, separately. All statistical analyses were performed using R 4.1.1 and the significance level was at two-tailed probability <0.05.

3. Results and discussion

3.1. Characteristics of participants and exposure to air pollutants and ambient temperature

Table 1 summarizes the maternal covariates, including birth outcomes and environmental exposures, stratified by PTB. The average gestational age at delivery was 274.6 d (39.2 weeks), with 6.2% ($n = 6388$) of newborns being born preterm. Compared with term birth, mothers who delivered preterm were more likely to be slightly older ($P < 0.001$), with higher pre-pregnancy BMI levels ($P < 0.001$), and of lower socioeconomic status (SES), such as income ($P < 0.001$) and education ($P < 0.001$). No significant differences were observed in ethnicity ($P = 0.16$), or self-reported proximity to main road ($P = 0.764$) or self-reported noise disturbance ($P = 0.966$).

During the study period, the participants' average exposure to $PM_{2.5}$, O_3, and NO_2 in third trimester

Table 1. Characteristics of participants in the study.

Variable	Mean ± SD, *n* (%) Total (*n* = 103 040)	Term birth (*n* = 96 652)	Preterm birth (*n* = 6388)	P[a]
Mothers				
Age (years)	30.7 ± 5.0	30.7 ± 5.0	31.2 ± 4.9	<0.001
Pre-pregnancy BMI (kg m^{-2})	21.8 ± 3.6	21.8 ± 3.6	22.1 ± 3.7	<0.001
Gestational age (days)	274.6 ± 11.8	276.6 ± 7.9	243.7 ± 16.5	<0.001
Ethnicity				0.16
Han	85 943 (83.4%)	80 574 (83.4%)	5369 (84.0%)	
Others	17 097 (16.6%)	16 078 (16.6%)	1019 (16.0%)	
Education				<0.001
Middle High school or lower	56 125 (54.5%)	52 416 (54.2%)	3709 (58.1%)	
Higher education	46 915 (45.5%)	44 236 (45.8%)	2679 (41.9%)	
Annual family income (CNY)				<0.001
⩽100 000	31 415 (30.5%)	29 275 (30.3%)	2140 (33.5%)	
100 000–400 000	61 352 (59.5%)	57 673 (59.7%)	3679 (57.6%)	
⩾400 000	10 273 (10.0%)	9704 (10.0%)	569 (8.9%)	
Environmental tobacco exposure	41 270 (40.1%)	38 632 (40.0%)	2638 (41.3%)	0.037
Working time (hours/week)	39.9 ± 10.9	39.9 ± 11.0	39.6 ± 10.6	0.037
Sex of newborn (boys)	53 650 (52.1%)	50 085 (51.8%)	3565 (55.8%)	<0.001
Environmental factors				
Use of air purifier (yes)	23 132 (22.4%)	21 821 (22.6%)	1311 (20.5%)	<0.001
Close to main road (yes)	32 685 (31.7%)	30 670 (31.7%)	2015 (31.5%)	0.764
Noise disturbance (yes)	5924 (5.7%)	5558 (5.8%)	366 (5.7%)	0.966
$PM_{2.5}$ (μg m^{-3})[b]	37.7 ± 17.9	37.8 ± 17.7	36.2 ± 20.6	<0.001
MDA8 O_3 (μg m^{-3})[b]	96.1 ± 37.0	96.1 ± 37.0	95.5 ± 38.5	0.242
NO_2 (μg m^{-3})[b]	31.6 ± 11.8	31.7 ± 11.6	30.2 ± 13.8	<0.001
Temperature (°C)[b]	16.4 ± 9.4	16.4 ± 9.4	16.7 ± 9.7	0.001

[a] *P*-values were derived using two-sample t-tests for continuous variables and chi-squared test for categorical variables.
[b] Exposure level in the third trimester.
Abbreviations: BMI, body mass index; CNY, Chinese yuan; MDA8 O_3, daily maximum 8-hour average ozone; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter ⩽2.5 μm; SD, standard deviation.

was 37.7 (standard deviation, SD:17.9) μg m^{-3}, 96.1 (SD:37.0) μg m^{-3}, and 31.6 (SD:11.8) μg m^{-3}, respectively. Slightly higher concentrations of $PM_{2.5}$ and NO_2 were observed among term birth cases ($P < 0.001$) while higher temperature levels were observed among PTB cases ($P = 0.001$). As presented in table S1 and figure S5, temperature was negatively correlated with air pollutants levels except for O_3, and $PM_{2.5}$ and NO_2 concentrations were positively correlated, while were both negatively correlated with O_3 level.

3.2. Associations between temperature, air pollution and PTB

The associations between exposure to temperature, air pollutants and PTB were not statistically significant during the first and second trimester of pregnancy (figures S6 and S7), except for exposure to HT during second trimester. However, for the third trimester, consistent nonlinear associations with threshold effects were detected (figure 2). Increased concentrations of $PM_{2.5}$, O_3, NO_2, and temperature, as shown at 75th to 95th percentiles above thresholds were associated with elevated risks of PTB (table 2). The analysis for other air pollutants provided by CNEMC were also performed and results were included in the Supplementary Materials (figure S8).

Threshold effects have been reported by several previous studies. For example, Fleischer *et al* [30] used the World Health Organization Global Survey on Maternal and Perinatal Health database and found that $PM_{2.5} \geqslant 36.5$ μg m^{-3} was associated with significantly higher risks of PTB, compared with lower exposure (<36.5 μg m^{-3}) in China. Another study from Spain revealed that using threshold of NO_2 at 46.2 μg m^{-3} could differentiate the elevated risks of PTB [33].

Several studies have shown that exposure to both heat and cold temperature extremes increase the risks of PTB. A study in Brisbane, Australia, detected U-shaped associations between daily average temperature and PTB, with similar RRs observed for LT and HT in the third trimester of pregnancy [28]. Another study from China indicated 17.9% and 10% higher risks of PTB when exposed to extreme cold and extreme heat, respectively, during the last four weeks of pregnancy [6]. It is worthy of note that when we considered this association separately in

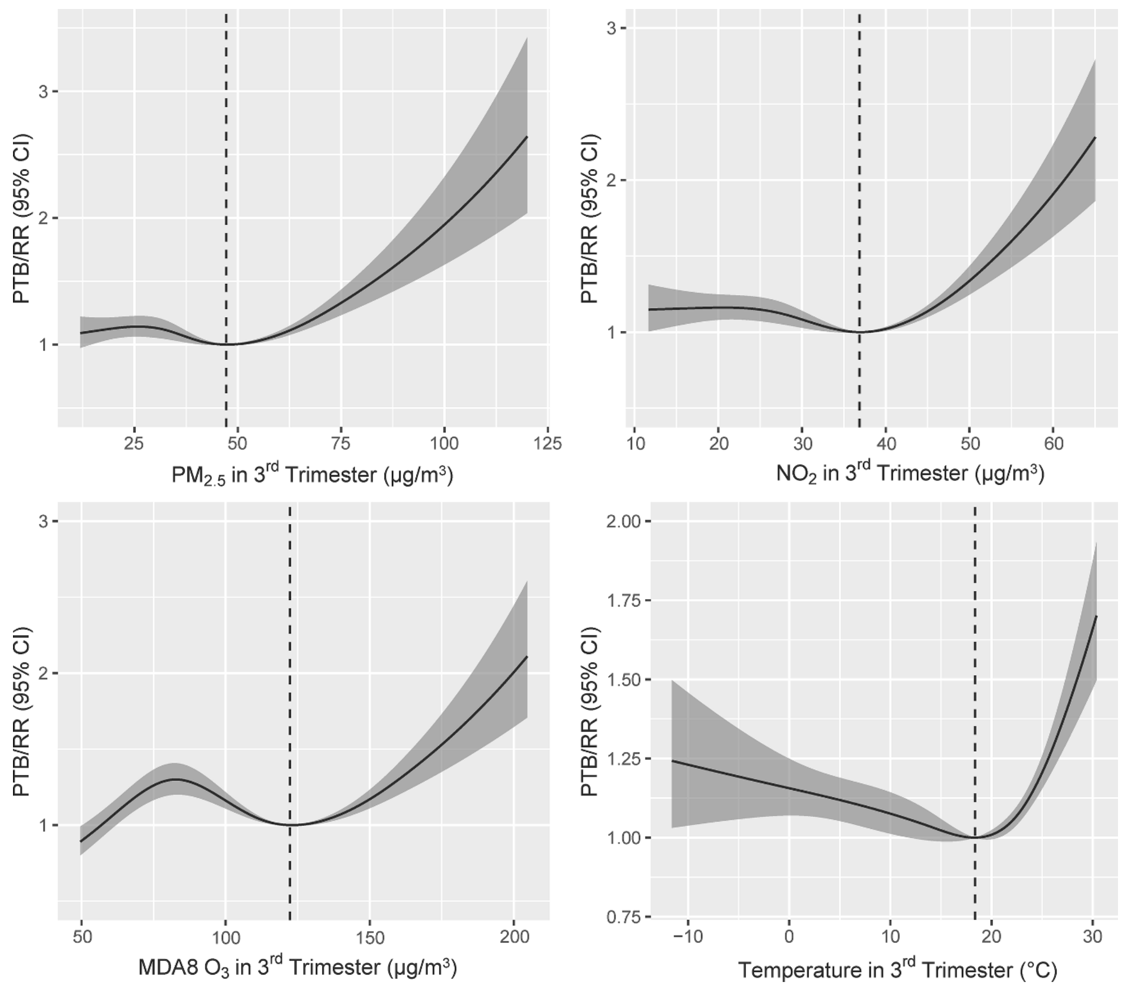

Figure 2. Associations between air pollutants, temperature and preterm birth.
Footnote: The RRs were adjusted for sex of newborn, maternal age, ethnicity, education, income, environmental tobacco exposure, use of air purifier, proximity to main roads and noise disturbance.

Table 2. The risks of preterm birth at 75th to 95th percentiles of air pollution against the minimum preterm birth concentration of air pollution (threshold) in single-pollutant models.

		Adjusted RR (95% CI)[a]				
Variable	Threshold	75th vs. threshold	80th vs. threshold	85th vs. threshold	90th vs. threshold	95th vs. threshold
$PM_{2.5}$ (μg m^{-3})	47.3	47.4	51.9	56.2	62.4	74.1
		1.00 (1.00, 1.01)	1.00 (1.00, 1.01)	1.04 (1.01, 1.06)	1.11 (1.07, 1.15)	1.32 (1.23, 1.42)
MDA8 O_3 (μg m^{-3})	122.3	126.0	134.5	142.9	151.1	160.3
		1.07 (0.96, 1.18)	1.10 (1.00, 1.22)	1.16 (1.05, 1.29)	1.23 (1.11, 1.38)	1.33 (1.18, 1.50)
NO_2 (μg m^{-3})	36.9	40.4	42.9	45.3	47.8	51.6
		1.00 (1.00, 1.00)	1.03 (1.02, 1.05)	1.10 (1.07, 1.13)	1.21 (1.16, 1.27)	1.44 (1.33, 1.56)
T (°C)	18.4	24.5	25.3	26.0	26.7	27.7
		1.06 (1.04, 1.07)	1.15 (1.12, 1.18)	1.27 (1.22, 1.32)	1.42 (1.34, 1.51)	1.70 (1.56, 1.85)

[a] Adjusted for sex of newborn, maternal age, ethnicity, education, income, environmental tobacco exposure, use of air purifier, proximity to main roads and noise disturbance.
Abbreviations: CI, confidence interval; MDA8 O_3, daily maximum 8 h average ozone; NO_2, nitrogen dioxide; $PM_{2.5}$, particulate matter $\leqslant$2.5 μm; RR, risk ratio; T, temperature.

north and south China, we observed higher threshold values in north than south, for instance, 52.2 μg m^{-3} vs. 24.5 μg m^{-3} for $PM_{2.5}$, 123.0 μg m^{-3} vs. 117.7 μg m^{-3} for MDA8 O_3 (figures S9–S11). The overall patterns were similar with an except that cold temperature extremes seemed to pose higher adverse effects on PTB in south than north China (figure S12). This could be due partially to the presence of central heating service in north China but not in south China.

Previous studies have shown some inconsistencies in the association between air pollution or temperature and PTB across the three trimesters of pregnancy. Several studies have reported significant associations between air pollution and PTB during the first and third trimesters. For instance, Huynh *et al* [34] found that high total pregnancy $PM_{2.5}$ exposure was associated with PTB, and this association remained consistent during the first month of pregnancy and the last two weeks of pregnancy. Liu *et al* also reported increased risks of PTB associated with air pollutants during the first and third trimesters [25]. But a study in China identified a significant effect of outdoor air pollution only with 8-week exposure before PTB [35]. Nevertheless, some studies reported insignificant associations for the third trimester [36–38]. Similar inconsistency also exists in studies investigating the linkage between temperature and PTB [7]. These inconsistent findings regarding the critical exposure trimester during pregnancy can be attributed to the heterogeneity in study populations, variation in exposure assessment and different risk factors involved. Further investigation on the trimester-specific effects of air pollution and temperature on PTB is warranted.

The shapes of the exposure-response functions are essential in assessing disease burden and health benefits of tackling air pollution and climate change. Previous studies examining the effects on mortality revealed approximately linear associations within relatively narrow ranges of air pollution exposure [39], but nonlinear associations for wider air pollution exposure ranges that include high levels of air pollution [40]. The threshold effects could be explained partially by individual susceptibility, duration and intensity of exposure and other biological mechanisms. Recent studies have suggested that exposure to air pollution can induce systemic oxidative stress [41] and molecular biological damages [42]. This can occur through various mechanisms, including the generation of reactive oxygen species (ROS) [43] in the body and epigenetic changes such as DNA methylation. Both heat and cold extremes can also increase oxidative stress [44, 45]. Initially, these molecular damages may be subtle and not immediately result in observable macro symptoms, observable outcomes or acute responses from the body. The body's inherent repair and compensatory mechanisms might mitigate the damages caused by these environmental exposures. However, when the exposure to air pollution is prolonged or the damages accumulate beyond the body's capacity for repair and compensation, the adverse health outcomes may become evident. The nonlinear associations between environmental exposure and health outcomes can be partially explained by the accumulated damage and disruption to biological processes over time. In this context, the nonlinear association observed in our study may be a result of the cumulative effects of exposures below a certain level. However, in terms of actual health impacts (including the subtle changes unobserved) caused by the exposures, using the threshold values as reference levels can possibly lead to underestimation of the health risk. However, the lack of evidence on PTB prevented us from further comparing the observed patterns. Thus, the results should be interpreted with caution. Future studies investigating both the exposure-response associations and potential interactive effects of air pollution and temperature are warranted.

3.3. Additive interactions between air pollution and temperature

We observed positive additive interaction of $PM_{2.5}$–HT, O_3–HT and O_3–LT, but the additive effects of $PM_{2.5}$ and LT were negative (RERI < 0), as shown in table 3. The results from adjusted models indicated that approximately 48% (RERI $=$ 0.99, 95% CI: 0.29, 1.69), 17% (RERI $=$ 0.16, 95% CI: 0.12, 0.20) and 7% (RERI $=$ 0.07, 95% CI: 0.03, 0.10) of the excess risks of the total observed effects could be attributed to additive interactions of $PM_{2.5}$–HT, O_3–LT, and O_3–HT, respectively.

It is plausible that HT could act synergistically with $PM_{2.5}$ to affect health. Previous studies have shown that PM toxicity may increase with higher temperature, and elevated temperature may increase the uptake of $PM_{2.5}$ in human body through elevation in minute ventilation and skin blood flow [46]. In addition, the observed pattern of $PM_{2.5}$–LT could also be partially explained by behavioral changes [20], as either higher $PM_{2.5}$ level [47] and cold temperatures [48] to be negatively associated with outdoor physical activity, thus resulting in less actual exposure to ambient $PM_{2.5}$.

Under both low and HT conditions, O_3 showed significant additive effects with temperature on PTB, with approximately 10% excessive additive effects under LT condition, compared to HT condition. Link between heat exposure and PTB has been previously suggested to be attributed to dehydration (via prostaglandin or OT release), altered blood viscosity [7], and premature rupture of membranes triggered by HT [49]. Increase in oxidative stress and inflammatory markers following exposures to high or low ambient temperatures may also play an important role [50]. As an oxidant, O_3 could increase

Table 3. Relative excess risk (95% CI) and attributable proportion (95% CI) due to interaction of temperature and air pollutant exposure on preterm birth.

	RERI (95% CI)		AP (95% CI)	
Variable	Adjusted[a]	Crude	Adjusted[a]	Crude
$PM_{2.5}$–LT	−0.43 (−0.65, −0.20)	−0.43 (−0.66, −0.21)	−0.48 (−0.74, −0.22)	−0.49 (−0.75, −0.23)
$PM_{2.5}$–HT	0.99 (0.29, 1.69)	0.92 (0.25, 1.59)	0.48 (0.30, 0.66)	0.46 (0.28, 0.64)
MDA8 O_3–LT	0.16 (0.12, 0.20)	0.13 (0.09, 0.17)	0.17 (0.13, 0.21)	0.13 (0.10, 0.17)
MDA8 O_3–HT	0.07 (0.03, 0.10)	0.07 (0.04, 0.11)	0.07 (0.03, 0.10)	0.07 (0.03, 0.10)

[a] Adjusted for sex of newborn, maternal age, ethnicity, education, income, environmental tobacco exposure, use of air purifier, proximity to main roads and noise disturbance.

Abbreviations: AP, attributable proportion; CI, confidence interval; HT, high temperature; LT, low temperature; MDA8 O_3, daily maximum 8 h average ozone; $PM_{2.5}$, particulate matter $\leqslant 2.5$ μm; RERI, relative excess risk due to interaction; RR, risk ratio.

oxidative and inflammatory stress in human body [51], thus acting synergistically with low and/or HT extremes. In addition to the biological mechanisms, HT is a well-documented factor that favor formation of O_3 through photochemical reactions [52], whereas under certain conditions (i.e., a stagnant, high-pressure, low wind speeds, etc), LT during cold seasons was also reported to trigger photolytic O_3 production [53], leading to more commonly co-occurrence of O_3 and temperature extremes.

3.4. Sensitivity analyses

The results were consistent when adjusted for another pollutant (i.e., double-pollutant models). Effects of $PM_{2.5}$ was independent of NO_2 (figure S13), although the detected thresholds for each exposure changed slightly. The sensitivity analysis using double-pollutant models showed that the health effects of $PM_{2.5}$ and O_3 on PTB appeared independent of temperature, and vice versa. In addition, the observed additive interactions between both temperature and air pollution exposures indicate potentially higher risk of PTB than observed alone. Nevertheless, future studies are also warranted to examine and validate the joint effect of air pollutants with temperature extremes, as both intense heat events and cold temperature would be more frequent in the context of global warming [54].

3.5. Limitations

There are also several limitations to this study. First, we focused on the associations between exposure to air pollutants and extreme temperature specifically in the late pregnancy period, particularly the third trimester. By examining this relatively short-term exposure window, the potential influence of short-term exposure on PTB outcomes might be minimized. Although our study design aimed to focus on the specific period of late pregnancy to minimize the potential confounding by short-term exposure, we acknowledge that these sub-acute effects may still play a role in the associations observed. Future research should consider examining both short-term and longer-term exposures to gain a more comprehensive understanding of the complex relationships between air pollutants, temperature, and adverse pregnancy outcomes. Second, as the COVID-19 lockdown took place in our study period, behavioral change might have potential influence on the observed associations. Future research is needed to explore the interplay between environmental exposures, pandemic-related factors, and their collective impact on pregnancy outcomes. Another important consideration is that while we employed the term ‘threshold’ to describe and analyze the observed nonlinear associations, it is crucial to note that this does not imply the existence of an ‘optimal’ air pollutant concentration greater than zero. We also observed increased level of risk below the threshold values, which might be caused by residual confounding. Therefore, the interpretation of these threshold values should be approached with caution and without assuming a biologically plausible optimal concentration.

In conclusion, this study found that maternal exposure to higher levels of $PM_{2.5}$, NO_2, O_3, and both low and HT were independently associated with increased risk of PTB. Positive additive interaction effects were observed between $PM_{2.5}$ and–HT and between O_3 and–HT and LT conditions. Our results may highlight the significant of adaptation of health measures and also the co-benefits of tackling air pollution and mitigating global warming.

Data availability statement

The data cannot be made publicly available upon publication because they contain sensitive personal information. The data that support the findings of this study are available upon reasonable request from the authors.

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Author contributions

X X, R L, Y Y were responsible for the conceptualization, methodology, software, validation, formal analysis, investigation, writing-original draft and writing-editing. Z Z, L D K, B J, L M, S C D, J H, S P, Y M G, and Y Y X were responsible for the writing-reviewing and editing of the whole manuscript. L J, Y K G, W Y, J Y, Y Z, C W, S G, E Z, S S and T Z were responsible for the data acquisition and validation. G H D, M G and C Y have full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis, funding acquisition, resources, supervision and Project administration.

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