Environment International 173 (2023) 107832

Contents lists available at ScienceDirect

Environment International

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

Full length article

Identifying the critical windows and joint effects of temperature and PM$_{2.5}$ exposure on small for gestational age

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ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Heat
Cold
Climate change
Air pollution
Interactive effect
Small for gestational age

ABSTRACT

The potential critical windows for extreme ambient temperature, air pollution exposure and small for gestational age (SGA) are still unclear, and no study has explored their joint effects on SGA. In a national multi-center prospective cohort, we included 179,761 pairs of mother-infant from 16 counties of 8 provinces in China during 2014–2018. Daily averaged temperature and PM$_{2.5}$ concentration were matched to the maternal residential address to estimate personal exposure. Extreme temperature exposures were categorized by a series of percentile in each meteorological and geographic division for the entire pregnancy, each trimester and gestational week (GA-week). Generalized linear mixed models (GLMMs) and distributed lag nonlinear models (DLNMs) were used to estimate the whole pregnancy-, trimester-specific, and weekly-specific associations of extreme temperature and PM$_{2.5}$ exposures with SGA. Combined effects were evaluated with the relative excess risk due to interaction (RERI) and proportion attributable to interaction (AP). We observed that by referring to temperature at the 41st − 50th percentile, heat (>90th percentile) exposure during 13th − 29th GA-weeks was associated with SGA; odds ratio (OR) and 95 % confidence intervals (CI) was 1.16 (1.06, 1.28). For cold (<=10th percentile), inverse associations were observed during the 1st − 8th GA-weeks. PM$_{2.5}$ exposure during the 2nd − 5th and 19th − 27th GA-weeks was associated with SGA, with the strongest association in the 2nd GA-week (OR = 1.0017, 95 % CI: 1.0001, 1.0034, for a 10 $\mu g/m^3$ increase). No interactive effects between ambient temperature and PM$_{2.5}$ on SGA were observed. Our findings suggest the weekly susceptibility windows for heat and PM$_{2.5}$ exposure were primarily the gestational weeks within the 2nd trimester, therefore, corresponding protective measures should be conveyed to pregnant women during routine prenatal visits to reduce exposures.

1. Introduction

Small for gestational age (SGA), defined as newborns weighing less than the 10th percentile birth weight within a given sex and gestational age (GA), is the most common indicator of intrauterine fetal growth restriction (IUGR) in resource constrained low- and middle-income countries (LMICs) (Lee et al., 2013). Children who are born SGA are more likely to have birth complications, cognitive deficits, and increased risk of obesity, precocious puberty and cardiovascular disease, etc. (Malpique et al., 2019; Milovanovic et al., 2014; Sacchi et al., 2020; Surkan et al., 2004; Van Wassenaer, 2005; Verkauskiene et al., 2013).

SGA is known to be affected by many intrinsic and extrinsic factors,

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Abbreviations: SGA, Small for gestational age; IUGR, Intrauterine fetal growth restriction; LMICs, Resource constrained low- and middle-income countries; OR, Odds ratio; CI, Confidence intervals; DLNM, Distributed lag nonlinear model; AGA, Appropriate size for gestational age; LGA, Large for gestational age; LMP, Last menstrual period; NCWCH, National Center for Women and Children's Health; DAG, Directed acyclic graph; BMI, Body mass index; RH, Relative humidity; PM$_{2.5}$, Ambient particulate matter with an aerodynamic diameter of $\leq 2.5 \mu m$; NO$_2$, Nitrogen dioxide; CO, Carbon monoxide; O$_3$, Ozone; SO$_2$, Sulfur dioxide; IDW, Inverse distance weighting; GLMM, Generalized linear mixed model; E-R, Exposure-response relationship; RERI, Relative excess risk due to interaction; AP, Proportion attributable to interaction.

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https://doi.org/10.1016/j.envint.2023.107832
Received 27 October 2022; Received in revised form 6 February 2023; Accepted 14 February 2023

including environmental factors (e.g., air pollution and meteorological factors) (Brauer et al., 2008; Smith et al., 2017; Stieb et al., 2016; Sun et al., 2019; Yitshak-Sade et al., 2021). In a national Canadian study including 3 million live births, Stieb et al. (Stieb et al., 2016) reported that maternal exposure to $PM_{2.5}$ during the entire pregnancy was associated with a 4 % higher risk of SGA per 10 μg/m^3 increase. Sun et al. study in the United States (Sun et al., 2019) found that high ambient temperatures were associated with a higher risk of term SGA [odds ratio (OR) = 1.04, 95 % confidence interval (CI): 1.03, 1.05]. Meanwhile, the evidence from experimental studies suggested that prenatal exposure to non-optimal temperatures was probably related to the abnormal development and function of the placenta and maternal vascular malperfusion, leading to fetal growth restriction (Aplin et al., 2020; Thureen et al., 1992; Wang et al., 2020a). For example, heat exposure during pregnancy was associated with a reduction in placental weight and volume and an increase in the placental weight/birth weight ratio, which indicates dysfunction of the placenta (Wang et al., 2020a). Another animal study on sheep observed a reduced placental glucose transport capacity and lower fetal and placental masses in the group with heat stress (Thureen et al., 1992). Prior studies have also suggested that exposure to high temperatures could induce a redistribution of the maternal bloodstream, which may cause lower uterine artery blood flow and inefficient nutrients and oxygen exchange, resulting in IUGR (Aplin et al., 2020). Additionally, Oken et al. (Oken et al., 2003) stressed that using gestational-age-specific weight allows for a more precise evaluation of the effects on IUGR. However, there were relatively few studies on the effects of ambient temperature on SGA.

In addition, maternal exposures during some periods of gestation may be more critical than others and identifying these critical windows will assist us to understand the potential biological mechanisms and make targeted preventive interventions (Barker et al., 1989). However, current studies on temperature and SGA have mainly used trimester-specific exposure windows (3-month intervals) (Ha et al., 2017; Kloog et al., 2018; Sun et al., 2019), which might be biased, whether using three models controlling for each trimester separately or one model containing all trimesters (Wilson et al., 2017). Although clinically defined trimesters are generally accepted and convenient to implement, biological susceptible windows might not completely align with trimester, for example, spanning multiple trimesters or shorter than 3 months, which may lead to incorrect window identification. Slama and Wilson proposed that investigating on finer time scales (e.g., gestational weeks) might be a more informative and reasonable approach, using distributed lag nonlinear models (DLNMs) (Slama et al., 2008; Wilson et al., 2017). To the best of our knowledge, no published study has examined the weekly susceptible windows between ambient temperature exposure and SGA.

Compared to the temperature, numerous studies have explored the associations between ambient $PM_{2.5}$ and adverse birth outcomes, such as SGA. However, these results are inconclusive, given the variability in study design, exposure assessment, covariates, and statistical methodology (Lamichhane et al., 2015; Percy et al., 2019; Yuan et al., 2019). Even among studies that found positive relationships, the identified exposure windows were inconsistent (Bravo and Miranda, 2022; Chen et al., 2022; Gray et al., 2014; Hyder et al., 2014; Liu et al., 2007; Mannes et al., 2005; Rich et al., 2009; Smith et al., 2017; Stieb et al., 2012; Tapia et al., 2020; Zhu et al., 2022). For example, Zhu (Zhu et al., 2022) and Mannes et al. (Mannes et al., 2005) found prenatal $PM_{2.5}$ exposure in the second trimester was correlated with a higher risk of SGA. Tapia et al. (Tapia et al., 2020) discovered a positive relationship in the first and third trimester. Just like previous studies of temperature exposure windows, most studies among $PM_{2.5}$ and SGA have only explored trimester-specific associations, however, the weekly-specific critical windows for ambient $PM_{2.5}$ exposure and SGA are still unclear.

Owing to climate change, increasing extreme events and poor weather conditions may exacerbate air pollution, especially $PM_{2.5}$ (Hong et al., 2019). Recently, a literature review emphasized the effects of joint exposure to climate change and air pollution on children's health, which might lead to larger health impacts than each exposure alone, particularly in LMICs (Perera and Nadeau, 2022). Our previous study have showed a synergistic effect of heatwaves and $PM_{2.5}$ on preterm birth during the last GA-weeks (Wang et al., 2020b). Grigorieva and Lukyanets (Grigorieva and Lukyanets, 2021) also found that heatwaves and outdoor air pollution were synergistically linked to the hospital admissions for childhood asthma. However, these interaction researches have mainly focused on the effects of short-term exposure, less on long-term exposure. So far, no published studies on the interactive effects of ambient temperature and air pollution on SGA have been reported.

To address these knowledge gaps, we aim to explore the associations between ambient temperature and $PM_{2.5}$ and the risk of SGA, identity the critical windows, and further investigate their joint effects.

2. Methods

2.1. Study design and participants

This multi-center prospective cohort study was based on the National Maternal and Newborn Health Monitoring Project, conducted by the National Center for Women and Children's Health, Chinese Center for Disease Control and Prevention from March 6, 2013 to December 31, 2018 The project primarily aimed at understanding and collecting information about women's and infants' health status and risk factors dynamically, including the record of prenatal care, maternal age, parity, maternal education, weight and height before pregnancy, as well as neonates' sex, gestational age, and birth weight, and improving their health conditions. Considering the number of newborns and the infrastructure of perinatal health care, 16 counties of 8 provinces in China (Liaoning, Sichuan, Yunnan, Hebei, Fujian, Hubei, Hunan, Guangdong) were selected (**Figure S1 and S2**). More detailed descriptions of this project have been presented elsewhere (Ren et al., 2022; Wu et al., 2021; Zhu et al., 2022).

In the final main analysis, we restricted the population to singleton term live births. Due to the missing data of $PM_{2.5}$ exposure, we excluded those participants during 2013 and early 2014. In addition, we included neonates weighing 500–5000 g with gender records, according to the normal range of birth weight.

2.2. Outcome

SGA, appropriate size for gestational age (AGA), and large for gestational age (LGA) were defined as newborn's GA-specific weight < 10th percentile, 10th − 90th percentile, and > 90th percentile. GA was determined by a confirmatory ultrasound and the date of self-reported last menstrual period (LMP). The reference of gender and GA-specific birth weight was based on a representative birthweight curve in China (Dai et al., 2014). Since the reference ranged from 28 to 44 GA-weeks, we excluded neonates with < 28 and > 44 GA-weeks. Considering that we aimed to investigate the associations between environmental factors and SGA, we excluded LGA participants because LGA is another abnormal birth weight for gestational age. The final analytic sample consisted of 179,761 "mother-newborn" pairs (**Figure S3**).

This study was approved by the medical ethics committee of the National Center for Women and Children's Health (NCWCH) (No. FY2015-007) and the School of Public Health, Sun Yat-sen University (No. 2021–014).

2.3. Covariates

Covariates were selected based on our prior knowledge and intuitive directed acyclic graphs (DAGs) (**Figure S4**). The final models included following covariates: maternal age, maternal education (≤6, 7–9, 10–12, >12 years), body mass index (BMI) before pregnancy (<18.5, 18.5–23.9, >23.9 kg/m^2), parity (primiparous or multiparous), maternal residence (local or migrant), season of conception (spring, summer, fall, winter), year of birth (2015, 2016, 2017, 2018), meteorological and geographic divisions (northeast, southwest, northern China, eastern China, central China, southern China) (Wang et al., 2021). Data on maternal pre-pregnancy BMI, parity, education level, and residence were missing partially (0.01–3.43 %), so we used complete-case analyses in our main model and multiple imputations in the sensitivity analysis to assess the potential bias caused by missing data (Sterne et al., 2009).

2.4. Exposure assessment

Daily average temperature and relative humidity (RH) during 2014–2018 were collected from the 680 weather stations of the China Meteorological Data Service Center (https://data.cma.cn/). Daily mean concentrations of $PM_{2.5}$, nitrogen dioxide (NO_2), carbon monoxide (CO), ozone (O_3), and sulfur dioxide (SO_2) during 2014–2018 at 1597 sites were collected from the China National Environmental Monitoring Center (https://www.cnemc.cn).

The assessment of meteorological factors and air pollutant exposure followed the method from our previous studies (Ren et al., 2022; Wu et al., 2021). In short, inverse distance weighting interpolation (IDW) was applied to estimate daily exposure at 1 × 1 km resolution in ArcGIS 10.5. Then we assigned daily observations to each pregnant woman according to maternal residence address during pregnancy and used the estimated date of conception and the actual date of delivery to determine the start and end date of each gestational week for the pregnancy. Finally, daily individual measurements were averaged for each exposure window (gestational week, trimester, entire pregnancy). Since the GA of participants were inconsistent, some women lacked the exposure data of meteorological factors and air pollutants after 37 GA-weeks. Therefore, to facilitate assessment of potential window, we set the exposure period from 1 to 37 GA-weeks (the minimum GA of term births), and the windows were divided as follows: the 1st trimester: 1–12 GA-weeks, 2nd trimester: 13–27 GA-weeks, 3rd trimester: 28–37 GA-weeks and the entire pregnancy (1–37 GA-weeks).

Populations from different regions tend to have varied patterns of climate adaptation. Therefore, we transformed absolute temperature into categorical variables based on the percentiles of temperature distribution of all mothers within each meteorological and geographic division. Specifically, average temperatures during each window were converted into a variable with ten categories. We defined the 41st − 50th percentile category as the reference, colder-than-average temperatures as those below the reference (<=10th, 11th − 20th, 21st − 30th, 31st − 40th percentile) and warmer-than-average temperatures as those above the reference (61st − 70th, 71st − 80th, 81st − 90th, >90th percentile) (Basagaña et al., 2021).

2.5. Statistical analyses

2.5.1. Generalized linear mixed model

We applied a standard logistic regression and generalized linear mixed model (GLMM) to estimate the associations between mean temperature and $PM_{2.5}$ with SGA in each trimester and the entire pregnancy. Considering the possible clustering effect and adaptation of populations within the same region, we treated the meteorological and geographic division as a random intercept, other confounders as fixed-effect terms.

$g[E(Y)] = X\beta + Zu + \varepsilon$ Model 1.

Where g is the link function (binomial distribution, log link function), Y is the outcome variable (SGA = 1, AGA = 0); X is the fixed effect variable, including maternal education level, age, residence, parity, pre-pregnancy BMI, season of conception, year of birth, relative humidity, pregnancy- and trimester- average temperature and $PM_{2.5}$ exposure; Z is the random effect variable, i.e. the meteorological and geographic divisions; ε is the residual. Maternal age and relative humidity were included as the natural cubic spline with 3 degrees of freedom (dfs). Temperatures were included as categorical variables, with OR and corresponding 95 % CI calculated vs the reference. Average $PM_{2.5}$ exposure was included as a continuous variable, with the ORs and 95 % CI calculated per 10 μg/m^3 increase. Three trimesters of exposure were included in a single model to reduce the bias from separate adjustment (Neophytou et al., 2021; Wilson et al., 2017).

2.5.2. Distributed lag nonlinear model

Distributed lag nonlinear model (DLNM) is a framework that can incorporate with several regression models to estimate traditional exposure–response relationship (E-R) and additional delayed effect, by establishing a flexible “cross-basis” function (Gasparrini, 2014). Therefore, we applied DLNMs and GLMMs to further assess the exposure-lag-response association of each week (from the 1st to the 37th GA-weeks) ambient temperature and $PM_{2.5}$ exposure with the risk of SGA, by accounting for all past (lagged) exposures and adjusting for the same covariates in Model 1 (Jakpor et al., 2020). Considering the causal structures among temperature, $PM_{2.5}$ and SGA, we believe that ambient temperature affects the concentration of $PM_{2.5}$ and not the converse. Therefore, in the analysis of $PM_{2.5}$ and SGA, we adjusted the mean temperature, but for the effect of temperature and SGA, $PM_{2.5}$ was not adjusted (Buckley et al., 2014).

In the same way, firstly, absolute temperatures were categorized by the deciles of temperature distribution in each meteorological and geographic division. Then, to explore the effects of extreme temperatures, we further used the 95th and 5th percentile as cut-offs and defined the > 90th and > 95th percentiles of each zone as heat, the <=10th and <=5th percentiles as cold, the 41st − 50th category as the reference. According to the classification of temperature, a strata function was applied to model E-R. For $PM_{2.5}$, we assumed a linear association with SGA. For the lag association between exposure and outcome, which was assessed by each gestational week (independent lag), we assumed that the lag association varies smoothly across weeks and therefore used natural cubic splines with 2 dfs for temperature and 3 dfs for $PM_{2.5}$. The selection of dfs was based on the minimum Akaike Information Criterion (AIC). Estimation of the effects was presented as ORs and 95 % CI, calculated by each temperature category (vs the reference) and per 10 μg/m^3 increment in $PM_{2.5}$.

2.5.3. Joint effects of ambient temperature and $PM_{2.5}$ exposure on SGA

To investigate whether there is an additive interaction between temperature and $PM_{2.5}$ exposure on the risk of SGA, we calculated the relative excess risk due to interaction (RERI) and proportion attributable to interaction (AP). An RERI > 0 indicates joint effects are greater than that of each exposure alone and an RERI < 0 indicates negative additive interactive effects. AP is calculated by RERI divided by the OR of co-exposure, with RERI or AP = 0 indicating the absence of interactions.

In the analysis of interaction, we followed the method developed by Hosmer and Lemeshow, dividing temperature and $PM_{2.5}$ exposure into two dichotomous determinants within the critical window of the SGA (Hosmer and Lemeshow, 1992). Specifically, in each meteorological and geographic division, we used the 75th percentile of $PM_{2.5}$ and the 90th or 95th (for heat) and 10th or 5th (for cold) percentile of temperature as cut-off points to convert the exposure into a binary variable, then we combined the two exposures to create a new dummy variable (P_0T_1: exposure to extreme temperatures only, T_0P_1: exposure to $PM_{2.5}$ only, and P_1T_1 co-exposure to both extreme temperatures and $PM_{2.5}$), where the P_0T_0 as the reference. We fitted GLMM and used bootstrap percentile method to calculate the ORs and 95 % CI.

2.6. Sensitivity analyses

To test the stability, we presented several sensitivity analyses. First, we applied a two-pollutant model to examine the effects of CO, NO_2, SO_2 and O_3 on the associations. Second, we repeated analyses in all live births. Third, to assess the bias from missing covariates, we used multiple imputation with outcome and other variables to generate five data sets. Maternal residence and parity were imputed using the logistic regression, and maternal pre-pregnancy BMI and education level were imputed using the proportional odds model. Fourth, due to the problems of collinearity and over-adjustment, we evaluated the effects of weekly temperature and $PM_{2.5}$ on SGA separately in DLNMs. Therefore, we repeated the analysis by establishing two cross bases of them in a single model. Finally, we evaluated additive interactions in DLNMs by establishing cross-basis with dummy variables and calculating the weekly RERI and AP.

We conducted all analyses in the R software (version 4.1.2), mainly using lme4, boot, splines, and dlnm (Gasparrini, 2014) package.

3. Results

3.1. *Summary characteristics of participants and exposure to ambient temperature and $PM_{2.5}$*

We included 179,761 singleton term live births, of these, 10.4 % were SGA (Table 1). The mean birth weight of SGA (2,597 g) was much lower than that of the total population (3,208 g) and AGA (3,279 g). Compared with mothers of AGA, those of SGA were younger, less educated and had lower pre-pregnancy BMI. The distributions of maternal residence, the year of birth, season of conception were similar between SGA and AGA.

Table 2 shows the daily mean $PM_{2.5}$ and temperature among all participants. The mean values of ambient temperature and $PM_{2.5}$ for SGA and AGA during the whole pregnancy were 17.62 °C, 50.74 μg/m^3 and 17.07 °C, 52.92 μg/m^3, respectively. The summary statistics of exposure during each week of pregnancy were in the supplementary material (**Table S1-S2**).

3.2. *Associations between temperature, $PM_{2.5}$ and SGA*

Table 3 shows the estimated effects of ambient temperatures and $PM_{2.5}$ exposure on SGA for the whole pregnancy and each trimester. We found that warmer-than-average temperatures were associated with higher ORs of SGA. For example, pregnancy-average temperatures in the 80th − 90th and > 90th percentile were associated with a 14 % (OR = 1.14, 95 % CI: 1.03, 1.25) and 16 % (OR = 1.16, 95 % CI: 1.06, 1.28) higher risk of SGA, relative to the reference group (41st − 50th percentile). The associations for the first and second trimesters were similar to those observed across the entire pregnancy. For example, temperatures between the 81st − 90th percentile were associated with SGA, with ORs and 95 % CIs were 1.16 (95 % CI: 1.01, 1.33) and 1.17 (95 % CI: 1.04, 1.32), respectively, but associations in the 3rd trimester were null. Colder-than-average temperatures were not associated with SGA. $PM_{2.5}$ exposures were associated with a higher risk of SGA during the whole pregnancy (OR = 1.02, 95 % CI: 1.01, 1.04). The trimester-specific positive associations were observed in the 1st and 2nd trimester, with both ORs were 1.01 (95 % CI: 1.00, 1.02).

3.3. *Critical windows for temperature and $PM_{2.5}$*

DLNM estimates of the association between weekly temperature and SGA suggested heat (>90th, >95th percentile) were associated with a higher risk of SGA during the 13th − 29th and 18th − 28th GA-weeks respectively, with the strongest associations observed at the 21st and the 22nd (OR = 1.03, 95 % CI: 1.01, 1.05) gestational week (vs. the 41st − 50th percentile). The relationship between SGA and cold (<=10th, <=5th percentile) showed inverse associations in the 1st − 8th and 1st − 11th gestational weeks respectively (Fig. 1**, Table S3-S4**). For GA-week-specific $PM_{2.5}$, two critical windows were identified at the 2nd − 5th and the 19th − 27th GA-weeks, with ORs and 95 % CIs of SGA ranging from 1.001 (95 % CI: 1.0001, 1.0018) to 1.0017 (95 % CI:

Table 1
Summary characteristics of participants.

Variables	SGA (n = 18,612)	AGA (n = 161,149)	Total (n = 179,761)
Gestational age (weeks)	39.23 (1.08)	39.16 (1.13)	39.16 (1.12)
Maternal age (years)	32.84 (6.76)	33.85 (6.47)	33.74 (6.51)
Birth weight (g)	2,597 (234.57)	3,279 (273.14)	3,208 (340.26)
Pre-pregnancy BMI (kg/m^2)			
<18.5	3,931 (21.12)	20,717 (12.86)	24,648 (13.71)
18.5–23.9	11,216 (60.26)	101,880 (63.22)	113,096 (62.91)
≥24	3,137 (16.85)	35,754 (22.19)	38,891 (21.63)
Unknown	328 (1.76)	2,798 (1.74)	3,126 (1.74)
Infant sex			
Male	9,243 (49.66)	85,291 (52.93)	94,534 (52.59)
Female	9,369 (50.34)	75,858 (47.07)	85,227 (47.41)
Meteorological and geographic divisions			
Northeast	624 (3.35)	9922 (6.16)	10,546 (5.87)
Southwest	3378 (18.15)	27,474 (17.05)	30,852 (17.16)
Northern China	3225 (17.33)	31,075 (19.28)	34,300 (19.08)
Eastern China	3078 (16.54)	29,089 (18.05)	32,167 (17.89)
Central China	5115 (27.48)	48,751 (30.25)	53,866 (29.97)
Southern China	3192 (17.15)	14,838 (9.21)	18,030 (10.03)
Maternal education			
≤6 years	669 (3.59)	4,639 (2.88)	5,308 (2.95)
7–9 years	6,533 (35.1)	50,237 (31.17)	56,770 (31.58)
10–12 years	5,682 (30.53)	49,828 (30.92)	55,510 (30.88)
>12 years	5,136 (27.6)	50,878 (31.57)	56,014 (31.16)
Unknown	592 (3.18)	5,567 (3.45)	6,159 (3.43)
Maternal residence			
Local	16,626 (89.33)	145,658 (90.39)	162,284 (90.28)
Migrant	1,318 (7.08)	12,119 (7.52)	13,437 (7.47)
Unknown	668 (3.59)	3,372 (2.09)	4,040 (2.25)
Parity			
Primiparous	11,296 (60.69)	89,424 (55.49)	100,720 (56.03)
Multiparous	7,308 (39.26)	71,710 (44.5)	79,018 (43.96)
Unknown	8 (0.04)	15 (0.01)	23 (0.01)
Year of birth			
2015	3,854 (20.71)	34,932 (21.68)	38,786 (21.58)
2016	5,171 (27.78)	48,984 (30.4)	54,155 (30.13)
2017	5,603 (30.1)	46,394 (28.79)	51,997 (28.93)
2018	3,984 (21.41)	30,839 (19.14)	34,823 (19.37)
Season of conception			
Spring	4,594 (24.68)	40,574 (25.18)	45,168 (25.13)
Summer	4,952 (26.61)	42,504 (26.38)	47,456 (26.4)
Fall	4,724 (25.38)	40,818 (25.33)	45,542 (25.33)
Winter	4,342 (23.33)	37,253 (23.12)	41,595 (23.14)

Note: Categorical variables are reported as n (%), continuous variables are reported as means (SD).
SGA, small for gestational age; AGA, appropriate for gestational age; BMI, body mass index.

Table 2
Summary statistics of the daily mean $PM_{2.5}$ and temperatures during pregnancy.

Pregnancy period	Mean ± SD	25th	50th	75th
SGA				
$PM_{2.5}$ (μg/m^3)				
WP	50.74 ± 25.73	29.53	45.07	64.81
T1	51.05 ± 31.43	29.43	41.30	64.59
T2	50.80 ± 30.87	29.81	40.22	63.55
T3	50.26 ± 32.74	29.86	39.72	61.24
Temperature (°C)				
WP	17.62 ± 4.14	14.86	18.40	20.61
T1	17.87 ± 7.70	12.71	18.96	24.66
T2	17.54 ± 7.33	12.90	18.48	23.84
T3	17.46 ± 7.80	12.59	18.41	24.13
AGA				
$PM_{2.5}$ (μg/m^3)				
WP	52.92 ± 25.68	30.37	49.67	67.08
T1	53.38 ± 31.92	31.01	44.99	67.22
T2	52.93 ± 30.93	31.10	42.95	66.32
T3	52.42 ± 33.41	31.06	41.93	64.32
Temperature (°C)				
WP	17.07 ± 4.31	14.50	17.90	20.25
T1	17.37 ± 8.07	11.84	18.65	24.49
T2	16.96 ± 7.65	11.91	18.14	23.45
T3	16.88 ± 8.18	11.73	17.91	23.84

Note: WP: the whole pregnancy (1–37 weeks); T1: the first trimester (1–12 weeks); T2: the second trimester (13–27 weeks); T3: the third trimester (28–37 weeks).

Table 3
Estimated effects of ambient temperatures and $PM_{2.5}$ exposure on SGA.

	WP	T1	T2	T3
	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)	OR (95 % CI)
Temperature				
<=10	0.96 (0.89, 1.04)	0.91 (0.79, 1.06)	1.00 (0.90, 1.12)	0.90 (0.79, 1.03)
11–20	1.00 (0.92, 1.08)	0.97 (0.85, 1.11)	1.02 (0.92, 1.13)	0.91 (0.80, 1.02)
21–30	1.02 (0.94, 1.10)	0.94 (0.84, 1.05)	0.98 (0.90, 1.08)	0.94 (0.84, 1.04)
31–40	1.00 (0.93, 1.07)	0.98 (0.90, 1.07)	1.00 (0.93, 1.08)	0.92 (0.84, 1.00)
41–50	Reference	Reference	Reference	Reference
51–60	1.03 (0.95, 1.11)	1.06 (0.96, 1.17)	1.06 (0.98, 1.16)	1.08 (0.98, 1.19)
61–70	1.09 (1.00, 1.18)	1.11 (0.98, 1.25)	1.07 (0.97, 1.19)	1.09 (0.96, 1.24)
71–80	1.09 (0.99, 1.19)	1.16 (1.02, 1.33)	1.09 (0.97, 1.22)	1.15 (0.99, 1.32)
81–90	1.14 (1.03, 1.25)	1.16 (1.01, 1.33)	1.17 (1.04, 1.32)	1.14 (0.98, 1.33)
>90	1.16 (1.06, 1.28)	1.15 (0.99, 1.33)	1.13 (1.00, 1.28)	1.15 (0.97, 1.35)
$PM_{2.5}$ (per 10 μg/m^3)	1.02 (1.01, 1.04)	1.01 (1.00, 1.02)	1.01 (1.00, 1.02)	1.00 (0.99, 1.01)

Note: WP: the whole pregnancy (1–37 weeks); T1: the first trimester (1–12 weeks); T2: the second trimester (13–27 weeks); T3: the third trimester (28–37 weeks).

1.0001, 1.0034). (Fig. 2, **Table S5**). Effects of two-pollutant model, multiple imputation, DLNM with two cross bases and analysis including all live infants were consistent with our main results (**Table S6-S10**).

3.4. Additive interactions between temperature, $PM_{2.5}$ and SGA

Since the exposure windows differed for each temperature percentile, we investigated the additive interactive effects of heat and cold temperature and $PM_{2.5}$, during their corresponding windows of SGA. No significant additive interaction patterns of heat and $PM_{2.5}$ were detected (>90th percentile, RERI = 0.08, 95 % CI: (-0.35, 0.60), AP = 0.08, 95 % CI: (-0.52, 0.38); >95th percentile, RERI = -0.14, 95 % CI: (-0.83, 0.76), AP = -0.16, 95 % CI: (-4.18, 0.43)). Similar results of joint effects were found in the analyses of cold and DLNMs (Table 4**, Table S11-S14**).

4. Discussion

We evaluated the independent and joint effects of ambient temperature and $PM_{2.5}$ on SGA in a national multi-center prospective cohort study in China. Our findings showed that heat and $PM_{2.5}$ (per 10 μg/m^3 increase) exposure during the pregnancy were independently associated with higher risks of SGA, and susceptible windows were primarily the gestational weeks within the second trimester. Cold temperature was inversely associated with SGA, especially in the first trimester. We did not observe the combined effects of temperature and $PM_{2.5}$ on SGA.

Pregnant women were among the groups most vulnerable to extreme temperatures. Only four previous studies examined the relationship between temperature and SGA, two of which found a null association and the others found positive and negative associations, respectively (Ha et al., 2017; Kloog et al., 2018; Sun et al., 2019; Yitshak-Sade et al., 2021). One study in southern Israel observed higher pregnancy temperature (>75th percentile) might decrease the risk of SGA and lower temperature (<25th percentile) may increase the risk of SGA, compared to mild temperature (25-75th percentile) (Kloog et al., 2018). We believe that these inconsistencies may be a result of: 1) The research area in Israel had four unique geo-climatic zones that varied widely, but these zones were not adjusted in the model. 2) the lack of some important covariates, for example, maternal height and weight, which plays a significant role in neonatal birth weight (Rahman et al., 2015). In accordance with our results, another U.S. study containing 403 counties, reported that the 80th − 90th and > 90th percentiles of the county- and pregnancy-specific mean temperature were significantly associated with SGA in the 2nd and 3rd trimester, relative to the 40th − 50th percentile (Sun et al., 2019). In our study, the heat exposure windows of SGA were identified in the 13th − 29th gestational weeks (>90th percentile) and the 18th − 28th gestational weeks (>95th percentile), spanning the 2nd and 3rd trimester.

Heat could disrupt several aspects of the reproductive process, including the development of embryonic and foetal growth. In response to heat stress, humans have produced a range of physiological and behavioral adaptations (Browne et al., 2015; Galan et al., 2005; Hansen, 2009; Regnault et al., 2002; Wells, 2002). For example, the thermoregulatory system distributes the blood flow from the core to the periphery, which reduces vascular perfusion of the placenta and internal organs (e.g. stomach), decreasing the exchange of placental substances and food intake, resulting in fetal weight loss (Hansen, 2009; Wells, 2002). Additionally, angiogenesis can be altered, due to inappropriate gene expression of vascular endothelial growth factors, leading to increased placental vascular resistance and reduced fetal weight. The effects of heat exposure on growth may be stronger in the middle of pregnancy because angiogenesis occurs mainly in the second trimester (Galan et al., 2005; Regnault et al., 2002).

Compared with heat, fewer researchers have focused on cold exposure and fetal growth. Basagaña et al. have reported a non-significant protective effect between cold exposure (<=10th percentile) and term LBW, using DLNMs (Basagaña et al., 2021). In this study, we also found that cold temperatures were associated with a reduced risk of SGA and the corresponding exposure windows were in the 1st − 8th (<=10th percentile) gestational weeks and 1st − 11th (<=5th percentile) gestational weeks. The findings may represent an adaptive-evolutionary mechanism to environmental cold temperatures. When faced with deleterious environmental perturbations, humans would produce some adaptive strategies to keep robustness, which promoted the evolution of populations (Masel and Trotter, 2010; Stewart et al., 2012). Early pregnancy is the period of embryo implantation, and exposure to cold temperatures during this period is likely to cause "selection in utero" that removes fetuses in poor health, which is an essential adaptation

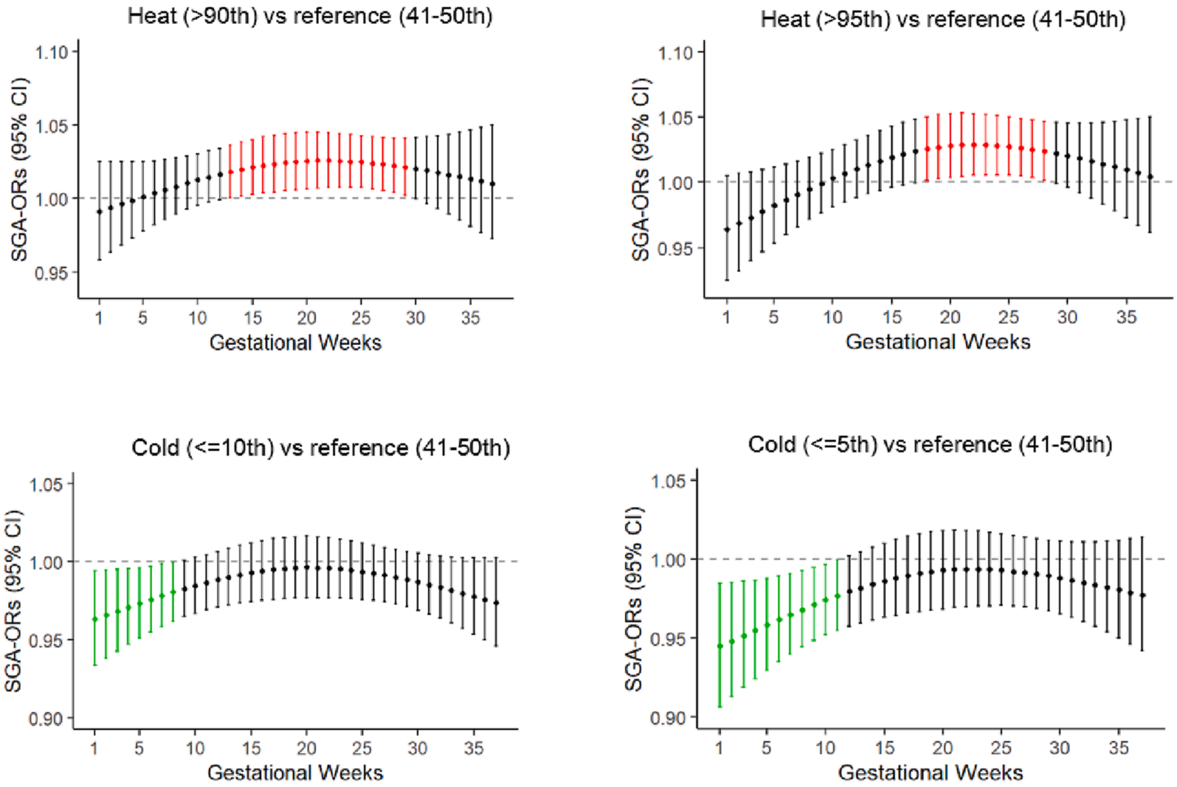

Fig. 1. Multivariable-adjusted ORs and 95 % CI for small for gestational age in association with heat and cold temperatures (>90th, >95th, <=10th, <=5th percentile for each meteorological and geographic division, relative to the 41st – 50th centile) during 1–37 weeks of pregnancy. Distributed lag nonlinear models (DLNMs) incorporated with logistic mixed-effects models were used to calculate OR and 95 % CI and lag-response function modeled as a natural cubic spline with 2 dfs. Models were adjusted for maternal age, education, parity, body mass index before pregnancy, residence, season of conception, year of birth, mean temperature from 38th week to birth. Maternal age and mean relative humidity were included by a natural cubic spline with 3 dfs, meteorological and geographic divisions were fitted as random effects.

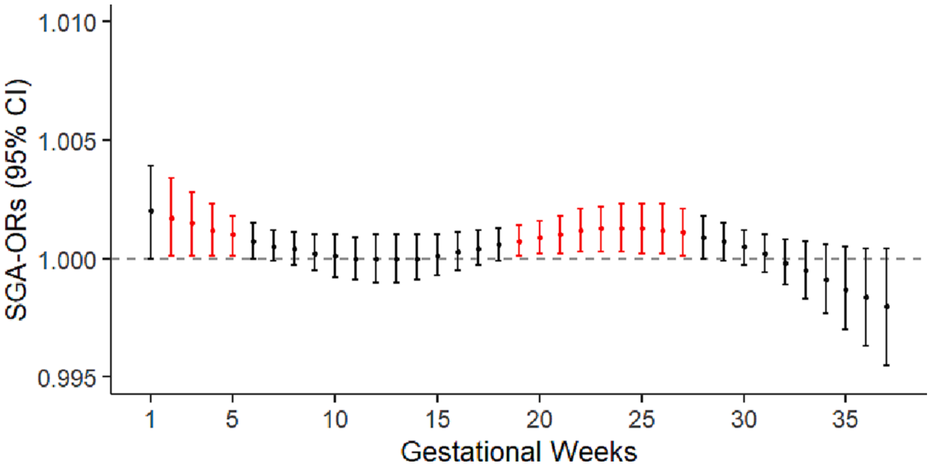

Fig. 2. Multivariable-adjusted ORs and 95 % CI for small for gestational age in association with weekly-specific $PM_{2.5}$ exposure during 1–37 weeks of pregnancy. Distributed lag nonlinear models (DLNMs) incorporated with logistic mixed-effects models were used to calculate OR and 95 % CI and lag-response function modeled as a natural cubic spline with 3 dfs. Models were adjusted for maternal age, education, parity, body mass index before pregnancy, residence, season of conception, year of birth, mean temperature and mean $PM_{2.5}$ from 38th week to birth. Maternal age and relative humidity were included by a natural cubic spline with 3 dfs, meteorological and geographic division were fitted as random effects.

strategy (Almond and Currie, 2011; Baird, 2009; Bruckner and Catalano, 2018). In the meantime, pregnant women might also adopt corresponding behavioral adaptations, such as wearing warmer clothes and consuming more food. Thus, the comprehensive results of adaptability may result in a reduced risk of SGA associated with cold exposure during early pregnancy.

In the present study, we observed a positive associations between $PM_{2.5}$ and SGA in the 1st and 2nd trimester and the whole pregnancy, which strengthens the evidence of prenatal $PM_{2.5}$ exposure and SGA. Moreover, in the evaluation of effects between weekly $PM_{2.5}$ with SGA, we found that the sensitive exposure windows were in the 2nd – 5th and the 19th – 27th GA-weeks. To our knowledge, only one study in Tianjin, China, used DLNM to evaluate $PM_{2.5}$ and SGA, and exposure windows were the 1st – 9th pre-conceptional weeks and the 1st – 2nd GA-weeks (Chen et al., 2022). In contrast to our results, Chen et al. found that $PM_{2.5}$ at the 19th to 27th week was associated with a lower risk of SGA. As the authors said, the contradictory conclusion may be due to the selection bias, because the enrolled participants were restricted to women who were preparing to be pregnant and did not cover those with unplanned pregnancies. As a result, they may have better physical conditions and immunity than the general pregnant population.

Concurrent exposure to climate change and poor air quality is

Table 4
Interactive effects of extreme temperatures and $PM_{2.5}$ exposure on SGA.

Temperature (°C)[a]	$PM_{2.5}$ (μg/m^3)[b]	OR/RERI/AP	95 CI%
>90th	>75th		
No	No	Reference	–
Yes	No	1.01	0.95, 1.07
No	Yes	0.99	0.95, 1.04
Yes	Yes	1.08	0.71, 1.64
RERI		0.08	−0.35, 0.60
AP		0.08	−0.52, 0.38
>95th	>75th		
No	No	Reference	–
Yes	No	1.03	0.95, 1.11
No	Yes	1.00	0.96, 1.04
Yes	Yes	0.88	0.38, 2.06
RERI		−0.14	−0.83, 0.76
AP		−0.16	−4.18, 0.43
<=10th	>75th		
No	No	Reference	–
Yes	No	0.93	0.87, 1.00
No	Yes	1.02	0.97, 1.07
Yes	Yes	0.97	0.88, 1.07
RERI		0.02	−0.10, 0.13
AP		0.02	−0.11, 0.13
<=5th	>75th		
No	No	Reference	–
Yes	No	0.91	0.84, 0.98
No	Yes	1.02	0.97, 1.07
Yes	Yes	0.96	0.87, 1.06
RERI		0.03	−0.09, 0.14
AP		0.03	−0.10, 0.14

Note: -, not applicable; CI, confidence interval; OR, odds ratio; RERI: relative excess risk due to interaction; AP: attributable proportion.

[a] Extreme high temperature was defined by daily averaged temperature (90th, 95th percentile, for each meteorological and geographic division) in the 13th − 29th and 18th − 28th gestational weeks. Extreme low temperature was defined by daily averaged temperature (10th, 5th percentiles, for each meteorological and geographic division) in the 1st − 8th and 1st − 11th gestational weeks.

[b] $PM_{2.5}$ was classified as a binary variable using the 75th percentile of each meteorological and geographic division during the 2nd − 5th and 19th − 27th gestational weeks.

common, and extreme weather conditions may intrinsically exacerbate the impacts of air pollution (Ha, 2022; Perera and Nadeau, 2022). Therefore, the combined effects of extreme temperature and air pollution are extremely significant, especially for populations with lower physical capacity or socioeconomic status. Among the previous studies, Sun et al. and Wang et al. (Sun et al., 2020; Wang et al., 2020b) found that exposure to heatwaves and $PM_{2.5}$ can synergistically trigger preterm birth during the last week of gestation (RERI > 0). Grigorieva and Lukyanets (Grigorieva and Lukyanets, 2021) also reported synergistic effects of co-exposure to heat and air pollution on the incidence of hospitalization related to childhood asthma. However, in a study from Guangzhou, China, there were no interactive effects of extreme temperature, diurnal temperature range and air pollution on gestational diabetes mellitus (Zhang et al., 2021). Similarly, the estimated RERIs and APs were non-significant in our study, which need to be confirmed in future studies.

There are some strengths in our study. Firstly, conducting the project in 16 counties of 8 provinces across China in a 5-year time span, we obtained a large number of representative Chinese population samples, with high data quality, which increases the generalizability of our findings. In addition, compared to studies based on birth records, we can collect more information about mothers and babies to reduce potential confounding bias due to unmeasured variables. Nonetheless, this study still has the following limitations: 1) The lack of biochemical, physiological, and experimental evidence on the impact of $PM_{2.5}$ and extreme temperatures, like other observational studies, makes us impossible to provide a more complete frame of reference to understand the observed association and prove the causality. 2) Exposure misclassification bias. In this study, we combined the daily observations from all monitoring sites and the residential address of each pregnant woman to assess exposures, and information on the pregnant woman's activity pattern, indoor exposure, work address was not available, so the exposures we used may not represent the actual personal exposure level. 3) Other individual variables, such as socioeconomic status, consumption of supplements and medical complications, were also unavailable.

5. Conclusion

In this large, nationwide, prospective multi-center cohort study in China during 2014–2018, we found that both heat and $PM_{2.5}$ exposure during the pregnancy were independent risk factors of SGA, and both susceptible exposure windows were mainly the gestational weeks within the 2nd trimester. Cold temperature was inversely associated with the risk of SGA, probably due to maternal physiological and behavioral adaptations. Although this study found no interactive effects of extreme ambient temperature and $PM_{2.5}$ on SGA, more studies are needed to elucidate this issue. Pregnant women should be communicated to reduce exposure to heat and $PM_{2.5}$ during routine prenatal visits, especially in the middle of pregnancy.

Declaration of Competing Interest

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

Data availability

The authors do not have permission to share data.

Acknowledgments

We appreciate the efforts of all staff in data collection, data entry and reporting in the monitoring areas (including Zhengding, Taian, Yueyang, Rong county, Tonghai and Huaning, Xinhua, Tiedong, Lishan, Yueyanglou, Haicang, Jimei and Gongjing). We acknowledge and thank the managers of the Maternal and Newborn Health Monitoring Program in the above monitoring areas. This study was supported by the grants from National Key R&D Program of China (2018YFA0606200), National Natural Science Foundation of China (42075178, 42175183), and Guangdong Basic and Applied Basic Research Foundation (2021A1515011947).

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2023.107832.

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Update

Environment International
Volume 186, Issue , April 2024, Page

DOI: https://doi.org/10.1016/j.envint.2024.108634

Environment International 186 (2024) 108634

Contents lists available at ScienceDirect

Environment International

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

Corrigendum

Corrigendum to “Identifying the critical windows and joint effects of temperature and $PM_{2.5}$ exposure on small for gestational age” [Environ. Int. 173 (2023) 107832]

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The authors regret that using the notation “1”, which has been updated above.

The authors would like to apologise for any inconvenience caused.

DOI of original article: https://doi.org/10.1016/j.envint.2023.107832.

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https://doi.org/10.1016/j.envint.2024.108634