Environment International 142 (2020) 105851

Contents lists available at ScienceDirect

Environment International

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

Ambient temperature and the risk of preterm birth: A national birth cohort study in the mainland China

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ARTICLE INFO

Handling Editor: Adrian Covaci

Keywords:
Preterm birth
Ambient temperature
BIrth cohort

ABSTRACT

Background: Little is known about the effect of ambient temperature on preterm birth, especially for the trimester-specific effects.
Objective: To evaluate whether exposure to relatively low or high temperature during pregnancy is associated with increasing risk of preterm birth or not.
Method: We analysed the data of a birth cohort with 1,281,859 singleton pregnancies during 2013–2014 and matched the home address of each pregnant women to the model based daily meteorological and air pollution data. Then we used the Cox proportional hazard regression models with random effect to estimate the non-linear associations between exposure to relatively low or high temperature at each trimester of pregnancy and the risk of preterm birth, after controlling for air pollution and individual-level covariates.
Finding: The overall preterm birth rate was 8.1% (104,493 preterm births). Exposure to relatively low or high temperatures during the entire pregnancy significantly increase the risk of preterm birth, with hazard ratios (HRs) [95% confidence intervals (CIs)] of 1.03 (95%CI: 1.02, 1.04) for relatively low (9.1 °C, the 5th percentile) temperature and 1.55 (95%CI: 1.48, 1.61) for relatively high (23.0 °C, the 95th percentile) temperature in comparison with the thresholds (12.0 °C). Pregnant women at the early pregnancy (the 1st and 2nd trimester) are more susceptible to high temperatures while pregnant women at the late pregnancy (the 3rd trimester) are more susceptible to low temperatures.
Conclusion: These findings provide new evidence that exposure to relatively low or high temperatures during pregnancy increases the risk of preterm birth, which can serve as scientific evidence for prevention of preterm birth.

1. Introduction

Preterm birth is the leading risk for neonatal mortality, which accounts for 35% of all neonatal deaths (March of Dimes et al. 2012). Preterm birth can also increase the risk of neurologic, pulmonary and circulatory disorders, resulting in life long morbidity (Shapiro-Mendoza et al. 2016). In 2010, there were more than 15 million preterm births worldwide and the rate has been increasing in almost all countries (March of Dimes et al. 2012). With the irreversible damage and substantial incidence, preterm birth can result in great social economic burden. In United Sates, preterm births resulted in more than $26 billion losses per year (Chernausek 2012). Increasing studies tried to explore the etiology and corresponding preventive strategy of preterm birth during the recent decades. The common risk factors such as

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https://doi.org/10.1016/j.envint.2020.105851
Received 11 November 2019; Received in revised form 24 April 2020; Accepted 16 May 2020
Available online 22 June 2020

previous preterm birth history, multiple pregnancies, infections and gestational diabetes mellitus have been identified. However, the reason for nearly half of the spontaneous preterm births is still unclear (March of Dimes et al. 2012). Meanwhile, some studies suggested that climate factors such as ambient temperature might play a significant role (Zhang et al. 2017).

Relatively low or high temperature has been documented to cause numerous health losses in various ways (Basu 2009; McMichael et al. 2006; Ye et al. 2012). Previous studies have reported that exposure to relatively low or high temperatures was associated with mortality and morbidity regarding cardiopulmonary system, infectious and mental health (Gasparrini et al. 2015; Peng et al. 2017; Ye et al. 2012). They also indicated that exposure to relatively low or high temperatures could restrict the function of circulating system and induce cytokines release, which were hypothesised to have potential influence on the process of pregnancy (Li et al. 2018).

In very recent years, there are increasing studies that had estimated the relationship between relatively low or high temperature during pregnancy and the risk of preterm birth. However, to our best knowledge, most of the previous studies were conducted in developed areas such as Australia, Europe, and North America. The participants usually came from restricted communities or cities, and share similar lifestyle and climate zone, which may restrict the external validity (Basu et al. 2010; Basu et al. 2017; Kloog et al. 2015; Li et al. 2018; Schifano et al. 2013; Schifano et al. 2016; Zhang et al. 2017).

Previous studies were often conducted with ecological design and/or time series analysis by linking the birth registry data and station-based temperature exposure (Liang et al. 2016; Schifano et al. 2013; Schifano et al. 2016; Weng et al. 2018). The presence of individual adjustments such as history of preterm birth, maternal socioeconomic status, body mass index and tobacco or alcohol consumption caused potential biases for estimating the association between temperature and preterm birth.

Moreover, the recent report of World Health Organization presented that 12 out of every 100 babies were premature in China, and the total number of preterm births exceeded 1 million in China per year (March of Dimes et al. 2012). We only found one study estimated the effects among multiple Chinese cities (Guo et al. 2018). However, the city-level exposure used in this study can introduce considerable exposure misclassification. Due to the limitation of the statistical strategies, they also failed to describe the response curve of the associations. In addition, the effects of temperature in various exposure windows have been mentioned in previous study, with inconsistent results (He et al. 2016; Li et al. 2018; Liang et al. 2016; Schifano et al. 2013). Whether there are trimester-specific effects or not and which trimester of pregnancy is the most susceptible period are unclear.

Given the evidence gap, the present study sought to estimate the association between temperature exposure during pregnancy and preterm birth by analysing the data of ambient temperature and detailed individual characteristics of a national birth cohort with more than 1.2 million nulliparous in mainland China. The primary objective of the study was to estimate trimester-specific effects of ambient temperature on preterm birth. The study also aimed to identify potential effect modification of maternal socio-demographic status, physical conditions and climate zones.

2. Methods

2.1. Study design and participants

Since 2010, Chinese National Health and Family Planning Commission and Ministry of Finance have launched National Free Preconception Health Examination Project (NFPHEP) to provide free preconception health check-up, early gestation and postpartum follow-up for couples planning to get pregnant throughout mainland China (Zhang et al. 2015). Base on the NFPHEP, we have established a cohort including more than 1.5 million nulliparous who had delivered a baby from Dec 1. 2013 to Nov 30. 2014 (Wang et al. 2018). In the present cohort study, after excluding women being minority, with gestational age < 20 weeks or more than 42 weeks, history of preterm birth, multiple-gestation pregnancies, pre-pregnancy diseases, migration during pregnancy, and whose essential information was missing (See eFigure1 in the Supplemented file for additional information regarding the exclusion procedure), we finally included 1,281,859 singleton live births in analyses. The institute review board of the National Research Institute for Family Planning, Beijing, China, approved this study. All participants provided written informed consent.

2.2. Outcome definition

Preterm birth was defined as a live birth with gestational age < 37 complete weeks (World Health Organization 1977). Gestational age was derived from the first day of the last menstrual period (LMP). Women's LMP times were recorded during the early gestation follow-up visit (conducted no later than 12 weeks after conception) by a doctor. Each woman's gestational age was asked again at the postpartum follow-up visit (conducted no later than six weeks after delivery), and then determined (Wang et al. 2018). We further categorized preterm birth into very preterm birth (VPTB, 28 to < 32 complete weeks) and extremely preterm birth (ExPTB, < 28 complete weeks).

2.3. Exposure assessment

We collected daily mean temperature during the study period from the 824 weather stations of China Meteorological Data Sharing Service System (http://data.cma.cn/). Then we used kriging methods to interpolate the daily mean temperature for areas in mainland China which was not covered by the weather stations at a resolution of $0.1^{\circ} \times 0.1^{\circ}$. Detailed information about the interpolation procedure can be found elsewhere (Chen et al. 2018). We also predicted daily concentrations of particulate matters < 2.5 μm ($PM_{2.5}$) at the same resolutions based on the satellite remote data, meteorological data and land use information by using a random forest models (Chen et al. 2018). We assessed the trimester-specific and entire pregnancy average exposure to ambient temperature and air pollution for each woman by linking their home addresses and the time span of pregnancy to the predicted daily temperature and $PM_{2.5}$ via the longitude and latitude (Wang et al. 2018). The trimesters were defined as follows: the 1st trimester, 1–13 gestational weeks; the 2nd trimester, 14–26 gestational weeks; the 3rd trimester, 6 weeks before delivery. As preterm birth had shorter gestation in comparison with term birth, the shorter length makes the cumulative exposure not comparable, especially in the 3rd trimester of VPTB and ExPTB, when we estimated the trimester-specific effect. Due to the primary objective of the present study is to estimate the impact of trimester-specific temperature exposure on preterm birth, and more than 80% of preterm births occur between 32 and 37 weeks of gestation (March of Dimes et al. 2012), we removed VPTB and ExPTB in the main model analyses and defined the 3rd trimester as 6 weeks before delivery.

2.4. Statistical analyses

We used the cox proportional hazard regression to estimate the effects of trimester-specific temperature exposure on the risk of preterm birth (births with 32 to < 37 complete weeks). Gestational age was fitted as the time scale and spontaneous PTB was defined as event. Trimester-specific temperature levels were fitted as time independent variables, respectively. Considering the non-linear relationship between temperature and preterm birth (He et al. 2016), we architected a penalized cubic spline with 4 knots to estimate the non-linear effect of temperature as the initial analysis showed it produced best model fit judged by lowest value of Akaike Information Criterion (AIC). As air pollution could modify the health impact of temperature (Malley et al.

2017; Stanisic Stojic et al. 2016), we controlled the exposure to $PM_{2.5}$ with the same resolution as temperature in our model. Apart from environmental variables, we adjusted for other potential individual adjustments in the models based on a literature review (Zhang et al. 2017), including maternal age (< 25, 26 to 30, 31 to 35, or greater than 35 years), urban dwellers (yes, no), education time (≤9, 10 to 12, or greater than 12 years), occupation (farmers, workers, or others), body mass index before conception (≤18.5, 18.6 to 23.9, or ≥ 24.0 kg/m^2), active or passive smoking during pregnancy (yes, no), alcohol consumption during pregnancy (yes, no), organic solvent, heavy metal, or pesticide exposure during pregnancy (yes, no) and season of conception (spring, summer, autumn, or winter). We also added a random intercept for each province in the model to handle the potential cluster effects. To study the potential effect modification of temperature on preterm birth by demographic characteristics, we extended the spline of temperature to interaction term including factor and smooths, and then presented the effect curve of each subgroup respectively (Rose et al. 2012; Wood 2017). We also conducted stratified analysis among temperature zone, subtropical zone, and tropical zone to estimate whether there was any geographic difference (Jingyun et al. 2010). In the present study, results were reported by hazard ratios (HRs) and corresponding 95% confidence intervals at the of 5^{th}, 25^{th}, 75^{th} and 95^{th} percentile of temperature at each exposure window, referring to the threshold (defined as the temperature with the minimum hazard of preterm birth), respectively.

Several sensitivity analyses were conducted to check the robustness of our primary findings. As ExPTB and VPTB was removed in the main model analysis, we rebuilt the model which included them to check whether the associations existed or not. We also estimated the effects of temperature on the risk of ExPTB and VPTB separately. As the 3^{rd} trimester was defined as 6 weeks before delivery, we also performed sensitivity analysis by using 5 and 4 weeks before delivery as the definition. We further rebuilt model by changing the basis type (P-spline) of the spline of temperature as sensitivity analyses. All analyses were performed by using the "mgcv" packages in the R environment (version 3.4.4, R Core Team). A P value < 0.05 was statistically significant.

3. Results

There were 1,281,859 live birth with gestational age of 20 to 42 weeks included in the present cohort study. Participants derive form 24,412 township-level units of the mainland China (there are 41,636 township-level units in mainland China in 2014) and the annual temperature of these units range from below freezing to more than 20 ℃. Fig. 1 presents the residential locations of participants and the annual average temperature of each location in 2014. Table 1 presents the descriptive statistics of individual characteristics. There were 104,493 (8.1%) preterm births (20 to < 37 complete weeks). Pregnant women with older age (> 30 years), shorter educational time (≤9 years), being farmers, being overweight before conception (BMI ≥ 24.0 kg/m^2), exposure to tobacco smoking or alcohol during pregnancy, having caesarean delivery, being conceived in winter tended to have a higher risk of preterm birth than their counterparts.

Table 2 presents the percentile distribution of trimester-specific temperature and air pollution exposure. The median temperature over the entire pregnancy for all pregnant women was 16.6 ℃, with an interquartile range of 6.6 ℃. While the median $PM_{2.5}$ exposure over the entire pregnancy for all pregnant women was 62.8 μg/m^3, with an interquartile range of 27.0 μg/m^3.

Fig. 2 shows the effects of temperature at each trimester and entire pregnancy on the risk of preterm birth. We found relatively low and high temperatures during the entire pregnancy significantly increase the risk of preterm birth, and the association between temperature and the risk of preterm birth demonstrates a U-shape curve. Compared to the threshold (12.0 ℃), we observed a HR of 1.03 (95%CI: 1.02, 1.04) for the relatively low (5th percentile) temperature and a HR of 1.55 (95%CI: 1.48, 1.61) for relatively high (95th percentile) temperature (Table 3). For trimester-specific exposure, we found relatively high temperatures at the 1^{st} trimester was significantly associated with increased risk of preterm birth [75th vs. threshold: 1.78 (95%CI: 1.69, 1.87); 95th vs. threshold: 1.96 (95%CI: 1.85, 2.08)]. We also found relatively high temperatures at the 2^{nd} trimester was significantly associated with increased risk of preterm birth, and the effects tend to diminish but remains significant [75th vs. threshold: 1.41 (95%CI: 1.34, 1.47); 95th vs. threshold: 1.30 (95%CI: 1.23, 1.38)]. On the other hand, we noticed that relatively low temperatures at the 3^{rd} trimester were significantly associated with increased risk of preterm birth [25th vs. threshold: 1.16 (95%CI: 1.13, 1.20); 5th vs. threshold: 1.17 (95%CI: 1.12, 1.22)].

Fig. 3 compared the magnitude of the effects of temperature during the entire pregnancy on the risk of preterm birth among different subgroups. We noticed the threshold of pregnant women working as farmers (11.6 ℃) was obviously lower than that of pregnant women working as workers (18.3 ℃). The HRs for the low (5th percentile) and high (95th percentile) temperature on the risk of preterm birth were 1.02 (95%CI: 1.00, 1.03) and 1.90 (95%CI: 1.80, 1.99) among pregnant women working as farmers, while the HRs were 1.35 (95%CI: 1.23, 1.48) and 1.05(95%CI: 1.00, 1.10) among pregnant women working as workers. We also noticed the effect of pregnant women being overweight was more obvious than that of normal ones. The HRs for the low (5th percentile) and high (95th percentile) temperature on the risk of preterm birth were 1.11 (95%CI: 1.06, 1.16) and 1.84 (95%CI: 1.66, 2.04) among pregnant women being overweight, while the HRs were 1.02 (95%CI: 1.01, 1.04) and 1.57 (95%CI: 1.49, 1.66) among pregnant women being normal weight.

Fig. 4 shows the effects of temperature during the entire pregnancy on the risk of preterm birth among temperature zone, subtropical zone and tropical zone in mainland China. The association between temperature and the risk of preterm birth showed similar U-shape curve in three climate zones. We noticed the threshold of pregnant women living in temperature zone (13.6 ℃) was lower than that of pregnant women living in subtropical (16.6 ℃) or tropical zone (23.0 ℃). The HRs for the relatively low (5th percentile) and relatively high (95th percentile) temperature on the risk of preterm birth were 1.40 (95%CI: 1.33, 1.47) and 2.48 (95%CI: 2.37, 2.59) among pregnant women living in temperature zones, while the HRs were 1.42 (95%CI: 1.38, 1.47) and 1.39 (95%CI: 1.33, 1.46) among pregnant women living in subtropical zones; the HRs were 1.46 (95%CI: 1.20, 1.77) and 1.62 (95%CI: 1.36, 1.93) among pregnant women living in tropical zones.

For sensitivity analyses, we rebuilt the model which included ExPTB and VPTB in analyses and found the associations did not change. When we estimated the effects of temperature on ExPTB and VPTB separately, similar associations were found regarding the mean temperature of 1st trimester and entire pregnancy. When we used 5 and 4 weeks before delivery as the definition of the 3^{rd} trimester, the associations did not change. Our results were also robust for changing the basis of the spline of temperature. See eFigures 2–6 in the supplemental files for the above results of sensitivity analyses in detail.

4. Discussion

In the study, we estimated the trimester-specific effects of temperature on preterm birth by analysing a birth cohort with more than 1.2 million primipara across mainland China. We found that exposure to relatively low or high temperatures during entire pregnancy could increase the risk of preterm birth. Pregnant women at the early pregnancy (the 1^{st} and 2^{nd} trimester) are more susceptible to high temperatures, while pregnant women at the late pregnancy (the 3^{rd} trimester) are more susceptible to low temperatures. These findings can serve as scientific evidence for improving the health of pregnant women and infant.

Several studies in limited communities or cities have suggested that

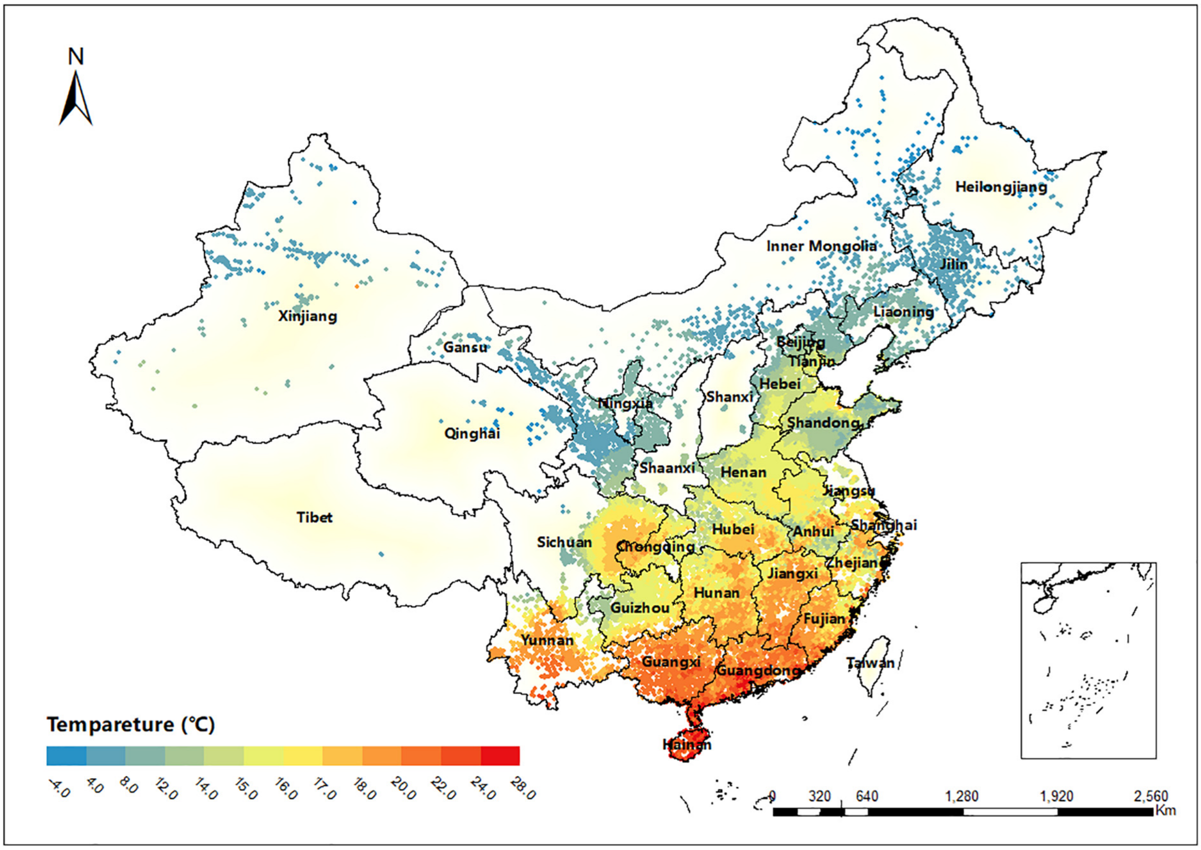

Fig. 1. Map showing the residential location of the participants and the annual average temperature of each location (℃) in 2014.

the risk of preterm birth could be related to either low or high temperatures during pregnancy, but the evidence are inconsistent so far, especially for the trimester-specific effects. An ecology study in a coastal city of Australia indicated that the risk of preterm birth was associated with high [HR of 95th percentile vs. threshold: 1.21 (95%CI: 1.16, 1.26)] or low [HR of 5th percentile vs. threshold: 1.21 (95%CI: 1.16, 1.27)] temperatures at the 3rd trimester. But they didn't find evidence that temperatures at the 1st and 2nd trimesters and entire pregnancy had effect on the risk of preterm birth (Li et al. 2018). Another study in Rome and Barcelona reported that a unit increase in maximum temperature at the 2nd trimester increased the risk of preterm birth, but they did not find evidence regarding other trimesters or entire pregnancy (Schifano et al. 2016). A ecological study conducted in a coastal city of China reported that high [HR of 95th percentile vs. threshold: 1.07 (95%CI: 1.02, 1.14)] or low [HR of 5th percentile vs. threshold: 1.09 (95%CI: 1.03, 1.15)] temperatures during the entire pregnancy increased the risk of preterm birth (He et al. 2016). On the contrary, another study in adjacent coastal city reported that low temperature at the last 4 gestational weeks was a risk factor [HR of 95th percentile vs. threshold: 1.72 (95%CI: 1.28, 2.33)] of preterm birth, while high temperature was its protective factor [HR of 5th percentile vs. threshold: 0.69 (95% CI: 0.60, 0.80)] (Liang et al. 2016). In addition, ecological study among multiple Chinese cities reported that compared with moderate temperatures (5th to 95th percentile), heat exposure (above 95th percentile) within 3 months before pregnancy increased the risk of preterm birth, with a OR of 1.23 (95% CI: 1.17, 1.30). They also reported that cold exposure (below 5th percentile) reduced the risk of preterm birth (Guo et al. 2018). The conflicting results published to date might be due to difference in definitions of exposure, methods of exposure assessment, participants, and climate zones (Li et al. 2018). However, the limitation of previous evidence (e.g., study design and methodologies) also precluded us from making conclusion for the associations (Strand et al. 2011).

During pregnancy, maternal immune responses within the uterus are tightly regulated to prevent immunological rejection of the foetus allograft. Heat stress may result in releases of cytokines such as prostaglandin, oxytocin and heat-shock proteins (Dadvand et al. 2011; Daugaard et al. 2007; Dreiling et al. 1991), which may disrupt the delicate balance of cytokines at the maternal-foetus interface and then activate the parturition mechanism prematurely (Peltier 2003; Schifano et al. 2016). On another hand, dehydration caused by heat stress in the mother can reduce her fluid, which may decrease uterine blood flow, induce the uterine contraction, and consequently impact the blood supply of foetus, thus may also contribute to the onset of parturition (He et al. 2016). For the possible pathways for cold-related effect on preterm birth, a few studies suggested that low temperature is related to peripheral vasoconstriction and hypertensive disorders of pregnancy, which might alter uteroplacental perfusion and adversely affect the developing foetus (Bruckner et al. 2014).

The present study novelty reported that pregnant women at the early pregnancy are more susceptible to high temperature while pregnant women at the late pregnancy are more susceptible to low temperature. The mechanism of the variability is unclear and needs further study. The effect of low temperature is mainly explained by the change of hemodynamic while the effect of high temperature is mainly explained by change of immunity and inflammatory (Bruckner et al. 2014; Peltier 2003; Schifano et al. 2016), which could be an explanation for the difference in the susceptible window. However, evidence regarding the potential pathways between temperature and preterm birth is limited, and more studies are needed.

Our study additionally estimated the potential effect modification of temperature on preterm birth by individual socio-demographic. We found that the thermoneutral zone of farmers were lower than that of workers. Compared with company and government employees, who

Table 1
Individual characteristics of participants in the present study.

Characters	Term Birth [a]	Preterm Birth	*p* value [b]
Maternal age, years			
18–25	491,527 (92.0)	42,506 (8.0)	< 0.001
26–30	513,640 (92.0)	44,681 (8.0)	
31–35	139,577 (90.8)	14,147 (9.2)	
36–45	32,676 (91.3)	3,105 (8.7)	
Urban dwellers			
No	1,108,938 (91.8)	98,925 (8.2)	< 0.001
Yes	68,476 (92.5)	5,514 (7.5)	
Educational time, years			
≤9	741,505 (91.4)	69,754 (8.6)	< 0.001
10–12	238,433 (92.6)	19,014 (7.4)	
greater than12	177,431 (92.9)	13,530 (7.1)	
Occupation			
farmer	867,833 (91.5)	80,206 (8.5)	< 0.001
worker	204,425 (92.9)	15,614 (7.1)	
other [c]	81,727 (93.0)	6,188 (7.0)	
Body mass index before conception (kg/m^2)			
≤18.5	175,345 (92.0)	15,351 (8.0)	< 0.001
18.5–23.9	835,699 (92.0)	72,255(8.0)	
≥24.0	155,355 (90.8)	15,815 (9.2)	
Active smoking during pregnancy			
No	1,156,744 (91.9)	101,738 (8.1)	< 0.001
Yes	12,069 (90.7)	1,238 (9.3)	
Passive smoking during pregnancy			
No	889,351 (92.0)	78,236 (8.1)	< 0.001
Yes	279,300 (91.9)	24,702 (8.1)	
Alcohol consumption during pregnancy			
No	115,791 (91.9)	101,625 (8.1)	< 0.001
Yes	13,321 (91.3)	1,268 (8.7)	
Organic solvent, heavy metal, or pesticide exposure during pregnancy			
No	1,170,028 (91.9)	103,789 (8.1)	0.831
Yes	7,392 (92.0)	650 (8.1)	
Baby sex			
Female	560,750 (92.4)	45,955 (7.6)	< 0.001
Male	615,888 (91.5)	57,530 (8.5)	
Mode of delivery			
Caesarean	350,425 (91.6)	32,221 (8.4)	< 0.001
Vaginal	826,995 (92.0)	72,218 (8.0)	
Season of conception			
Spring	30,1528 (92.4)	24,685 (7.6)	< 0.001
Summer	302,382 (91.8)	27,067 (8.2)	
Autumn	301,350 (92.3)	25,176 (7.7)	
Winter	272,160 (90.8)	27,511 (9.2)	
Overall	1,177,420 (91.9)	104,439 (8.1)	–

[a] Term birth indicates a live birth with 37 to 42 gestational weeks; Preterm birth indicates a live birth with 20 to < 37 gestational weeks.
[b] *p* value of chi-square test for categorical variable.
[c] Other occupations included individual business, housewife or other unspecific occupations.

Table 2
Percentile distribution of average temperature (°C) and air pollution during pregnancy by exposure period (μg/m^3).

Term	1th	5th	25th	50th	75th	95th	99th	IQR
Temperature								
1st Trimester	−2.5	2.2	9.5	17.5	24.4	28.2	29.9	14.9
2nd Trimester	−3.2	2.2	9.5	17.2	23.6	27.9	29.7	14.1
3rd Trimester	−4.5	1.2	8.9	17.5	24.0	27.6	29.8	15.1
Entire pregnancy	3.8	9.1	13.2	16.6	19.8	23.0	25.8	6.6
Air pollution ($PM_{2.5}$)								
1st Trimester	21.2	27.2	42.4	56.4	74.8	105.2	118.2	32.4
2nd Trimester	22.8	29.0	45.1	59.2	75.3	105.1	118.7	30.3
3rd Trimester	21.2	28.2	45.5	58.2	74.6	110.3	127.2	29.1
Entire pregnancy	26.5	33.8	49.7	62.8	76.7	90.2	97.1	27.0

* $PM_{2.5}$, particles with aerodynamic diameters ≤ 2.5; IQR, interquartile range; The 3rd trimester was defined as 6 weeks before delivery.

were defined as workers in the present study, women working as farmers tend to take part in agricultural activity, which may increase their exposure to cold-weather environments (e.g., high winds, rain/water exposure and low temperature). Chronic cold exposures can produce metabolic adjustments to keep thermal balance, which is also called as cold acclimatization (Castellani et al. 2016). For example, residents in cold climates reportedly maintain higher resting metabolic rates than subjects from temperate climates, enabling them to maintain warmer skin temperatures with less shivering during cold exposure (Young, 2011). Another study also reported that women who had more exposure to cold-weather environments exhibited greater tissue insulation, a measure of the individual's ability to resist body heat loss, than their counterparts (Hong, 1973). Conversely, they may be more susceptible to high temperatures due to the mentioned cold acclimatization. When look at the geographic variation, we also noticed that pregnant women living in temperature zone are more susceptible to high temperatures. The "acclimatization" is thought to be a key point to understand this phenomenon.

We found the effect of relatively low or high temperatures on pregnant women being overweight before conception was stronger than that on normal-weight women. Overweight before conception is an independent risk factor of preterm birth (McDonald et al. 2010), and previous studies also indicated that pre-pregnancy overweight women might be more sensitive to the inflammatory effects (Dong et al. 2015), which could be a reason for the enhanced effect among pregnant women who were overweight before conception. However, the mechanism behind the effect modification is unclear, which need further study.

There are three main advantages in the present study. First, the cohort study design, with the obviously spatial and temporal variation in exposure and large sample size, enabled us to evaluate effects of high or low temperature. Second, the model-based temperature, detailed personal addresses and the geographic information system technique used in present study allowed us to include participants in rural areas where do not have monitor station and enhance the accuracy of exposure assessment (He et al. 2016). Previous studies usually used the data from a few stations in the study city or nearest airport. Temperature may vary both spatially and temporally and the studies can result in considerable bias in exposure assessment. Kloog et al. compared the above methods and reported no association between temperature and preterm birth when they use the closest monitor temperature as exposure, but they do find significant association when they use model-based temperature as exposure (Kloog et al. 2015). Lastly, taken the advantages of cohort design, detailed individual adjustments such as kind of preterm birth (spontaneous preterm birth or iatrogenic preterm birth), pregnancy history, chronic illness, body mass index before conception, alcohol and tobacco assumption and socio-demographic status were considered in our analyses, which enhanced the chance to obtain effect estimates close to reality (Basu et al. 2017; He et al. 2016; Zhang et al. 2017). Based on the study findings, we suggest improving the women's awareness and behaviours of self-protection (e.g., controlling body weight before pregnancy, using air-conditioning or heating to build a micro-environment with suitable temperature and avoid exposure to relatively high and low temperature during pregnancy) from the adverse effect of temperature on the risk of preterm birth.

However, some limitations of the present study should be acknowledged. Even we use a model-based temperature and adjusted for maternal occupation in our analysis, the activity patterns of pregnant women may contribute to misclassification in exposure. Similarly, we did not have information on use of air conditioning or heating. Even most of the participants (greater than 90%) were rural residents, and the utilization rate of heating and conditioning was lower than urban residents, the absence of the information may mitigate the extreme heat and cold exposure. The absence of physical activity and dietary intakes, which may influence adverse birth outcomes, is also a limitation of the

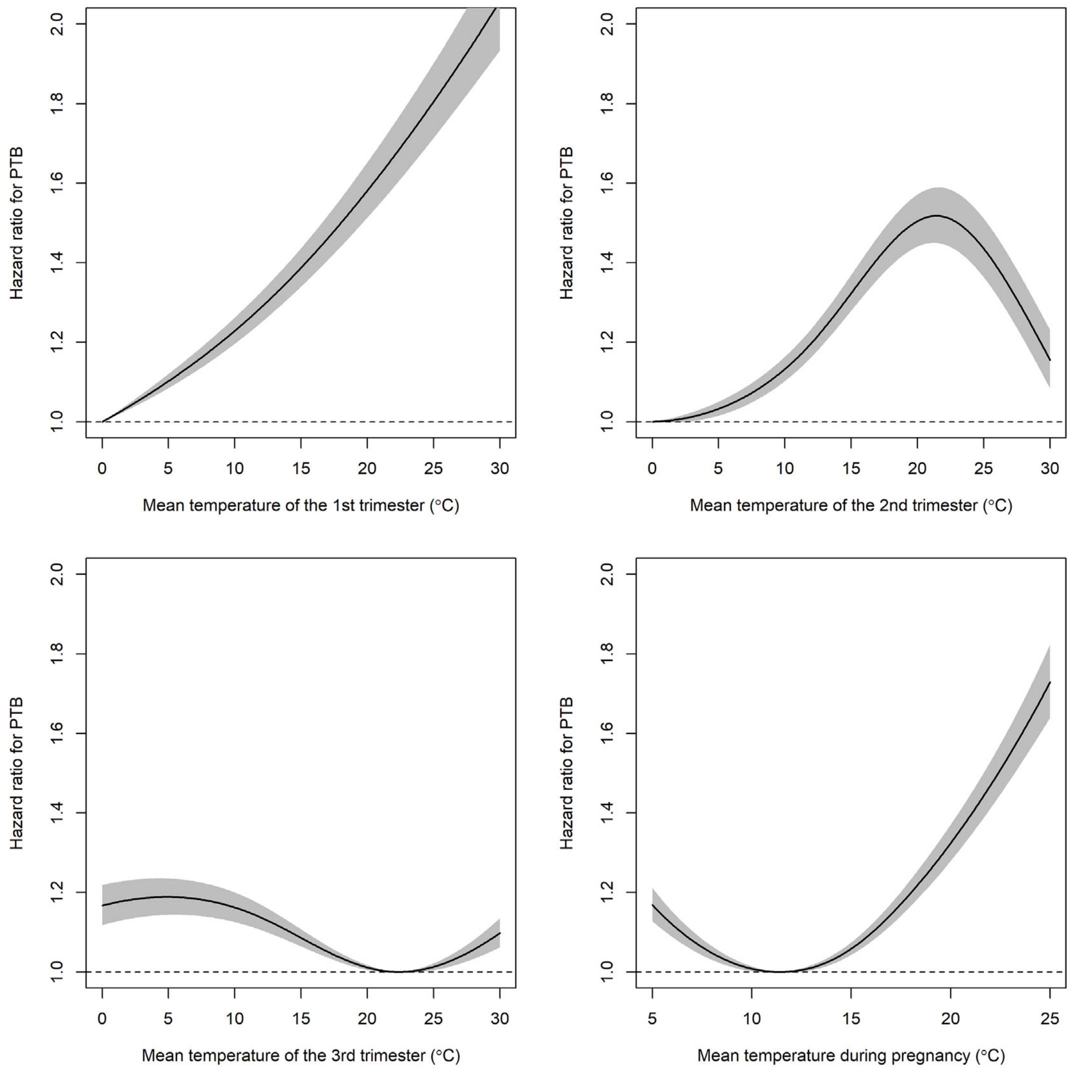

Fig. 2. Adjusted hazard ratio (solid line) and 95% confidence intervals (shadow area) for the association of temperature at each exposure window with risk of preterm birth. Legend: PTB, preterm birth; Cox proportion model adjusted for maternal age, household registration, education, occupation, pre-pregnancy BMI, organic solvent/heavy metals/pesticide exposure, smoking, drinking, mate smoking, conception season, air pollution and the random intercept for each province; Estimates are relative to the temperature with the minimum hazard rate.

Table 3
Adjusted hazard ratios (95% CIs) for the association of temperature during pregnancy with risk of preterm birth or early term birth [a.]

	1st trimester Tempera-ture (°C)	HR (95%CI)	2nd trimester Tempera-ture (°C)	HR (95%CI)	3rd trimester Tempera-ture (°C)	HR (95%CI)	Entire pregnancy Tempera-ture (°C)	HR (95%CI)
Preterm birth								
Threshold [b]	0.0	ref	0.2	ref	21.3	ref	12.0	ref
5th	2.2	1.04 (1.03, 1.05)	2.2	1.01 (1.00, 1.01)	1.2	1.17 (1.12, 1.22)	9.1	1.03 (1.02, 1.04)
25th	9.5	1.21 (1.18, 1.24)	9.5	1.14 (1.11, 1.17)	8.9	1.16 (1.13, 1.20)	13.2	1.01 (1.00, 1.01)
75th	24.4	1.78 (1.69, 1.87)	23.6	1.41 (1.34, 1.47)	24.0	1.01 (1.00, 1.02)	29.8	1.27 (1.23, 1.32)
95th	28.2	1.96 (1.85, 2.08)	27.9	1.30 (1.23, 1.38)	27.6	1.04 (1.02, 1.06)	23.0	1.55 (1.48, 1.61)

[a] Hazard ratios were based on Cox proportion model adjusted for maternal age, household registration, education, occupation, pre-pregnancy BMI, organic solvent/heavy metals/pesticide exposure, smoking, drinking, mate smoking, mode of delivery, air pollution and the random intercept for each province.
[b] The reference temperature (threshold) refers to the temperature with the minimum hazard of preterm birth or early term birth.

present study.

5. Conclusion

Exposure to relatively low or high temperatures during pregnancy was associated with an increased risk of preterm birth. Pregnant women are more susceptible to high temperature at the first and second trimester, while they are more susceptible to low temperature at the third trimester. The findings can serve as scientific evidence for prevention of preterm birth, especially for vulnerable populations.

Ethical approval

The institutional review board of the National Research Institution for Family Planning, Beijing, China, approved this study. All participants provided written informed consent.

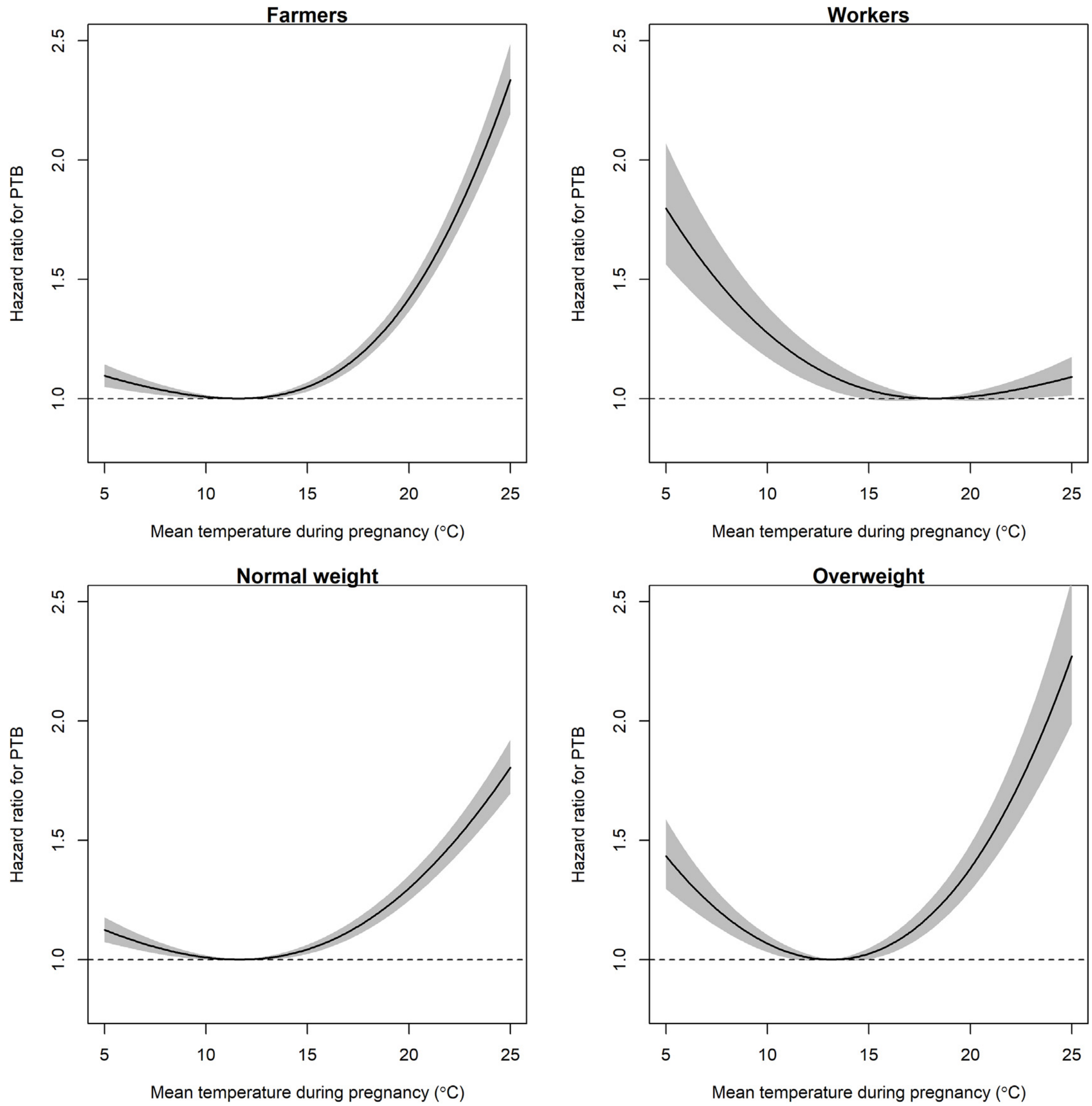

Fig. 3. Adjusted hazard ratio (solid line) and 95% confidence intervals (shadow area) for the association of temperature during entire pregnancy with risk of preterm birth among subgroups. Legend: PTB, preterm birth; Cox proportion model adjusted for maternal age, household registration, education, pre-pregnancy BMI, organic solvent/heavy metals/pesticide exposure, smoking, drinking, mate smoking, conception season, air pollution and the random intercept for each province, excepting the categorized variable; Estimates are relative to the temperature with the minimum hazard rate.

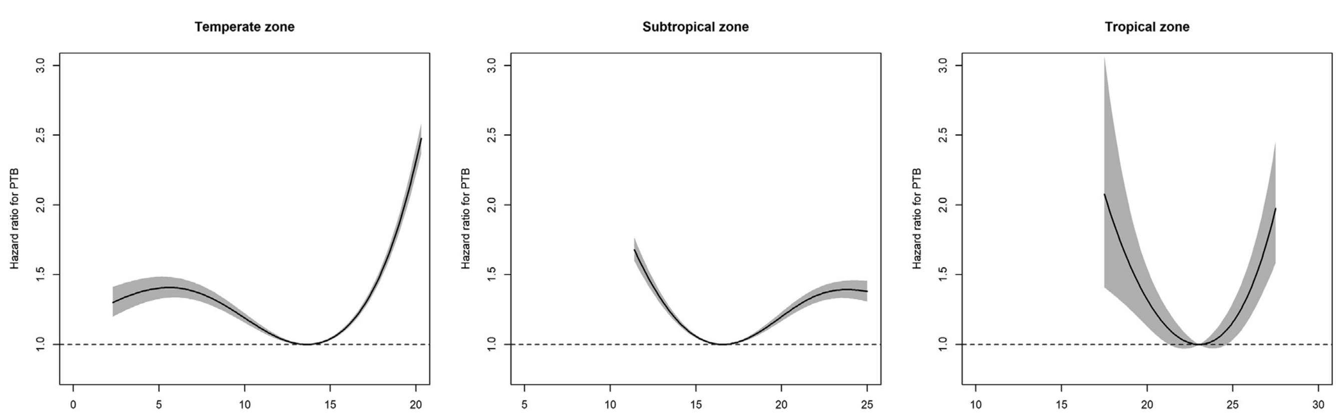

Fig. 4. Adjusted hazard ratio (solid line) and 95% confidence intervals (shadow area) for the association of temperature during entire pregnancy with risk of preterm birth among three climate zones. Legend: PTB, preterm birth; Cox proportion model adjusted for maternal age, household registration, education, occupation, pre-pregnancy BMI, organic solvent/heavy metals/pesticide exposure, smoking, drinking, mate smoking, conception season, air pollution and the random intercept for each province; Estimates are relative to the temperature with the minimum hazard rate.

Data sharing: No additional data available.

Transparency: The manuscript's guarantor (H.J. Wang and X. Ma) affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

CRediT authorship contribution statement

Yuan-Yuan Wang: Conceptualization, Data curation, Writing - review & editing. **Qin Li:** Conceptualization, Methodology, Formal analysis, Writing - original draft. **Yuming Guo:** Conceptualization, Environmental data curation, Writing - review & editing. **Hong Zhou:** Data curation, Writing - review & editing. **Qiao-Mei Wang:** Data curation, Writing - review & editing. **Hai-Ping Shen:** Data curation, Writing - review & editing. **Yi-Ping Zhang:** Data curation, Writing - review & editing. **Dong-Hai Yan:** Data curation, Writing - review & editing. **Shanshan Li:** Environmental data curation, Writing - review & editing. **Gongbo Chen:** Environmental data curation, Writing - review & editing. **Shuang Zhou:** Writing - review & editing. **Yuan He:** Data curation, Writing - review & editing. **Ying Yang:** Data curation, Writing - review & editing. **Zuo-Qi Peng:** Data curation, Writing - review & editing. **Hai-Jun Wang:** Conceptualization, Supervision, Project administration, Funding acquisition, Writing - review & editing. **Xu Ma:** Conceptualization, Project administration, Funding acquisition.

Declaration of Competing Interest

The authors declared that there is no conflict of interest.

Acknowledgements

YYW and XM were supported by the National Key Research and Development Program (No. 2016YFC1000300, No. 2016YFC1000307). QL and HJW were supported by the National Natural Science Foundation of China (81573170) and Beijing Natural Science Foundation (7162106), YG was supported by an Australian National Health and Medical Research Council Career Development Fellowship (APP1107107). SL was supported by the Early Career Fellowship of the Australian National Health and Medical Research Council (APP1109193) and Seed Funding from the National Health and Medical Research Council (NHMRC) Centre of Research Excellence (CRE)–Centre for Air quality and health Research and evaluation (CAR) (APP1030259). The funders had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; and preparation, review, or approval of the manuscript; and/or the decision to submit the manuscript for publication. We thank health professionals in 30 provinces across China for their great efforts in the NFPHEP project.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2020.105851.

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