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Running title: Ambient temperature and preterm birth

Abstract

Background: Although effects of weather changes on human health have been widely reported, there is limited information regarding effects on pregnant women in developing countries.

Objective: To investigate the association between maternal exposure to ambient temperature and the risk of preterm birth (< 37 weeks of gestation) in Guangzhou, China.

Methods: We used a Cox proportional hazards model to estimate associations between preterm birth and average temperature during each week of gestation, with weekly temperature modeled as a time-varying exposure during four time windows: 1-week, 4-week, late pregnancy (gestational week 20 onwards), and the entire pregnancy. Information on singleton vaginal birth between 2001 and 2011 was collected. Daily meteorological data during the same period were obtained from the Guangzhou Meteorological Bureau.

Results: A total of 838,146 singleton vaginal births were included, amongst which 47,209 (5.6%) were preterm births. High mean temperatures during the previous 4 weeks, late pregnancy, and the entire pregnancy were associated with an increased risk of preterm birth. Compared with the median temperature (24.4°C), weekly exposures during the past 4 weeks to extreme cold (7.6°C, the 1st percentile) and extreme heat (31.9°C, the 99th percentile) were associated with 17.9% (95% CI: 10.2, 26.2%) and 10.0% (95% CI: 2.9, 17.6%) increased risks of preterm birth, respectively. The association between extreme heat and preterm birth was stronger for preterm births during weeks 20–31 and 32–34 than those during weeks 35–36.

Conclusions: These findings might have important implications in preventing preterm birth in Guangzhou as well as other areas with similar weather conditions.

Introduction

Preterm birth, defined as birth < 37 completed weeks of gestation, is a complex syndrome and

remains a major global public health problem (Goldenberg et al. 2008; Muglia and Katz 2010). It

is estimated that approximately 15 million babies were born preterm in 2010 worldwide,

accounting for 11% of all live births (Blencowe et al. 2012). Preterm birth is associated with a

variety of adverse outcomes, including infant mortality, acute morbidity, long-term

neurocognitive disorders, poor growth, respiratory illnesses, behavioral problems and other

complications (Saigal and Doyle 2008). Although a number of risk factors have been explored

and relevant interventions have been developed, the incidence of preterm birth has been

increasing during the past two decades in most countries (Blencowe et al. 2012), indicating that

further research is needed to elucidate its etiology.

Seasonal weather changes have extensive effects on human health outcomes, especially for

overall mortality, infectious diseases and cardiovascular diseases (Woodward et al. 2014). As a

specific population, pregnant women might be susceptible to effects of weather changes.

Compared to elderly people, however, pregnant women have received less attention. Recently,

there is an emerging interest in examining the effects of environmental temperature on the risk of

preterm birth (Strand et al. 2011a). Several time-series studies observed that maternal short-term

exposure to high temperature was associated with an increased risk of preterm birth (Schifano et

al. 2013; Vicedo-Cabrera et al. 2014). On the other hand, negative results were also reported in a

few studies (Lee et al. 2008; Wolf and Armstrong 2012). Furthermore, a recent cohort study in

Sweden reported that extremely cold temperature was associated with an increased risk of

preterm birth (Bruckner et al. 2014). In the context of global climate change and high medical

cost for preterm birth, it is necessary to clarify the effects of environmental temperature on the

risk of preterm birth.

The most biologically relevant time period for effects of temperature on preterm birth is not

known. Previous studies mainly focused on the short-term exposure, which was defined as a few

days or weeks before delivery (Basu et al. 2010; Lee et al. 2008; Schifano et al. 2013;

Vicedo-Cabrera et al. 2014). Because long-term exposure to temperature might also be relevant

for preterm birth (Strand et al. 2011a), we used a Cox proportional hazards model with

gestational age as the time axis to evaluate the relationship between short- and long-term

temperature exposures and the risk of preterm birth from 2001 to 2011 in Guangzhou, a

subtropical city in China. Considering time-dependent exposures, the Cox proportional hazards

model has been shown to be useful for evaluating exposure windows for preterm birth (Chang et

al. 2012; Suh et al. 2009).

Animal studies suggested that high temperature exposure could lead to dehydration, reduce

uterine blood flow (Stan et al. 2013) and increase the secretion of proinflammatory cytokines and

oxytocin (Dreiling et al. 1991; Wolfenson et al. 1993), thereby inducing the uterine contraction

and onset of labor. Previous studies also proposed that cold temperature could lead to elevated

blood viscosity and vascular constriction (Bruckner et al. 2014) and increase exposure to risk

factors of preterm birth, such as passive smoking (Ronchetti et al. 1994) and infectious agents

(Murray et al. 2000). These studies suggested that temperature might affect the timing for

initiation of spontaneous labor. In the present study, we aimed to examine the effects of

temperature on the timing for natural labor. Similar to previous studies (Dadvand et al. 2011;

Murray et al. 2000; Schifano et al. 2013; Vicedo-Cabrera et al. 2014), we excluded cesarean

section deliveries as they would not reflect physiological mechanisms of temperature on

spontaneous birth timing.

Methods

Study population

Guangzhou is the largest metropolis in Southern China with a population of 12.9 million (Figure

1). It has a typical subtropical climate with mild winters and hot summers. Data on all singleton

births between January 1st, 2001 and December 31st, 2011 were collected from the Guangzhou

Perinatal Health Care and Delivery Surveillance System (GPHCDSS), which was initiated in

2000 and covered over 97% of deliveries in Guangzhou (Guo et al. 2014; He et al. 2014). In the

GPHCDSS, information on births is collected from hospitals via computer network and is used

to issue birth certificate. The information is confirmed by the Chief of Midwifes and the Chief of

Physicians in hospitals after data entry. When the birth certificate is issued, the Department of

Medical Administration and parents also confirm the birth information (Guo et al. 2014; He et al.

2014). Data obtained from GPHCDSS included date of birth, gestational age at birth, birth

weight, infant sex, maternal age, educational level, registered residence and parity. Registered

residence represents the permanent residence in the system of household registration (Hukou

system) in China, and generally categorized as rural and urban residence. Urban residents are

easier to get access to health services, medical insurance, education and other social welfare

(Wang 2005). The date of conception was calculated by subtracting the gestational age at birth from the date of birth.

All singleton vaginal births at the gestational age of 20-43 weeks were included in the present study. As the data were collected by the birth date, short pregnancies from the earliest possible conception dates that terminated before the start date of the study (January 1st, 2001) were not included in the analysis; similarly, long pregnancies from the latest possible conception dates that terminated after the end date of the study (December 31st, 2011) were also not included in the analysis (Barnett 2011; Strand et al. 2011b; Wolf and Armstrong 2012). As such, women included at the beginning of the study tend to have longer pregnancies, whereas those included at the end of the study tend to have shorter pregnancies (Barnett 2011; Strand et al. 2011b; Wolf and Armstrong 2012). This phenomenon could lead to artificial seasonal patterns in gestation length and distort the association between time-dependent exposures (e.g., temperature) and outcomes (Barnett 2011; Strand et al. 2011b). To avoid this potential "fixed cohort bias", we excluded those pregnancies conceived earlier than 20 weeks before the study's start date and those conceived later than 43 weeks before the study's end date to ensure that all pregnancies are entirely observable within the study period (Strand et al. 2012; Wolf and Armstrong 2012).

This study was approved by the institutional ethical committee board of Guangzhou Women and Children's Medical Center. Data used in this study were anonymous and no individual identifiable information was available for the analysis.

Outcome definition

Preterm birth was defined as birth < 37 completed weeks of gestation. Gestational age at birth

was determined according to an ultrasound examination in the first or second trimester (Fu and

Yu 2011). If the ultrasound examination was unavailable, the last menstrual period (LMP) was

used to calculate the gestational age. Preterm birth was also subdivided into three groups: 20-31,

32-34 and 35-36 weeks of gestation.

Meteorological and air pollution exposure

The daily meteorological data during the study period, including mean temperature (^{o}C) and

relative humidity (%), were collected from the Guangzhou Meteorological Bureau. The

meteorological data were recorded at a meteorological station in Guangzhou. Daily values for

temperature and relative humidity were calculated by averaging four measurements taken at

6-hour intervals over each 24-hour period. Daily air pollution data from 2006-2010 were

obtained from Environmental Monitoring Center, including particulate matter with an

aerodynamic diameter less than or equal to 10 μm (PM_{10}, μg/m^3), sulfur dioxide (SO_2, μg/m^3)

and nitrogen dioxide (NO_2, μg/m^3). Air pollution data were measured at a fixed environmental

monitoring station located in the center of Guangzhou. The monitoring station providing

meteorological and air pollution data follows the quality assurance and quality control programs

that were mandated by the Chinese government. These data on temperature and air pollution

have been widely used to explore their effects on mortality in Guangzhou (Liu et al. 2014; Xie et

al. 2013; Zeng et al. 2014).

We used the estimated date of conception to determine the start and end date of each gestational week for each pregnancy. We then derived the weekly average temperature during each gestational week by averaging the daily mean temperature on the last day of the corresponding gestational week and the 6 previous days (Chang et al. 2012). We used the same approach to estimate weekly average values for relative humidity, PM_{10}, SO_2, and NO_2 for each completed gestational week of pregnancy.

Statistical analysis

We used a Cox proportional hazards model with gestational age as the time axis and preterm birth as the outcome. Term births were censored at the end of the 36th week of gestation, as they were no longer at risk of being born preterm (Bruckner et al. 2014; Chang et al. 2012). We modeled weekly average temperature as a time-varying independent variable to estimate the hazard of preterm birth during each gestational week t in association with temperature during four exposure windows: 1) 1-week (the weekly mean temperature during week t); 2) 4-week (weekly mean temperature for each gestational week from week t–3 through t); 3) late pregnancy (weekly mean temperature for each gestational week from week 20 through week t) and 4) cumulative (weekly mean temperature for each gestational week from week 1 through week t) (Chang et al. 2012; Strand et al. 2012).

We modeled time-varying weekly temperatures during each time window as a cubic spline with 3 degrees of freedom to allow a nonlinear relationship with preterm birth, and plotted the resulting hazard ratios (HRs) and 95% confidence interval (CIs) to show the relationship over the entire temperature distribution. In addition, we calculated specific HRs relative to the local

median temperature (24.4 ^{o}C) for locally extreme cold (defined as the 1st percentile of

temperature, 7.6 ^{o}C) and moderate cold (the 5th percentile, 11.2 ^{o}C), and for locally extreme heat

(the 99th percentile, 31.9 ^{o}C) and moderate heat (the 95th percentile, 30.7 ^{o}C) (Chen et al. 2013).

In addition to estimating associations with all preterm births, we performed stratified analyses to

estimate associations with three preterm birth subgroups (births during gestational weeks 20–31,

32–34, and 35–36).

Maternal age was categorized into three groups (<20, 20–34, and >34 years) and included in

the model as a stratified variable (Wang et al. 2013), since we observed that both women aged

<20 and >34 years had higher risk of preterm birth. The following socio-demographic variables

were adjusted for: maternal education level (high school or below vs college, undergraduate,

master or above), parity (primiparity vs multiparity) and baby's sex (male vs female). To control

for long-term trend and seasonality, we included the year of conception and the month of

conception as indicator variables. Similar to the temperature, the relative humidity was included

as a time-dependent variable at each exposure windows using a spline with 3 degrees of freedom.

Sensitivity analyses were performed to evaluate the robustness of results. We included the

month of conception as a spline with 3 to 6 degrees of freedom. For pregnancies that took place

during 2006 to 2010, we performed separate models adjusted for weekly average concentrations

of $PM_{10,}$ SO_2 and NO_2 as time-varying covariates, using time windows corresponding to those

used for temperature. However, because air pollution exposures might be causal intermediates

between temperature and preterm birth, adjustment may block part of the total effects of

temperature (Buckley et al. 2014). Finally, we used a quasi-Poisson regression with distributed

lag non-linear model (DLNM) as an alternative approach to estimate the cumulative effects of

low and high temperatures on preterm birth for single-day lags (lag 0, representing temperature

on the same day of preterm birth, up to 27-day lag) and during three cumulative lag periods (lag

0–6, 0–13, and 0–27 days, where lag 0–6 represents the temperature on the day of preterm birth

and the previous 6 days , and so forth) (Gasparrini et al. 2010). The model used for analysis was:

$$\text{Log } [E(Y_t)] = \alpha + \beta \text{Temp}_{t,l} + NS(RH_t, 5) + NS(\text{Time}, 5/\text{year}) + \gamma DOW_t + \delta \text{Log}(Z_t),$$

where t represents the day of the observation; Y_t is the observed number of preterm births on day

t, $Temp_{t,l}$ is a matrix representing the two-dimensional relationship of mean temperature and lag

days, l denotes the maximum lag days, $NS(RH_t, 5)$ is a natural cubic spline with 5df for relative

humidity, $NS(Time, 5/year)$ is a natural cubic spline with 5 df/year for long-term trend and

seasonality, and DOW_t is the day of the week (a categorical variable with Sunday as the

reference). Z_t is a daily expected count of preterm births on day t:

$$Z_t = \sum_{j=20}^{36} \left(Z_{jt} \times W_j \right),$$

where Z_{jt} is the number of pregnancies at risk during gestational week j (ranging from 20 through

36 weeks) on day t, and W_j is the conditional probability of birth during gestational week j, as

proposed by Vicedo-Cabrera et al. (Vicedo-Cabrera et al. 2014). The Quasi-Akaike Information

Criteria (QAIC) was used to choose the df for temperature and lags (Gasparrini et al. 2010; Peng

et al. 2006), and the final model used a natural cubic spline with 4 df to estimate the nonlinear

effect of temperature, and 4 df to estimate the lag effects. We plotted relative risks (RRs) across

the entire temperature distribution for single-day lags, and estimated specific RRs for extremely low and high temperatures relative to the median (24.4 $^{\circ}$C) for the three cumulative lags.

All statistical analyses were performed using SAS statistical software version 9.3 (SAS Institute, Cary, NC) and the R statistical environment (version 2.15) (R Core Team 2013) with the smoothHR (Meira-Machado et al. 2013) and DLNM packages.

Results

A total of 1,420,348 singleton births at the gestational age of 20-43 weeks were recorded during the study period. After exclusion of 582,202 cesarean section births (with preterm birth rate, 5.2%), 838,146 singleton vaginal births were included in this study. Among them, 47,209 (5.6%) were preterm births, with a daily average of 11.8 preterm births. The demographic characteristics of the study population are shown in Table 1. Compared to the mothers of term babies, those of preterm babies tended to be primiparous and have higher percentage of age <20 and >34 years. Male infants were more likely to be born preterm. Preterm babies had a slightly higher percentage of being born in winter (December-February) (Table 1). The distributions of educational level and registered residence were similar between the preterm birth and term birth groups (Table 1).

The median of daily mean temperature and relative humidity was 24.4 $^{\circ}$C and 74% during the study period. The Spearman's correlations showed a week correlation between mean temperature and relative humidity (r_s, 0.098). Figure 2 shows the 11-year time series of temperature and preterm birth rate, which was calculated by dividing daily counts of preterm birth by daily births. The daily mean temperature was lowest in December and January and

peaked in July and August (Figure 2). The daily rate of preterm births appeared to be relatively

high in January to March, although the yearly variations were not completely consistent over the

study period (Figure 2).

Figure 3 shows adjusted HRs for weekly mean temperatures, relative to 24.4 ^{o}C, during

different exposure windows. Associations were U-shaped, with significant associations between

preterm birth risk and cold temperatures during all four time-windows, and significant

associations with high temperatures during the 4-week, late pregnancy ($\geq$20 weeks), and

cumulative (entire pregnancy) time windows, but not the 1-week time window. Associations

with extremely and moderately low and high temperatures were strongest for temperature during

the 4-week time window, and HRs for low temperatures were larger than corresponding HRs for

high temperatures during all time windows (Table 2). For example, relative to 24.4 ^{o}C, exposures

to extreme cold (7.6 ^{o}C) and extreme heat (31.9 ^{o}C) during the 4-week time window were

associated with 17.9% (95% CI: 10.2, 26.2%) and 10.0% (95% CI: 2.9, 17.6%) higher risks of

preterm birth, respectively.

Figure 4 presents the stratified relationship of preterm birth subgroups with the mean

temperature. Generally, the shapes of stratified relationships were similar to those in the overall

analysis. Associations with higher temperatures were stronger for preterm births during weeks

20–31 (n = 4988 preterm births) and 32–34 (n = 11,323) compared with preterm births during

weeks 35–36 (n = 30,898), though estimates for later preterm births were more precise, at least in

part due to larger numbers of observations (Figure 4) . Specifically, the HRs (95% CIs) of

extremely high temperature for preterm births during weeks 20-31 and 32-34 were 1.45 (95% CI:

1.15, 1.83) and 1.29 (95% CI: 1.08, 1.54) at the 4-week time window, respectively, while that

during weeks 35-36 was 1.08 (95% CI: 0.97, 1.21).

In the sensitivity analyses, we included the month as a spline with 3-6 degrees of freedom,

and the effect estimates for temperature remained similar (see Supplemental Material, Table S1).

HRs for temperature and preterm among pregnancies during 2006–2010 (n=450,230, including

25,329 preterm births) after adjustment for weekly average PM_{10}, SO_2, and NO_2 concentrations

during time windows corresponding to those for temperature were similar to those for overall

study population, although HRs were slightly attenuated and less precise after adjustment.

However, these differences may be at least partly due to the use of a different population

(2006-2010 vs 2001-2011), rather than being due to effects of adjustment for air pollutants per se

(see Supplemental Material, Figure S1).

Associations between preterm and temperature also tended to be U-shaped when estimated

using a quasi-Poisson regression with DLNM (Supplemental Material, Figure S2). Associations

with extreme cold and extreme heat both were strongest for temperature on the same day of

preterm birth (lag 0) and null after 4- and 6- day lags, respectively. The association with extreme

cold was strongest for the longest cumulative lag (lag 0–27), while HRs for extreme heat

were >1 at lag 0-6 but <1 for longer cumulative lags (Supplemental Material, Table S2).

Discussion

In the present study, both low and high temperatures during pregnancy were associated with an

increased risk of preterm birth. Extreme cold temperatures were associated with the risk of

preterm birth during all time windows examined (1-week, 4-week, late pregnancy, and entire

pregnancy), and extreme heat was associated with preterm birth risk during all but the shortest

time window of exposure. Furthermore, extreme heat was more strongly associated with preterm

births during 20–31 and 32–34 weeks of gestation than with preterm births during weeks 35–36.

To our knowledge, this study might be the first one to investigate the effects of ambient

temperature on the risk of preterm birth in developing countries (Beltran et al. 2013). Compared

to developed countries, air conditioning or central heating is less used in developing countries;

thus the population may be more susceptible to climate change, and the harmful effects of

extreme temperature on health may be more pronounced. Using the time-to-event model, we also

extended earlier work by examining different temperature exposure windows, including both

short- and long-term exposures. Moreover, our study has a larger sample size compared to

previous studies, which enabled us to evaluate expected subtle effects of temperature.

The prevalence of preterm birth among singleton in the study area (5.6% for vaginal

delivery, 5.2% for C-section delivery) was similar to those of previous reports in Guangzhou

(5.1%~6.4% from 2002 to 2012) (Fu and Yu 2011; Guo et al. 2014), Korea (5.3% in 2008) (Park

et al. 2013) and Japan (5.7% in 2012) (Vital Statistics 2009), which were lower than that of the

United States (9.7% in 2013) (Martin et al. 2015). The rate of preterm birth in China is lower

than some western countries. This may be explained by several factors, including genetic

predisposition (namely black women tend to have higher rates of preterm birth than other ethnic

groups) (Goldenberg et al. 2008), early prenatal identification and termination of pregnancies

with significant fetal anomalies that might otherwise result in a preterm birth (Purisch et al.

2008), and lower prevalence of risk factors, such as maternal advanced age and active smoking

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(Beck et al. 2010; Goldenberg et al. 2008). Furthermore, we did not observe significant differences in maternal educational level and status of registered residence between preterm birth and term birth subjects. This might be in part explained by implementation of several public health programs to promote maternal and children's health in Guangzhou, which improved the equality for access to antenatal care service among different social economic statuses.

Few studies have explored the effects of ambient temperature on the rate of preterm birth with inconsistent results (Strand et al. 2011a). Two large studies, conducted in London, UK and two German states, did not find any association between temperature and the risk of preterm birth (Lee et al. 2008; Wolf and Armstrong 2012). Nevertheless, a study in Rome, Italy reported a 1°C increase in maximum apparent temperature at lag 0-2 resulted in an increase of 1.9% in daily preterm birth in warm season (Schifano et al. 2013). In addition, a study in California showed that every 5.6^{o}C increase in apparent temperature at lag 0-6 increased preterm births by 8.6% (Basu et al. 2010). In the present study, we observed a U-shaped relationship between temperature and preterm birth over the whole year. This finding was in accordance with a recent study in Sweden, which also found that both cold and warm temperature extremes were associated with an increased risk of preterm birth (Bruckner et al. 2014). Furthermore, we observed association of extreme cold with preterm birth risk was stronger than that with extreme heat, although the low temperature is mild in our study region. This result might be explained by the fact that the population in Guangzhou, a subtropical city, is less accustomed to cold weather, and thus more susceptible to cold stress. In addition, central heating is rarely used in subtropical areas such as Guangzhou, which may lead to greater adverse effects of extremely cold weather on health (Xie et al. 2013).

There were several potential reasons for differences between our findings and those of

previous studies. Firstly, the range of climatic conditions, socio-economical level and population

susceptibility might vary across areas. In addition, we speculate that the study design, statistical

methods, exposure windows and sample size are important factors (Strand et al. 2011a). For

example, previous studies have examined non-linear relationships using logistic regression (Basu

et al. 2010; Lee et al. 2008; Wolf and Armstrong 2012), Cox proportional hazards model

(Bruckner et al. 2014; Strand et al. 2012), and Poisson generalized additive model (Schifano et al.

2013), while the delayed effects have been estimated using single-day lags and moving average

lags (Basu et al. 2010), distributed lag model (Schifano et al. 2013) or distributed lag non-linear

models (Vicedo-Cabrera et al. 2014). In the present study, estimates from both the Cox

proportional hazards model and the quasi-Poisson regression with DLNM indicated U-shaped

associations between preterm and mean temperature, though associations based on the

quasi-Poisson regression with DLNM showed were strongest for recent exposures (single-day

lags < 1 week), while high temperatures during the 1-week time window were not significantly

associated with preterm based on the Cox proportional hazards model. This indicated that

different statistical methods used might result in different estimates, even in the same study

population. Compared to other statistical methods, the Cox proportional hazards model has

several advantages. For example, considering time-varying exposures, the time-to-event analysis

could effectively evaluate both long- and short-term exposure windows (Chang et al. 2012; Suh

et al. 2009). Furthermore, the time-dependent survival analysis could also eliminate potential

confounding, which is caused by seasonal variation in the gestational age distribution of

pregnancies at risk (<37 weeks) and the increasing probability of birth with higher gestational

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age (Darrow et al. 2009), by comparing fetuses at the same gestational age (Strand et al. 2012).

Therefore, the Cox proportional hazards model has been recommended for future studies of

time-dependent exposures on preterm birth (Chang et al. 2012; Strand et al. 2012).

Biological mechanisms that might contribute to the association between ambient

temperature and preterm birth are unclear. Previous studies proposed several hypotheses. High

temperature exposure causes dehydration and reduces uterine blood flow in pregnant women,

which can induce the uterine contraction and onset of labor (Basu et al. 2010; Stan et al. 2013).

In addition, animal studies showed that heat exposure may increase the secretion of

proinflammatory cytokines and oxytocin to induce labor (Dadvand et al. 2011; Dreiling et al.

1991; Wolfenson et al. 1993). Furthermore, high temperature may increase blood viscosity and

cholesterol levels, which may be risk factors of preterm birth (Basu et al. 2010). In our study

population, extreme cold (7.6 ^{o}C) also was associated with preterm birth. There are several

explanations for the association of low temperature. Previous studies showed that cold

temperature could increase exposure to passive smoking (Ronchetti et al. 1994) and infectious

agents(Murray et al. 2000), and result in occurrence of pre-eclampsia and pregnancy-induced

hypertension (Bider et al. 1991), all of which are potential risk factors of preterm birth

(Goldenberg et al. 2008; Muglia and Katz 2010). In addition, cold temperature could also lead to

increased blood viscosity and vascular constriction (Bruckner et al. 2014), and thus might be

associated with an increased risk of preterm birth (Basu et al. 2010). Taken together, there are

many potential pathways through which temperature can affect the risk of preterm birth. Further

studies are needed to elucidate the underlying mechanisms.

Several limitations should be mentioned. First, we used data from one meteorological station to define the exposure for all women in Guangzhou. This could cause exposure misclassification. Second, we were unable to distinguish spontaneous preterm birth from iatrogenic preterm birth, although we restricted the study population to those with vaginal delivery. Exposure to temperature might have different effects on these subtypes of preterm birth. We have no data on the percentages of identification method of gestational age (LMP, clinical estimate, ultrasound) and their changes during the study period, which might influence the incidence of early preterm birth and late preterm birth. In Guangzhou, it is a routine practice to confirm gestational age using ultrasound examination in the first or second trimester (Fu and Yu 2011). However, some clinicians in poor rural areas might still be using the LMP-based or clinical estimation-based methods (estimated as <10% of all births). We also did not have information on the history of preterm delivery and pregnancy complications, all of which are potential risk factors for preterm birth. Finally, we are unable to distinguish the consequences of the temperature itself with other factors associated with changes in weather, such as nutrition, activity, and infectious exposures.

Conclusions

Exposure to both low and high temperatures during pregnancy was associated with an increased risk of preterm birth in our study population. These findings might have important implications in preventing preterm birth in Guangzhou as well as other areas with similar variations in weather conditions.

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Table 1. Characteristics of study population (2001-2011)

Characteristics	Preterm birth (n, %)	Term birth (n, %)
Total	47209 (5.6)	790937 (94.4)
Maternal age (years)		
<20	2415 (5.2)	27707 (3.5)
20-34	41017 (88.8)	719379 (91.9)
>34	2738 (5.9)	35613 (4.6)
Missing	1039	8238
mean (SD)	26.3 (4.7)	26.3 (4.4)
Educational level		
High school or below	41040 (86.9)	684596 (86.6)
College	3865 (8.2)	66272 (8.4)
Undergraduate	2037 (4.3)	35079 (4.4)
Master or above	267 (0.6)	4990 (0.6)
Registered residence [a]		
Rural	12411 (26.5)	207030 (26.3)
Urban	34430 (73.5)	580283 (73.7)
Missing	368	3624
Parity		
Primiparity	32404 (68.6)	510836 (64.6)
Multiparity	14805 (31.4)	280101 (35.4)
Baby's sex		
Male	27686 (58.7)	418262 (52.9)
Female	19523 (41.4)	372675 (47.1)
Birth weight (g)		
mean (SD)	2419 (529)	3193 (381)
Season of birth		
December-February	11836 (25.1)	188216 (23.8)
March-May	9677 (20.5)	165003 (20.9)
June-August	12198 (25.8)	202342 (25.6)
September-November	13498 (28.6)	235376 (29.8)
Preterm birth subgroups (weeks of gestation)		
20-31	4988 (10.6)	
32-34	11323 (24.0)	
35-36	30898 (65.5)	

[a]Registered residence represents the permanent residence in the system of household registration (Hukou system) in China.

Table 2. Adjusted hazard ratios (95% CI) for preterm birth in association with low and high temperatures during different time-windows of pregnancy.

Temperature[a]	Hazard ratios (95% confidence intervals)[b]			
	1-week	4-week	Late pregnancy	Cumulative
Extreme cold	1.143 (1.090,1.200)	1.179 (1.102,1.262)	1.124 (1.046,1.207)	1.123 (1.046,1.207)
Moderate cold	1.100 (1.063,1.140)	1.129 (1.074,1.187)	1.087 (1.030,1.148)	1.088 (1.031,1.148)
Moderate heat	1.019 (0.984,1.056)	1.075 (1.020,1.132)	1.073 (1.016,1.133)	1.074 (1.016,1.135)
Extreme heat	1.026 (0.981,1.074)	1.100 (1.029,1.176)	1.095 (1.021,1.175)	1.096 (1.022,1.175)

[a]Extreme cold, moderate cold, moderate heat and extreme hot were defined as local 1st (7.6°C), 5th (11.2°C), 95th (30.7°C) and 99th (31.9°C) percentile temperature over 11-year period, respectively.

[b]Hazard ratios are based on Cox proportional hazards models with average weekly temperatures modeled as time-dependent variables for exposures during four time windows: 1-week (average weekly temperature during the current week), 4-week (temperature during the current and 3 previous weeks), late pregnancy (average weekly temperatures for gestational week 20 through week 36 or birth), and cumulative (average weekly temperatures for gestational week 1 through week 36 or birth). Data for term births are censored after the 36th week of pregnancy. Estimates are relative to the median temperature for the study area (24.4°C). The following variables were adjusted for: maternal age, education, and parity, baby's sex, year and month of conception, and relative humidity (during the corresponding time window).

Figure Legends

Figure 1. Location of the study area (Guangzhou) in China.

Figure 2. Daily temperature (^{o}C) and preterm birth rate (%) over the study period. The red line represents the temperature and the black line represents the preterm birth rate.

Figure 3. Adjusted hazard ratios (solid line) and 95% confidence intervals (dashed lines) for preterm birth in association with weekly average temperature modeled as a time-dependent variable during 4 time windows: 1-week (A), 4-week (B), late pregnancy (C), and cumulative (D). Estimates are relative to the median temperature for the study area (24.4^{o}C). All values are based on Cox proportional hazards models with gestational age as the underlying time axis and adjusted for maternal age, education, parity, baby's sex, year and month of conception, and relative humidity (during the corresponding time window).

Figure 4. Adjusted hazard ratios (solid line) and 95% confidence intervals (dashed lines) for preterm birth (during weeks 20–31, 32–34, and 35–36) in association with weekly average temperature modeled as a time-dependent variable during 4 time windows: 1-week (A), 4-week (B), late pregnancy (C), and cumulative (D). Estimates are relative to the median temperature for the study area (24.4^{o}C). All values are based on Cox proportional hazards models with gestational age as the underlying time axis and adjusted for maternal age, education, parity, baby's sex, year and month of conception, and relative humidity (during the corresponding time window).
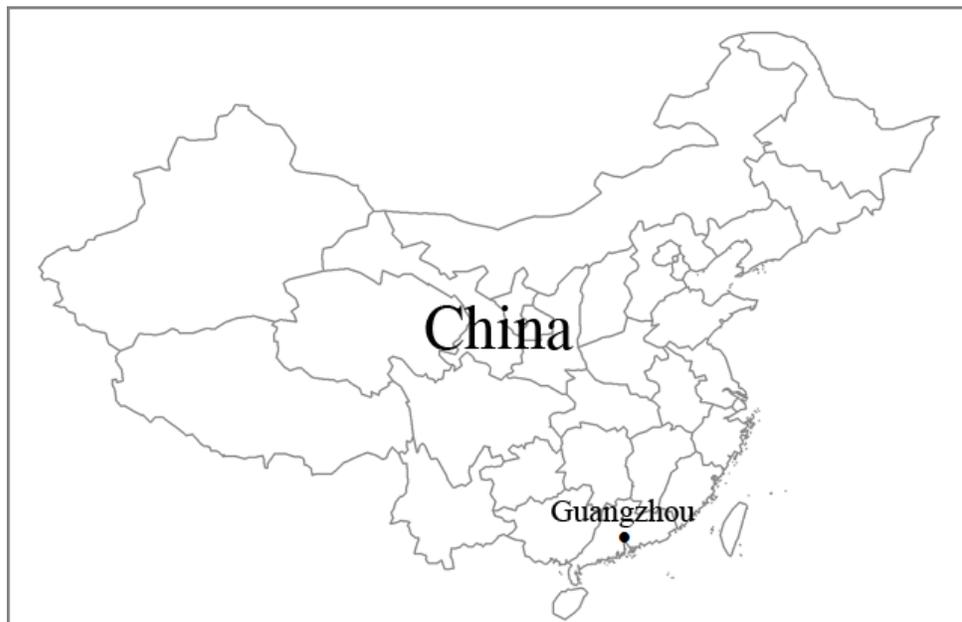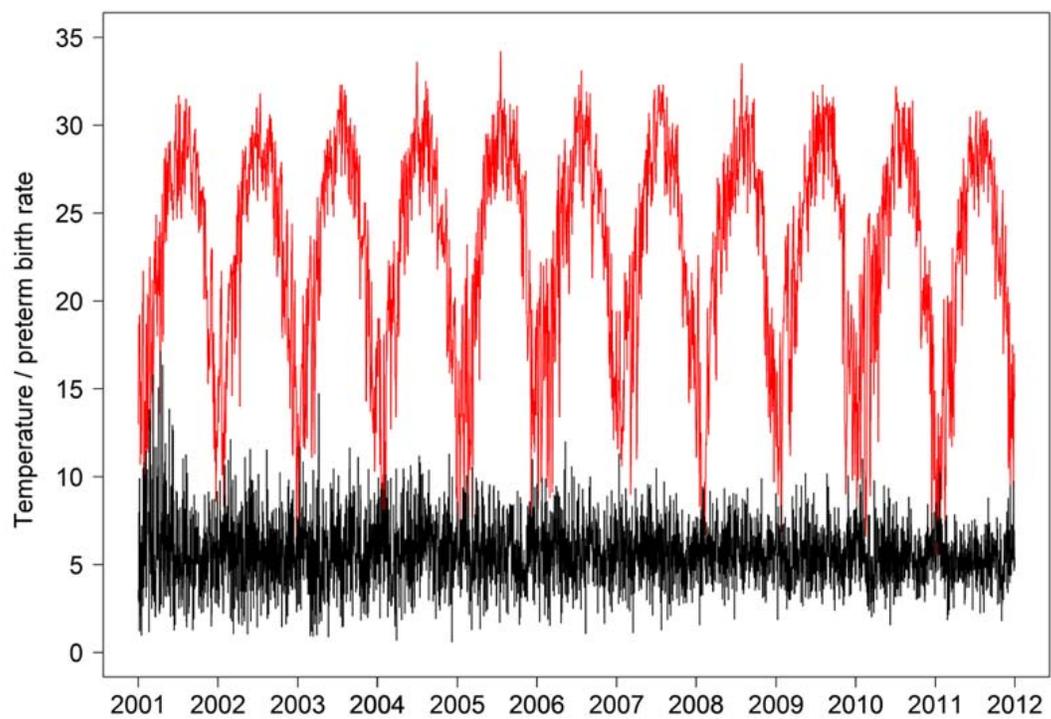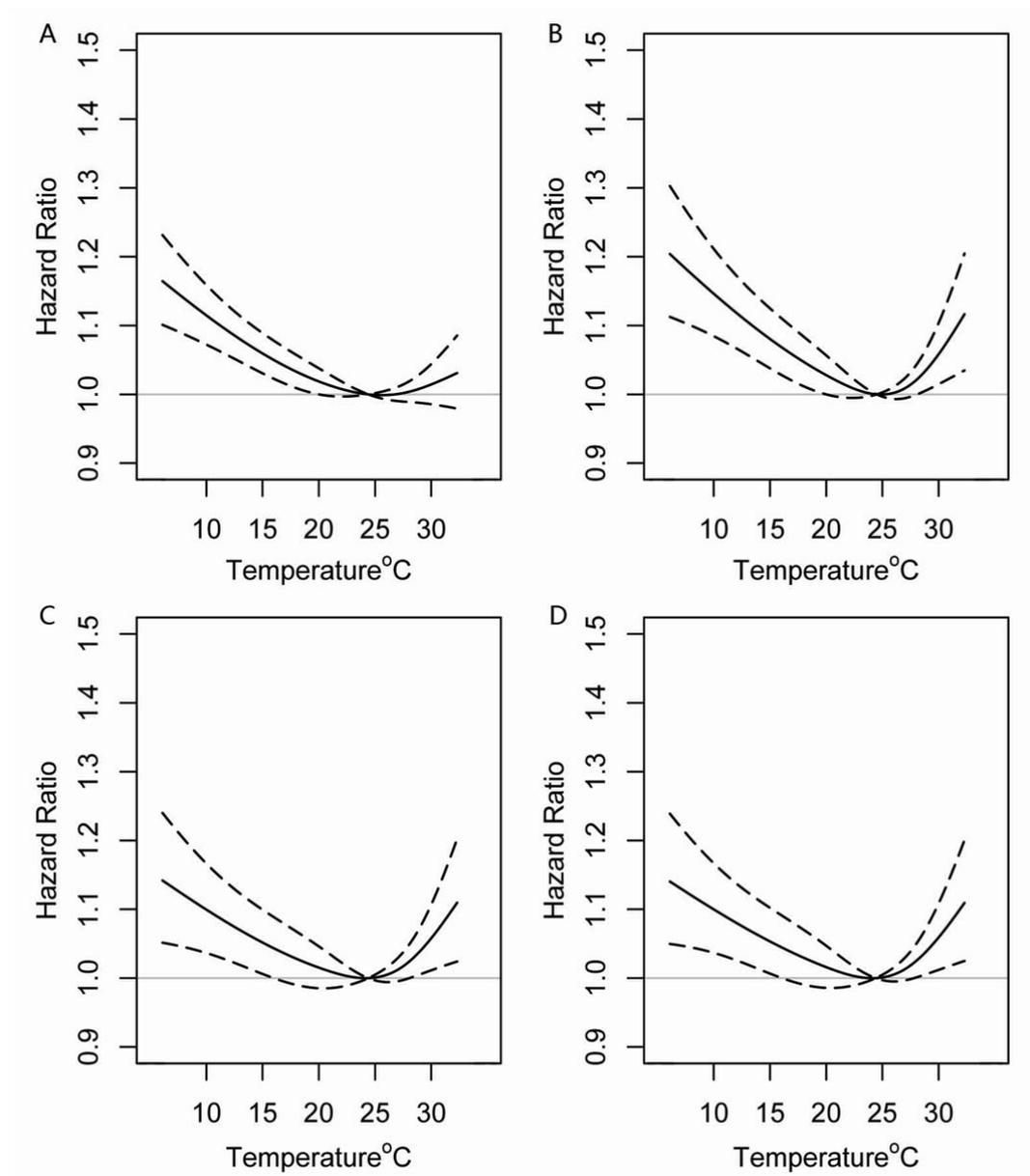
Figure 1.

Figure 2.

Figure 3.

Figure 4.