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Chapter 4 Maternal exposure to heatwave and preterm birth in Brisbane, Australia

Title Page

Article title: Maternal Exposure to Heatwave and Preterm Birth

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ABSTRACT

Objective: To quantify the short-term effects of maternal exposure to heatwave on preterm birth.

Design: An ecological study

Setting: A population-based study in Brisbane, Australia.

Population: All pregnant women who had a spontaneous singleton live birth in Brisbane between November to March in 2000-2010 were studied.

Methods: Daily data on pregnancy outcomes, meteorological factors and ambient air pollutants were obtained. The Cox proportional hazards regression model with time-dependent variables was used in this study to examine the short-term impact of heatwave on preterm birth. A series of cut-off temperatures and duration were used to define heatwave. Multivariable analyses were also done to adjust for socio-economic factors, demographic factors, meteorological factors and ambient air pollutants.

Main outcome measure: Spontaneous preterm births

Results: The adjusted hazard ratios (HRs) ranged from 1.13 (95% confidence interval (95%CI): 1.03-1.24) to 2.00 (95%CI: 1.37, 2.91) by using different heatwave definitions after controlling demographic, socio-economic factors, meteorological factors and air pollutants.

Conclusion: Heatwave was significantly associated with preterm birth; the associations were robust to the definitions of heatwave. The threshold temperatures, instead of duration, could be more likely to influence the evaluation of birth-related heatwaves. The findings of this study may have significant public health implications as climate change progresses.
Keywords: Preterm birth, heatwave, survival analysis, hazards ratio
Preterm birth is defined as a live childbirth occurring at less than 37 completed weeks or 259 days of gestation according to the definition of the World Health Organization. Children who are born preterm are more likely to experience early death, respiratory illnesses, neurodevelopmental disorders, lower cognitive abilities, and even increased behavioural problems. In addition to possible physical and psychological damage to a child’s health, it also may increase the economic burdens of the families in terms of more health care costs and/or educational expenditure.

There are three types of preterm birth: spontaneous preterm birth; medically indicated preterm birth as well as maternal elective preterm birth; and caesarean preterm birth.

Preterm birth is associated with a variety of factors, including genetic, socio-demographic, behavioural and environmental factors. In recent decades, the impact of ambient temperature on preterm birth has been increasingly recognised. However, the findings on how and to what extent ambient temperature might influence gestational age have been inconsistent. A time-stratified case-crossover analysis using almost 60,000 births occurred between May and September during 1999-2006 in California found that with a 5.6°C increase in weekly average (the cumulative average weekly lag) apparent temperature, the incidence of the preterm delivery increased by 8.6% (95% CI: 6.0%-11.3%). In contrast, the time-series analysis of short-term effects of meteorological factors on preterm births in London revealed that the risk of preterm birth did not increase when pregnant women were exposed to higher temperature through analyzing a large dataset which including 482,568 births covering 13 years.

Although the exact biological mechanism by which heatwave leads to preterm birth is still unknown, several animal experiments and human trials have been done to investigate this issue. An animal study on maternal endocrine and fetal metabolic response to heat stress
showed that heat stress could induce the hypersecretion of antidiuretic hormone (ADH) and oxytocin (OT), which either individually or collectively or might decrease the uterine blood flow (UBF), shift fetal metabolic pathways from anabolic to catabolic and then result in preterm birth\textsuperscript{17} (Figure 1).

Climate change has been accelerating over recent years\textsuperscript{18}. Heatwave will be one of the important public health challenges of this century as a consequence of the overall global warming, and the increased frequency, intensity and duration of extreme events. The definition of heatwave generally involves two indispensable aspects: the temperature exceeding a specific absolute temperature or percentile of the temperature distribution and the prolonged existence of the heat event\textsuperscript{19}. Some previous studies focused on the association between heatwave and health outcomes such as deaths and emergency hospital admissions showed that even a small change in the definition of heatwave can lead to considerable difference in the risk estimates of heatwave\textsuperscript{20, 21}. To our knowledge, several studies have examined the associations between high temperature or heat stress and preterm\textsuperscript{14, 22, 23}, but none of them have taken the duration of heat events into account. This study investigated the effects of heatwave on preterm birth during 2000-2010 in Brisbane, Australia. In addition, we examined how the birth-related effects of heatwave changed when different temperature thresholds and durations were utilized to define a heatwave.

**METHODS**

**Birth cohort** Data on all singleton births in Brisbane from 1\textsuperscript{st} January 2000 to 31\textsuperscript{st} December 2010 were collected from the Data Collections Unit (DCU) of the Queensland Health Statistics Centre, which recording antenatal, intrapartum and postpartum data of all live births, and stillbirths of at least 20 weeks gestation and/or at least 400 grams in weight, born in Queensland. The dataset we collected included the following variables: date of birth,
gestational age in weeks, gender of baby, weight of baby, onset of labour (spontaneous, induced and caesarean), mother’s residential area (post code), maternal age group, marital status, indigenous status and parity. We only included spontaneous live births which accounted for 56% of all births in this study to gain more accurate estimation of gestational effects attributed to heatwave as most induced and caesarean births were medically indicated. In addition, to focus on heatwave exposure as was done in another study \(^{14}\), only spontaneous births which occurred in warm seasons (1\(^{st}\) November- 31\(^{th}\) March) were used in our final analysis.

**Environmental exposure** As the earliest conception date of pregnant women in the birth cohort was 13\(^{th}\), March 1999; we collected the environmental data from 1999 to 2010 to get the information on environmental exposure for the whole pregnancy period. Data on meteorological factors which contain daily maximum temperature, relative humidity and ambient barometric pressure from eight monitoring stations in Brisbane during 1999-2010 were obtained from the Australian Bureau of Meteorology. We used nine definitions of heatwave in this study through combining a series of cut-off percentiles and different durations: daily maximum temperature exceeding the 90\(^{th}\), 95\(^{th}\), 98\(^{th}\) percentiles of daily maximum temperature distribution of the study period for at least 2, 3 or 4 consecutive days (Table 1). We estimated the effects of heatwave exposure of pregnant women in the last gestational weeks before delivery.

We also acquired data on ambient air pollutants which including particulate matter with a diameter less than 10 μm (PM\(_{10}\)), ozone (O\(_3\)), carbon monoxide (CO) and nitrogen dioxide (NO\(_2\)) from 5 stations in Brisbane as many previous investigations have found that ambient air pollution could affect birth outcomes\(^{24-26}\). The air pollution data were provided by the Queensland Department of Environment and Resource Management. Weekly average levels
of meteorological factors and ambient air pollution exposures were calculated by using the original daily data.

In addition, we also acquired the data on the Social Economic Index for Areas (SEIFA) from the Australian Bureau of Statistics (ABS) to estimate maternal socio-economic status. SEIFA is a product developed by the ABS that ranks areas in Australia according to relative socio-economic advantage and disadvantage. The index is based on information from the five-yearly Census and consists of four sub-indexes. In this study, we used SEIFA data released in 2001 and 2006 to represent the maternal economic status of births occurred during 2000-2005 and 2006-2010 separately. SEIFA data was linked by year and area post code to the birth records.

**Statistical analysis** Survival analysis was used in this study to explore the influence of heatwave on spontaneous preterm birth. Several studies have used the Cox proportional hazards regression model to investigate the birth effects of environmental factors such as temperature and air pollution\(^{13,24}\). The authors in these studies believed that survival analysis combined the advantages of cohort and time-series studies as this model allows for simultaneous examination of the impact of both subject-specific (e.g. individual behavior risk factors) and time-related factors (e.g. air pollution, humidity and other meteorological factors). Furthermore, the power of the survival analysis is increased compared with a case–crossover approach because all the subjects are examined\(^{24,25,27}\).

Preterm birth was defined as a live birth occurring at less than 37 completed weeks according to the definition of the World Health Organization\(^{1}\). We used the Cox proportional hazards regression model (Cox regression), which is widely used in survival analysis, with time-dependent covariates to estimate the acute effects of heatwave\(^{28}\). Cox regression has been used in epidemiological studies to analyse time-to-event data with censoring. The standard
Cox regression model assumes a constant hazard ratio over time; in other words, the effects on survival of covariates should be time-independent. However, in our study, we have to consider that the values of covariates, such as heatwave exposure at different times of the whole pregnancy period, were not fixed, so we fitted the Cox regression model with time-dependent covariates as follows:

$$h(t, X_t, X_i(t)) = h_0(t)\exp [\beta_l X_l + \beta_d X_d(t)]$$

Where $h_0(t)$ is the baseline hazard function, being the hazard function for individuals with all explanatory variables equal to zero; $X_l$ refers to the values of time-independent variables such as baby’s gender, mother’s age and parity; $X_d(t)$ are the values of the time-dependent variables (meteorological factors and air pollutants); $\beta_l$ and $\beta_d$ are vectors of model parameters for time-independent and time-dependent covariates.

Heatwave exposure in this study was assigned as a binary value (yes/no) which indicated whether they experienced at least one heatwave event in the last gestational weeks before delivery.

Preterm birth is the outcome of interest in this study. We divided the whole pregnancy period into gestational weeks and assumed that within each of these, time-dependent variables such as weekly air pollution levels could be fixed. Consequently the birth states of each pregnant woman were represented by a series of intervals of 1-week duration. Within each interval, a censoring variable was created which was 0 if a preterm birth did not occur, and 1 if a preterm birth occurred. For example, if one delivery occurred at 36 weeks, the pregnancy would be recorded as 36 intervals with the final censoring variable equal to 1; if a delivery occurred at 38 weeks, the pregnancy would be recorded as 38 intervals with all values of censoring variable equal to 0.
We classified maternal age into 3 groups: <20, 20-34 and >34 years and treated age groups as stratified variables in the model as previous studies have found a nonlinear relationship between maternal age and birth outcomes, that is women younger than 20 years or older than 34 years were more likely to suffer from adverse birth outcomes such as preterm birth, low birth weight and even stillbirth \(^{30,31}\). Indigenous status (yes/no), marital status (yes/no), parity (primiparity / multiparity), baby’s gender (male/female) as well as SEIFA scores were entered into the model to adjust for demographic factors and areal socio-economic status. In addition, we used both single-pollutant and multi-pollutant models to adjust for the confounding effects of air pollution. To control for long-term trends, we added “year” as a factor variable into the model.

We restricted the study to warm seasons to control the effects of seasonality of birth; meanwhile, a factor variable “Month” was also included in the model.

The graphical methods, which used cumulative sums of the martingale-based residuals, were performed to check the proportionality assumptions of the Cox models used in our study\(^{32,33}\). The results of the proportional hazard (PH) assumption on all covariates showed that for heatwave and most of other covariates except relative humidity, the standardized and the observed score processes fluctuated randomly around zero, and the P values of the supremum tests were larger than 0.05, which indicated that the PH assumptions on most variables were satisfied (Figure S1-S12 in supplements). However, for relative humidity, when we removed it from the model, the estimates of heatwave were barely changed. All analyses were conducted using SAS software, Version 9.2 (SAS Institute Inc., Cary, NC, USA).

**RESULTS**

A total of 275,465 singleton live births occurred between 1\(^{st}\) January, 2000 and 31\(^{st}\) December, 2010 in Brisbane.
The number of spontaneous births was 154,785 (56% of all singleton live births). Fifteen births were excluded because they lacked gestational age information. The prevalence of preterm birth was 6.4%. The gestational age ranged from 20 weeks to 43 weeks, and the mean gestational age was 39.20 weeks. Only the spontaneous births which occurred between November and March, of which the total number was 50,848, were used in the final analysis. Table 2 shows the summary statistics of the demographic factors and the proportions of preterm birth that occurred in different subgroups. The majority of mothers were non-indigenous (97.31%). The mothers’ ages ranged from 15 to 44 years and most (78.24%) were 20-34 years old. The majority (84.17%) were married. The percentages of primiparity and multiparity were 57.22% and 42.78%, respectively. Chi-square tests showed that the proportions of preterm birth in Indigenous population (10.46%) were considerably higher than in non-Indigenous population (6.48%) (P<0.05); women older than 34 years as well as primiparae were more likely to experience preterm birth. Proportions of preterm birth varied significantly according to the mothers’ marital status (Table 2).

Table 3 shows the summary statistics of the meteorological factors and air pollutants during 1999-2010 in Brisbane. We excluded environmental data before 13th March, 1999 as all the pregnant women’s gestational periods started after this date. The average weekly maximum temperature ranged from 14.00 to 37.85 °C during the study period, the medians of weekly concentrations of PM$_{10}$, CO, O$_3$ and NO$_2$ were 17.66 μg/m$^3$, 0.544ppm, 0.016 ppm and 0.004 ppm, respectively (Table 3).

Figure 2 shows the time series variations of all meteorological factors and air pollutants. The yearly variations in these variables were quite consistent over the study period except PM$_{10}$, which had a dramatically increase in September 2009 due to a dust storm in Brisbane on 23 September 2009.
Several exploratory analyses were also performed. Table 4 shows that the distributions of relative humidity, air pressure, air pollutants and SEIFA scores (the index of socio-economic disadvantage) in heatwave days and non-heatwaves were different (T test, P<0.05).

Table 5 summarizes the proportions of preterm birth by women’s heatwave exposure in their last gestational weeks before delivery. Increased proportions of preterm birth for women exposed to heatwave were observed when using the heatwave definitions although the Chi-square tests showed that these differences were not statistically significant.

Table 6 shows that when women were exposed to heatwave, the proportions of preterm birth were different from women unexposed to heatwave in the Indigenous subgroup, women older than 34 years of age and married / De Facto women (Chi-square test, P<0.05).

We examined the hazard ratios of preterm birth for women who experienced at least one heatwave event in their last gestational weeks by using a series of cut-off percentiles and durations to define a heatwave. Compared with the unadjusted-for-pollutant model, the results of single-pollutant models showed that the HRs of preterm birth for women exposed to heatwave in their last gestational weeks changed to some extent when different air pollutants were added into the model separately (Table S1 in supplements).

Finally, the model after adjustment for all air pollutants (CO, O3 NO2 and PM10) and all other confounding factors was used. We only reported the results of multivariable analysis.

Figure 3 shows the hazard ratios of preterm birth for women who experienced heatwaves. For most definitions used, we observed a statistically significant increase in the hazard ratios of preterm birth for women who had experienced at least one heatwave event in the last gestational weeks in warm seasons after controlling confounders. Hazard ratios of preterm birth ranged from 1.13 (95% CI: 1.03, 1.24) to 2.00 (95% CI: 1.37, 2.91) which showed that
even a minor change in the heatwave definitions may affect the assessment of the relationship between heatwave and preterm birth (Figure 3).

For 4-consecutive-day exposure, when higher cut-off percentiles were used to define a heatwave, we found that the hazard ratios increased from 1.13 (95% CI: 1.03, 1.24) to 2.00 (95% CI: 1.37, 2.91). However, for given cut-off percentiles (the 90th and 95th percentiles) to define heatwave, hazard ratios did not increase markedly with longer duration of heatwave exposure, but did increase for the 98th percentile from a 3-day to 4-day duration (Figure 3).

DISCUSSION

Main findings

In general, a positive association between heatwave exposure in the last gestational weeks and occurrence of preterm birth was found in this study after controlling for a range of potential confounders. Meanwhile, we also observed the changes of effect estimates of heatwave using a series of heatwave definitions. The highest hazard ratio of preterm birth for women who had experienced at least one heatwave event in the last gestational weeks was 2.00 (95% CI: 1.37, 2.91), when defining heatwave as a daily maximum temperature over the 98th percentile, which lasted for 4 consecutive days.

Strengths and limitations

This study has several key strengths. Firstly, to our knowledge, this is the first study which takes duration of heat exposure into account to explore the association between heatwave and preterm birth. Secondly, we excluded the other two types of preterm births to reduce the over-estimation of the preterm birth risk of heatwave as most induced preterm births are unlikely to be attributable to heatwave. Thirdly, we used a series of heatwave definitions with different cut-off percentiles and durations in this study. Our robust findings may shed some
light on how intensity and duration of heatwave might affect an assessment of birth-related impacts of heatwave. Finally, survival analysis was used in this study to estimate the effects of heatwave on preterm birth.

Several limitations must also be acknowledged. In this study, we used SEIFA data instead of individual data to represent the socio-economic status of the pregnant women which might produce misclassification bias to some extent. In addition, we did not take into account several confounders such as maternal smoking status, as this kind of individual information had too many missing values in our records. Meanwhile, meteorological and air pollution data obtained in ecological level might be less representative. However, these measurement errors are very likely to be non-differential, and therefore likely to result in under-estimation rather than over-estimation of heatwave effects. Finally, a fixed cohort bias occurred in this study. One methodological study suggests that a fixed cohort bias may occur when using a study period based on date of birth as a fixed cohort could only capture births with longer gestational age at the start period and births with shorter gestational age at the end of study. However, another study showed that this bias could only have minimal impacts on changing their results. In this study we only examined the short-term effects of maternal heatwave exposure in the last week before delivery. As most heatwave events occurred during the summer seasons, we could capture most subjects exposed to heatwave since we extended our study period to the warm seasons.

**Interpretation**

Eight studies have reported the effects of ambient temperature on gestational age or preterm birth. Our results are consistent to some extent with the findings of most previous studies, which showed that higher ambient temperature, especially extreme hot weather, might shorten the gestational age or result in preterm birth. A recent
study based on a birth cohort in Barcelona treated gestational age as a continuous variable and defined an extreme heat event as the Heat Index (HI) exceeded the 90th, 95th, 99th percentiles of heat indices. The results of that study showed a small reduction (0.2 day) in the average length of gestation when the HI on the day of delivery exceeded the 95th percentile (HI95: 30.5°C) 22. A survival analysis in Brisbane also found that exposure to high temperatures during the last gestational week was associated with an increase of the risk of preterm birth 13.

In this study, we identified heatwave as daily maximum temperatures exceeded certain percentiles of the temperature distribution for two or more consecutive days. For a given percentile, the effects were not increased when the durations of heatwave changed, except for the 98th percentile, where an increase trend aroused from a 3-day to 4-day durations. On the other hand, when duration equaled to 4 days, there was a dose-response effect with the increased cut-off percentiles. A recent study defined heatwave as daily mean temperatures of two or more consecutive days higher than the community’s 95% percentile of warm season and explored the effects of heatwave on mortality in 43 U.S communities. The result of that study found that on average, the mortality risk increased by 2.49% with every 1°F increase in heatwave intensity and 0.38% for every 1-day increase in heatwave duration 21. Our study and that study 21 both hint that relative thresholds instead of duration used for heatwave definition could be more likely to influence the evaluation of health-related effects of heatwave.

However, our results were partially inconsistent with the characteristic of mortality effects of heatwave as there is a greater mortality risk with more intensive or longer duration of heat 21, 39. One potential explanation is that when heatwave became more intense for a short period, pregnant women might be more likely to alter their behaviours to protect themselves from heatwave exposure, which is effective to some extent. However, when the intensity or
duration of heatwave increased to a certain degree, merely behavioural changes won’t be able to protect them from heatwave impacts.

In addition to the possible mechanism mentioned above\textsuperscript{17}, several studies proposed that the maternal-fetal hypothalamic-pituitary-adrenal (HPA) axis activation triggered by heat stress could also cause preterm birth\textsuperscript{40, 41}. A study in Denmark found that the increased Corticotrophin-Releasing Hormone (CRH) and cortisol secreted by the placenta, which could be activated by heat stress, were associated with preterm birth\textsuperscript{42}. Furthermore, studies also found a significant increase of the serum heat shock protein (HSP70) levels in women with preterm birth and pre-eclampsia as human cells and tissues may produce HSP70 rapidly to recover structural and functional damage due to the incorrect folding of proteins\textsuperscript{43-46}.

These associations in this study were robust to the definitions of heatwave, persisted after adjustment for confounders, followed a dose-response relationship with increasing temperature, and were constant with other international studies. In addition, there are plausible biological mechanisms which can explain the association; all of these factors approved the interpretation that the relationship between short-term heatwave exposure and preterm birth is causal.

**CONCLUSION**

In conclusion, heatwave was significantly associated with preterm birth, but the effect estimates were influenced by intensity and duration of heatwaves. The findings of this study showed that it is important for pregnant women to reduce heatwave exposure, which may have significant public health implications as climate change progresses. A number of measures can be implemented to reduce the risk of preterm birth associated with heatwave exposure \textsuperscript{47}. First of all, information related to heat stress and birth outcomes as well as recommendations on how to reduce heatwave exposure should be widely disseminated by
health-related organizations. Secondly, a community-based heat health warning system should be developed and implemented in a timely way to alert pregnant women. Interventions like changing the thermal capacity of living places and providing special supportive services to pregnant women during heatwave can also be developed and implemented.

In addition, more animal experiments and human trials on the biological mechanisms should be done in the future to help us improve our understandings of the causal relationship between heatwave and preterm birth.

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Disclosure of interests

The authors declare that they have no conflicting interests.

Contribution to authorship

ST designed the study. JW, GW and YG performed the procedure of data arrangement and data analysis. JW wrote the first draft of the manuscript. JW, ST, GW and XP contributed to the interpretation of analyses and manuscript revision. All authors approved the final manuscript.

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Details of ethics approval
Ethical approval was authorized by Human Research Ethics Committee of Queensland University of Technology. The Queensland Health approved the Public Health Act (PHA) application for birth data collection.
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