Prenatal acute thermophysiological stress and spontaneous preterm birth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis

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Abstract

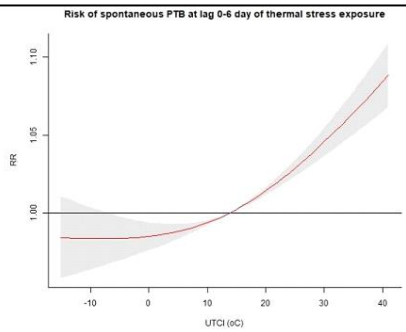
Epidemiologic evidence on acute heat and cold stress and preterm birth (PTB) is inconsistent and based on ambient temperature rather than a thermophysiological index. The aim of this study was to use a spatiotemporal thermophysiological index (Universal Thermal Climate Index, UTCI) to investigate prenatal acute heat and cold stress exposures and spontaneous PTB. We conducted a space-time-stratified case-crossover analysis of 15,576 singleton live births with spontaneous PTB between 1st January 2000 and 31st December 2015 in Western Australia. The association between UTCI and spontaneous PTB was examined with distributed lag nonlinear models and conditional quasi-Poisson regression. Relative to the median UTCI, there was negligible evidence for associations at the lower range of exposures (1st to 25th percentiles). We found positive associations in the 95th and 99th percentiles, which increased with increasing days of heat stress in the first week of delivery. The relative risk (RR) and 95% confidence interval (CI) for the immediate (delivery day) and cumulative short-term (up to six preceding days) exposures to heat stress (99th percentile, 31.2 °C) relative to no thermal stress (median UTCI, 13.8 °C) were 1.01 (95% CI: 1.01, 1.02) and 1.05 (95% CI: 1.04, 1.06), respectively. Elevated effect estimates for heat stress were observed for the transition season, the year 2005-2009, male infants, women who smoked, unmarried, ≤ 19 years old, non-Caucasians, and high socioeconomic status. Effect estimates for cold stress (1st percentile, 0.7 °C) were highest in the transition season, during 2005-2009, and for married, non-Caucasian, and high socioeconomic status women. Acute heat stress was associated with an elevated risk of spontaneous PTB with sociodemographic vulnerability. Cold stress was associated with risk in a few vulnerable subgroups. Awareness and mitigation strategies such as hydration, reducing outdoor activities, and affordable heating and cooling systems may be beneficial. Further studies with the UTCI are required.

Keywords: Universal Thermal Climate Index, preterm birth, heat stress, cold stress, thermal stress, temperature.

Graphical Abstract

- Maternal exposure to thermal stress from climate change extremes.
- This may trigger excessive and premature stimulation of immune-inflammatory activities.
- Risk of spontaneous preterm birth (PTB) is elevated.

Born too soon (< 37 gestational weeks)



The exposure-response curve of daily Universal Thermal Climate Index (UTCI) up to six preceding days of delivery and risk of spontaneous PTB using median UTCI of 13.8 °C (no thermal stress) as reference. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals.

Highlights

- We conducted a space-time-stratified case-crossover analysis.
- We used a Universal Thermal Climate Index rather than ambient temperature.
- Acute heat stress was associated with higher risk of spontaneous preterm birth.
- The risk was relatively elevated in sociodemographically vulnerable groups.
- Cold stress showed positive associations only in a few vulnerable groups.

1. Introduction

Preterm birth (PTB) – birth before 37 completed weeks of gestation remains the leading cause of child mortality and long-term health morbidity, and is accompanied by sizeable economic burdens (Vogel et al., 2018). Analysis across 107 countries estimated a global rise in PTB from 9.8% in 2000 to 10.6% in 2014, an equivalent of 15 million live PTB (Chawanpaiboon et al., 2019). In Australia, the rate increased slightly from 8.4% in 2010 to 8.7% in 2017 (Morris et al., 2020). Most PTB cases are spontaneous, and the causes are multifactorial and heterogeneous (Cobo et al., 2020; Vogel et al., 2018). Despite the several well-known risk factors, the majority of PTB have unspecified causes and unclear biological mechanisms for appropriate prevention strategies (Cobo et al., 2020; Vogel et al., 2018). For instance, an individual participant meta-analysis of 4.1 million singleton births in five high-income countries reported that the aetiology of about 65% of PTB could not be explained with a range of commonly reported risk factors (Ferrero et al., 2016). Recommendations included investigation of biological mechanisms and non-conventional risk factors (Ferrero et al., 2016; Vogel et al., 2018) such as environmental exposures.

Climate change continues to increase heat or cold extremes across the globe with potential impacts on health outcomes (IPCC, 2021). Emerging observational studies have indicated that prenatal exposure to extreme ambient temperatures (heat or cold stress) may contribute to the pathophysiology of PTB (Chersich et al., 2020). The hypothesised biological pathway is that thermal stress disrupts maternal thermoregulatory capacity and stimulates excessive immune-inflammatory activities prematurely, initiating labour and thereby leading to PTB (Green and Arck, 2020; Jee et al., 2021). However, the findings are disparate and have suggested both extreme heat and cold stress as risk factors (Cox et al., 2016; Li et al., 2018; Mathew et al., 2017), heat stress as a risk factor but 'protective' effect or no association with cold stress (Sun et al., 2019), and cold stress as a risk factor but 'protective' effect or no association for heat stress (Cheng et al., 2021; Liang et al., 2016; Yu et al., 2018). These differences may be attributed to heterogeneity in the study designs, geographic location, population characteristics, acclimatisation, adaptation, exposure assessment, and varied temperature metrics (Cheng et al., 2021; Chersich et al., 2020).

Most importantly, the existing literature is limited to the surrogate use of ambient temperature for heat or cold stress instead of the human thermophysiological index (Jendritzky et al., 2012; Vanos et al., 2020). The results have been criticised as unrealistic and physiologically less relevant for a better understanding of the associated health effects for appropriate interventions (Jendritzky et al., 2012; Staiger et al., 2019; Vanos et al., 2020). Four appropriate human thermophysiological indices were recently recommended (Staiger et al., 2019). These included Universal Thermal Climate Index (UTCI) which was reported in comprehensive comparative studies to be most suitable as it has high climatic sensitivity and best captures thermal stimuli similar to that of the human body, making it more thermophysiologically appropriate for medical and preventive medicine (Blazejczyk et al., 2012; Bröde et al., 2013; Jendritzky et al., 2012; Staiger et al., 2019). UTCI is a potential universal tool for monitoring the impacts of climate change on humans but it is underutilised in epidemiology and medical sciences until recently (Romaszko et al., 2022). Several recent studies are now using the UTCI in heatwave warning systems and medical or epidemiological fields as reviewed elsewhere (Krüger, 2021; Romaszko et al., 2022). Only one recent study has used UTCI derived with meteorological parameters from one synoptic meteorological station and investigated the association with preterm labour (Khodadadi et al., 2022), but no study has investigated PTB.

Here, we used spatiotemporal UTCI and conducted a space-time-stratified case-crossover analysis of the association between prenatal exposure to thermophysiological stress and spontaneous PTB in Western Australia over 16 years. We estimated the overall effects and the influence of sociodemographic vulnerabilities.

2. Materials and Methods

Our analysis and reporting of results were informed by the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines (Benchimol et al., 2015).

2.1 Study design and setting

A space-time-stratified case-crossover design was conducted (Wu et al., 2021). This is similar to the classic time-stratified case-crossover design, a case-only self-matched approach that compares the exposure at the time of the event ('case or hazard time') with related non-event periods ('control or referent times') (Maclure, 2017; Mostofsky et al., 2018). The classic time-stratified case-crossover design is applied for time-series data where all individuals have a shared area-level exposure (Armstrong et al., 2014; Mostofsky et al., 2018; Wu et al., 2021). However, the availability of space-time varying environmental exposure assessment led to the extension of this design into the so-called space-time-stratified case-crossover to accommodate the analysis of multiple space-time series datasets (Ragettli et al., 2017; Wu et al., 2021). The design has been applied previously for investigating acute effects (Lu et al., 2021; Lu et al., 2020; Nyadanu et al., 2022; Ragettli et al., 2017; Vicedo-Cabrera et al., 2020). Specifically, we matched the case and control times by a day of the week in the same calendar month and year within the same small spatial unit in the study location (Nyadanu et al., 2022; Ragettli et al., 2017; Wu et al., 2021). Thus, by design, the time-stratified case-crossover accounted for both measured and unmeasured individual-level characteristics and co-exposures that are short-term or time-invariant and controlled for long-term and seasonal trends (Mostofsky et al., 2018; Wu et al., 2021). The extension to space-time-stratified case-crossover further allowed for the analysis of multi-location time-series data, minimised exposure measurement bias and spatial confounding (Nyadanu et al., 2022; Vicedo-Cabrera et al., 2020; Wu et al., 2021).

This study was conducted for births between 1st January 2000 and 31st December 2015 in Western Australia. Western Australia is the largest state in Australia by area and covers 2.5 million km² areas with a population of 2.7 million as of 31 March 2021 (ABS, 2021). The state has diverse climatic conditions, ranging from temperate in the south-west, tropical in the north, and arid or semi-arid in the other parts.

2.2 Study population and case definition

We obtained de-identified data on births collected by the Midwives Notification System from the Western Australia Department of Health data linkage unit. The Midwives Notification System is a population-wide registry of all births with at least 20 weeks of gestation or at least a birth weight of 400 g if the gestational length is unknown (GoWA, 2021). The data contained maternal and neonatal information. Maternal residential address at the time of delivery was available as the statistical area level 1(SA1), the second smallest geographical unit in Australia. This study included 4,504 SA1s where eligible births were located. A total of 474,835 births were screened for eligibility. We included only singleton live births with spontaneous onset of labour and vaginal delivery at 20-36 weeks of gestation that had an SA1. The gestational age was estimated as the best clinical estimate from the perinatal records as the difference between the date of birth and start of pregnancy based on ultrasonography or the last menstrual period if ultrasound was not available. To eliminate the potential displacement of short-term effects by the reductions in the risk at longer periods, we considered a maximum lag of 21 days (Bhaskaran et al., 2013; Gasparrini et al., 2015; Khodadadi et al., 2022; Nyadanu et al., 2022). For this reason, we further excluded births within the first 20 days of the study period. Our final analytic sample included 15,576 spontaneous PTB (Figure 1).

We extracted the available sociodemographic information to derive subgroups. Infant-related subgroups were based on sex (male or female) and gestational age (20-27, 28-31, and 32-36 weeks) (Blencowe et al., 2013). We further obtained the extreme ends of the PTB as periviable birth (20-26 weeks, the range of viability) (Catalano et al., 2019) and late PTB (34-36 weeks) (Blencowe et al., 2013). Maternal-related subgroups were age at birth delivery (≤ 19, 20–34, and ≥ 35 years) (Wang et al., 2019; Wang et al., 2013), tobacco smoking status (non-smoker or smoker), marital status (married or unmarried), and race or ethnicity (Caucasian or non-Caucasian). We also categorised the season of birth into three (summer, December-February; winter, June-August; and transition, the remaining months that form autumn and spring) and year (2000-2004, 2005-2009, 2010-2015). The Index of Relative Socio-economic Disadvantage at a geographic area derived by the Australian Bureau of Statistics (ABS, 2018) was assigned to the maternal residence at the time of birth and categorised into quintiles in a previous study (Gebremedhin et al., 2019). We derived two socioeconomic status (SES) subgroups from the quintiles as high (1st and 2nd quintiles) and low (3rd-5th quintiles) SES (Nyadanu et al., 2022).

2.3 Spatiotemporal Universal Thermal Climate Index exposure assessment

The UTCI is an equivalent air temperature (°C) that assesses the ambient thermal environment and accounts for heat transfer and exchange, both within the body and between the body surface and the ambient air layer (Blazejczyk et al., 2013; Jendritzky et al., 2012). UTCI is computed through a six-order polynomial equation with four input variables: air temperature and dew point temperature or relative humidity at 2 m above ground level, wind speed at 10 m above ground level, and mean radiant temperature (Blazejczyk et al., 2013; Bröde et al., 2012; Di Napoli et al., 2021). The mean radiant temperature is a measure of thermal-related comfort and includes non-meteorological variables such as metabolic rate and the thermal properties of clothing (Blazejczyk et al., 2013; Bröde et al., 2012; Jendritzky et al., 2012). We used the open-access UTCI dataset recently derived from the ERA5 reanalysis (Di Napoli et al., 2021). ERA5 is the 5th historical global gridded climate dataset of several climate variables produced by the European Centre for Medium-Range Weather Forecasts by merging the global climate model, measurements made near the Earth's surface at land stations, and satellite observations (Hersbach et al., 2020). A novel global dataset, ERA5-HEAT (Human thErmAl comforT) which contains the UTCI was produced from the ERA5 reanalysis climate dataset at a spatial resolution of 0.25° × 0.25° at an hourly level from 1979 to the present (Di Napoli et al., 2021). Details on UTCI calculation and assumptions were described elsewhere (Blazejczyk et al., 2013; Bröde et al., 2012; Di Napoli et al., 2021). We accessed the daily gridded UTCI of the 24-hour averages from 1st January 2000 to 31st December 2015 across Australia. UTCI values were extracted at the SA1 level in Western Australia using ArcGIS software (version 10.8.1). UTCI has been used in several medical and epidemiologic studies (Romaszko et al., 2022).

2.4 Statistical analyses

2.4.1 Main and subgroup analyses

The analytical dataset was an SA1-level time-series of daily counts of spontaneous PTB and the corresponding daily UTCI exposures. To simultaneously investigate the immediate and cumulative risks, we combined a distributed lag non-linear model (DLNM) with conditional quasi-Poisson regression (Armstrong et al., 2014; Gasparrini et al., 2010). With the cross-basis term, the non-linear exposure–lag–response association was defined through natural cubic splines in both dimensions of the UTCI predictor and the lag days with 21 maximum lag days (Gasparrini et al., 2010; Khodadadi et al., 2022; Nyadanu et al., 2022). Spline knots were set at equally spaced values on the log scale of lags (Gasparrini et al., 2010). The selection of the optimum degrees of freedom (*df*) for UTCI predictor and lag days was based on the smallest Akaike Information Criterion (Gasparrini et al., 2010). This process resulted in 2 and 3 *df* for the UTCI predictor and lags being selected, respectively. The model specification was given as

$$\log\left[\mathrm{E}\left(\mathrm{Y}_{\mathrm{t,s}}\right)\right] = \alpha + \mathrm{cb}(\mathrm{UTCI}) + \mathrm{holiday}, \mathrm{eliminate} = \mathrm{factor}\ (stratum) \quad (1)$$

where α is the intercept; $Y_{t,s}$ is the observed number of spontaneous PTB at day *t* in spatial unit *s* (SA1); *cb* is the cross-basis function, the *holiday* is a binary indicator variable for public holidays, and *stratum* (introduced through the "eliminate" function in "gnm" package (Turner and Firth, 2020) was the conditional factor that defined the same day of the same week in the same calendar month of the same year at the same SA1.This analytical framework had been applied previously (Lu et al., 2021; Lu et al., 2020; Nyadanu et al., 2022; Ragettli et al., 2017; Vicedo-Cabrera et al., 2020; Wu et al., 2021).

With reference to the median UTCI, we estimated the relative risks (RRs) and 95% confidence intervals (CIs) at the 1st, 5th, 25th, 75th, 95th, and 99th percentiles of UTCI. Following previous reports (Basu et al., 2010; Cheng et al., 2021; Khodadadi et al., 2022), we reported the RR (95% CI) for only the immediate effects of exposure on the day of PTB (lag 0) and cumulative effects from event day 0 up to the preceding day N (lag 0-N). The results of the individual lag days in distributed lag models could be biased by temporal collinearity or autocorrelation with potential erroneous findings (Basagaña and Barrera-Gómez, 2021; Bhaskaran et al., 2013). Additionally, labour could last more than one day, or the pregnant woman may not be admitted until a day following the thermal stress exposure (Basu et al., 2016). The acute immediate and cumulative effects up to the first six preceding days were reported. We also reported results for 0-13 and 0-21 lag days, representing second and third weeks, respectively as "long-term" exposures (Khodadadi et al., 2022; Nyadanu et al., 2022).

Potential effect modifications were investigated by performing subgroup analyses for each of the subgroups described earlier. The RRs (95% CIs) for the 1st and 99th percentiles, relative to the median UTCI were reported. Furthermore, the respective reference subgroups were used to compare the two RRs (95% CIs) for each subgroup by estimating the ratio of relative risks (RRRs) and the corresponding 95% CIs for both 1st and 99th percentiles of UTCI exposure for lag 0-6 for each subgroup with the Altman and Bland test of interaction effects (Altman and Bland, 2003; Hutchon, 2005).

We also estimated the attributed risk (AR) as the number of excesses per 10,000 singletons spontaneous PTB that could be attributable to immediate (lag 0) and cumulative (lag 0-6) heat stress exposure, relative to the median UTCI by following Ha *et al* (Ha et al., 2017) as

$$AR = I_u\,(RR - 1) \qquad (2)$$

where I_u is the background rate which was defined as the study-specific incidence rate and calculated from the eligible spontaneous vaginal delivery births (7.2%). This was also equivalent to the average of 2009-2015 state-wide singleton PTB incidence reported elsewhere (Newnham et al., 2017).

2.4.2 Sensitivity analyses

The robustness of the main analysis was checked by performing several sensitivity analyses for varying model conditions or assumptions. The *dfs* were changed to 3 for both UTCI predictor and lags and then to 3 for UTCI predictor and 4 for lags dimensions. Two separate reference values (the mean UTCI and the average of the standard 'no thermal stress' range, 17.5 °C) were also used. All analyses were performed with R statistical software (version 4.1.1) (R, 2021). The DLNM was fitted with the "dlnm" package (Gasparrini et al., 2010) and the conditional quasi-Poisson regression with the "gnm" package (Turner and Firth, 2020). We reported and interpreted the RR (95% CI) contextually without a 'statistical significance' threshold as recommended by the American Statistical Association (Wasserstein et al., 2019).

3. Results

3.1 Exposure and cohort characteristics

The standard UTCI has 10 thermophysiological stress categories where 9 to 26 °C is considered as *no thermal stress,* and values below and above this range are varied intensities of *cold thermal stress* and *heat thermal stress*, respectively (Blazejczyk et al., 2013; Di Napoli et al., 2021). The mean UTCI (standard deviation) and median (interquartile range) across the entire study period were 14.5 °C (6.7 °C) and 13.8 °C (9.2 °C), respectively and both were within the standard *no thermal stress* category. The 1st percentile (0.7 °C) and the 99th percentile (31.2 °C) were within the *slight cold stress* and *moderate heat stress* categories, respectively (Blazejczyk et al., 2013; Di Napoli et al., 2021). The

UTCI distribution varied slightly among subgroups and the largest records were in summer (20.5 ± 5.3 °C) and 2010-2015 (15.1 ± 6.8 °C) (Table S1). Spontaneous PTB was fairly distributed across the seasons with half observed during the six months of transition season and approximately 25% each during the three months each of winter and summer. The prevalence of spontaneous PTB increased across the years. Most of the births were to women who had moderate PTB (86.6%), had male babies (56.2%), were non-smokers (75.8%), married (81.6%), aged 20-34 years (73.7%), Caucasian (71.6%), and low socioeconomic status, SES (64.7%) (Table 1).

3.2 Thermophysiological stress and risk of spontaneous PTB

The exposure-lag-response association for the short-term cumulative effects within a week showed changes from lower to greater risks across the exposures, relative to the median UTCI. The magnitude of effects began to decrease for exposures from the second week before birth (Figure 2). Relative to the median UTCI, there was negligible change in the risk in the 1^{st} to 25^{th} percentiles for all exposure periods. However, strong positive associations were found in the 95^{th} and 99^{th} percentiles (heat stress) which increased with increasing cumulative heat stress episodes for the first week but were lower afterward. Specifically, for 99^{th} percentile relative to median UTCI, immediate (lag 0 day) and cumulative acute exposure (lag 0-6 day) risks were 1% (RR= 1.01, 95% CI: 1.01, 1.02) and 5% (RR= 1.05, 95% CI: 1.04, 1.06) greater, respectively (Table 2). Both cold and heat stress showed the most elevated risk during transition season for both immediate and cumulative acute effects but either lower or small positive associations during winter and summer (Table S2a and Table S2b). Cumulative acute exposure to both 1^{st} and 99^{th} percentiles relative to median UTCI showed lower effects during both winter and summer as compared to the transition season. This was as low as 18% lower effect in summer as compared to the transition season, for exposure to 99^{th} percentile relative to median UTCI (RRR= 0.82, 95% CI: 0.80, 0.83) (Table 3). The risk was most elevated for the middle year 2005-2009 (Figure S1).

Compared to no thermal stress, attributable risks indicated excesses of 11(95% CI: 9, 13) and 36 (95% CI: 29, 43) per 10,000 liveborn singletons with spontaneous PTB due to immediate (lag 0) and cumulative acute (lag 0-6) heat stress (99^{th} percentile of UTCI) exposures, respectively. The attributable risk was not estimated for cold stress as it showed no association.

3.3 Thermophysiological stress and risk of spontaneous PTB in subgroups

Relative to median UTCI (no thermal stress), cold stress (1^{st} percentile of UTCI) showed essentially no association for both extreme and moderate PTB but strong positive associations for very PTB while heat stress (99^{th} percentile of UTCI) showed no association for very PTB but strong positive associations for both extremely PTB and moderate PTB (Table S3). Cumulative acute exposure (lag 0-6) showed 6% lower effect of cold stress exposure (RRR=0.94, 95% CI: 0.93, 0.95) and a 50% higher effect of heat stress exposure (RRR=1.50, 95% CI:1.47, 1.52) for extremely PTB as compared to moderate PTB. Conversely, cumulative acute exposure showed 35% higher effect of cold stress exposure (RRR=1.35, 95% CI:1.34, 1.36) but 5% lower effect of heat stress exposure (RRR=0.95, 95% CI: 0.94, 0.96) in very PTB as compared to moderate PTB (Table 3). The impact of the thermal stress was strong in the periviable births but essentially had no association with late PTB (Figure S2).

Relative to no thermal stress, both thermal stress exposures, particularly heat stress showed sociodemographic disparities (Table S3-S5). Specifically, cumulative acute exposure (lag 0-6) showed 15% higher effect of heat stress in male as compared to female infants (RRR=1.15, 95% CI: 1.14, 1.17). As compared to non-smokers, mothers who smoked during pregnancy showed 19% higher effect for cumulative acute exposure to heat stress (RRR=1.19, 95% CI: 1.17, 1.21). Cumulative acute exposure to heat stress showed 23% higher effect among unmarried as compared to married mothers (RRR=1.23, 95% CI: 1.21, 1.24). Non-Caucasians experienced higher effect as compared to

Caucasians and this was particularly stronger for cold stress exposure at 10 % higher (RRR=1.10, 95% CI: 1.09, 1.12) than heat stress exposure at 7% higher (RRR=1.07, 95% CI: 1.05, 1.08). Cumulative acute exposures to both cold and heat stress showed small lower effect among mothers in low SES as compared to high SES residential areas. Compared to mothers aged 20-34 years old, cumulative acute exposure to heat stress showed 46% higher effect among mothers aged ≤ 19 years old (RRR=1.46, 95% CI: 1.44, 1.47) and 1% higher effect among mothers aged ≥ 35 years old (RRR=1.01, 95% CI: 1.00, 1.02) (Table 3).

The results of the sensitivity analyses for varying modelling assumptions and conditions were similar to the main results (Tables S6 and S7).

4. Discussion

4.1 Thermophysiological stress and risk of spontaneous PTB

Relative to the median UTCI (no thermal stress), we found no association with exposures to the first to 25th percentiles but strong positive associations were observed for the 95th and 99th percentiles for immediate and cumulative acute effects. The risk increased with increasing duration of heat stress exposure episodes and was strongest during transition seasons (spring and autumn) and 2005-2009. Assuming causality, attributable risk indicated that heat stress (99th percentiles) exposure relative to no thermal stress on the event day and cumulatively up to six preceding days could account for 11 (95% CI: 9, 13) and 36 (95% CI: 29, 43) excess cases per 10,000 spontaneous PTB, respectively.

Given that we used a human thermophysiological index as recently recommended (Staiger et al., 2019; Vanos et al., 2020) and applied elsewhere (Krüger, 2021; Romaszko et al., 2022), our findings are unique as compared to the previous findings that were based on ambient air temperature metrics (Chersich et al., 2020). Previous studies considered extremes of high and low-temperature thresholds (1st or 5th and 99th or 95th percentiles as compared to median) as heat and cold stress. Our findings were consistent with a study in Belgium and the USA that also found a greater risk for acute heat stress but a small lower risk or essentially no association for cold stress based on ambient temperature metrics (Cox et al., 2016; Sun et al., 2019). For example, the USA study of 32 million singleton births reported an RRs (95% CI) for PTB of 1.03 (95% CI: 1.02, 1.04) and 0.99 (95% CI: 0.98, 0.99) over the previous four days for heat and cold stress, respectively, relative to the median ambient temperature (Sun et al., 2019). Furthermore, the only available meta-analysis that pooled 21 studies found 1% greater odds of PTB (OR= 1.01, 95% CI: 1.01, 1.02) during high versus low-temperature exposure periods of < 4 weeks which increased to 5% (OR=1.05, 95% CI: 1.04, 1.05) after excluding two studies (outliers) (Chersich et al., 2020). There were, however, a few contradictory findings. Two time-series analyses on the Chinese population found greater risks for cold stress but a small lower risk or no association for heat stress in Shenzhen and Xuzhou (Cheng et al., 2021; Liang et al., 2016). Another Chinese study found a greater risk for both heat and cold stress for the immediate effect but no association for short-term cumulative effects in Guangzhou (He et al., 2016). Vicedo-Cabrera *et al* found a greater risk for moderate heat but inconsistent associations for extreme cold and heat during the last one to four gestational weeks in Stockholm, Sweden (Vicedo-Cabrera et al., 2015). Specific to Australia, three previous studies examined the acute effect of ambient temperature on preterm birth (Jegasothy et al., 2022; Mathew et al., 2017; Wang et al., 2013). Matthew *et al* found a greater risk of PTB that ranged from 2% up to 8.3% for 90th, 95th, and 99th percentiles of minimum and maximum summer temperatures relative to the median temperature on the day of delivery and up to 21 preceding days in Alice Springs, Central Australia (Mathew et al., 2017). Wang *et al* analysed warm-season births in Brisbane, Queensland, and found the greatest hazard ratio of 2.00 (95% CI: 1.37, 2.91) for their highest heat stress, defined as a daily maximum temperature over the 98th percentile for four consecutive days in the last gestational week (Wang et al., 2013). The third study was conducted across New South Wales state with spatiotemporal exposure assessment and time-series analysis that reported the risk of spontaneous PTB at the 95th percentile of daily mean temperature (25℃) relative to the median (17℃). The results showed 3% greater risk (RR=1.03, 95% CI: 1.01, 1.05) on day 0 (day of initial exposure, defined as one day before the event) and 16% greater risk (RR= 1.16, 95% CI: 1.08, 1.25) for the cumulative effect of exposure up to seven preceding days (Jegasothy et al., 2022). Our results were similar, although, the cumulative effect estimate was greater than that of our study. This could be due to the one-day-delay exposure assessment, differences in population characteristics and climates, study design, and the use of ambient temperature. Given the geographical variability in climatic conditions and the influence of acclimatisation, adaptation, and mitigation strategies, even within a country or region, generalising location-specific findings to other parts is difficult and if necessary, should be done cautiously (Sexton et al., 2021; Vicedo-Cabrera et al., 2015). However, it is expected that there might be greater risks of PTB for heat stress than cold stress due to more severe heat stress episodes than cold stress across most regions in the world as the climate change crisis progresses (IPCC, 2021). Also, there could be better acclimatisation or easier adaptation to cold than heat stress (Sun et al., 2019).

4.2 Thermophysiological stress and risk of spontaneous PTB in subgroups

We found attenuation of risk in our latest period, similar to findings reported in Brisbane, Australia (Li et al., 2018). This may be attributed to thermal adaptation through acclimatisation or increasing mitigation responses such as the use of air conditioning (Barreca and Schaller, 2020), improved climate-specific clothing, thermal stress-resilient housing infrastructure, and improved healthcare system over the years (Adnan et al., 2022; Li et al., 2018; Sun et al., 2019). However, our observed elevated risk in the transition season as compared to other seasons could imply that pregnant women may not be able to quickly thermo-adapt when transitioning from high to low thermal stress or vice versa. It could also mean that pregnant women took more behavioural precautions such as reduced outdoor activities or increased use of heating or cooling systems during summer or winter seasons as compared with the transition season.

We observed lower risks of heat stress with increasing gestational age which was consistent with the previous findings (Avalos et al., 2017; Cox et al., 2016; He et al., 2016) and indicates a plausible causal link between prenatal heat stress and the shortening of gestational age (Barreca and Schaller, 2020; Strand et al., 2011). Basu *et al*, however, observed the strongest risk for near-term PTB in California, USA (Basu et al., 2010). We also observed that cold stress showed strong positive associations with very PTB but not for other types of PTB. A cold season analysis in California, USA, however, indicated the strongest odds of mean apparent temperature for near-term PTB (Avalos et al., 2017). Among the reasons stated earlier, the analytical design, exposure metrics, and climatic conditions could explain the differences. This requires further studies from other locations with a thermophysiological index. We found a stronger impact of heat stress in male neonates as compared with the female neonates similar to the largest cohort study conducted in the USA (Sun et al., 2019) but others reported otherwise (Avalos et al., 2017; Basu et al., 2010; Cox et al., 2016). However, it has been recognised extensively in the literature that male neonates are more vulnerable to pregnancy outcomes and the influence of environmental exposures (Al-Qaraghouli and Fang, 2017). As reported in a few previous studies, the comparatively higher-risk women for heat stress were women who smoked, unmarried, teenagers, and non-Caucasians (Basu et al., 2010; Mathew et al., 2017; Vilcins et al., 2021). These vulnerabilities are attributed to the level of outdoor activities, risky behaviours and lifestyle, poor antenatal care utilisation, resources for mitigation strategies, hereditary, and systemic racism (Adnan et al., 2022; Alson et al., 2021; Basu et al., 2010; Giudice et al., 2021; Mathew et al., 2017; Vilcins et al., 2021). Surprisingly, we observed a stronger risk of thermal stress for women that resided in the high SES areas but lower risk or no association for those in low SES areas. We used area-level SES as a proxy for individual SES which is known to produce misclassification bias to some extent (Wang et al., 2013). However, there are possible reasons for this finding. Women with low SES are more likely to be exposed to outdoor working conditions over long periods and lack cooling or heating systems at home (Adnan et al., 2022). Consequently, they are more likely to acclimatise to thermal stress as compared to women with high SES, resulting in the observed elevated risk in the high than low SES groups. Better individual-level indicators for SES such as occupation and further investigations are required. Given that climate change impacts are exacerbated by maternal sociodemographic and lifestyle factors, a better understanding and identification of higher-risk subpopulations is crucial for prioritised intervention (Ebi et al., 2021; Giudice et al., 2021).

Public health interventions and mitigation strategies may be required, particularly for the most vulnerable women. Examples include raising awareness and educating women to sufficiently hydrate and decrease outdoor activities during hot days, *greening* the environment to improve shade, provision of public shade structures, provision of affordable heating and cooling systems, and thermal stress warning systems that account for the human thermophysiology (Adnan et al., 2022; Giudice et al., 2021; Nyadanu et al., 2022).

4.3 Biological mechanisms

Several animal studies and clinical evidence have provided strong support for the pathophysiology of prenatal thermal stress exposure and PTB. Generally, any factor or exposure that initiates the breakdown of feto-maternal immune tolerance and excessive or premature activation of the inflammatory pathways causes uterine contractility, cervical ripening, and rupture of membranes which results in PTB (Di Renzo et al., 2018; Green and Arck, 2020). Heat or cold stress induces molecular and biochemical catalytic processes that cause oxidative damage, apoptosis, deregulate inflammatory production and abnormally high intracellular expression of heat shock proteins in the serum. These affect placental physiology and fetal development (particularly higher in sociodemographically vulnerable women) and cause implantation failure and feto-maternal complications such as pregnancy outcomes, including spontaneous PTB (Berestoviy et al., 2021; Collier et al., 2017; Di Renzo et al., 2018; Green and Arck, 2020; Jee et al., 2021). Heat stress also causes dehydration which reduces uterine blood flow and increases secretion of the pituitary antidiuretic hormone, prostaglandin, and oxytocin. These affect fetoplacental transport and induce spontaneous labour (Stan et al., 2002).

4.4 Strengths and limitations

Our study has several strengths. The novel study design and the modelling framework accounted for and substantially minimised both time-invariant and time-varying known and unknown confounding factors in the short-term periods, temporal autocorrelation, and spatial confounding (Armstrong et al., 2014; Gasparrini et al., 2010; Nyadanu et al., 2022; Wu et al., 2021). The space-time varying assessment of the UTCI exposure at the individual's residential microenvironment reduced exposure misclassification as compared to using ground-based monitoring stations that may be distant from the participants (Nazarian and Lee, 2021). To the best of our knowledge, this is the first study that used the available most suitable contemporary human thermophysiological index (UTCI) at a spatiotemporal resolution to examine the association between heat or cold stress and spontaneous PTB. This makes the findings more robust and physiologically relevant by combining knowledge from climate science, physiology, and epidemiology (Jendritzky et al., 2012; Romaszko et al., 2022; Staiger et al., 2019; Vanos et al., 2020). This was also the first study on this topic in Western Australia.

This study has some limitations, including our inability to account for indoor thermal environments (e.g., use of heating or cooling systems) and prenatal activity-time patterns. A prospective cohort with personalised activity-time exposure assessment using portable thermal sensors and indoor thermal environment assessments may help minimise some of these limitations. Given the space-time varying exposure assessment and acute exposure analysis, we expect any remaining exposure misclassification to be minimal and non-differential which would have rather attenuated the observed effect estimates towards the null (Sun et al., 2019). We also lacked information on other relevant sociodemographic factors such as maternal occupation, education, illicit drug or alcohol use, and nutrition. As the primary aim in the present study was to investigate short-term associations between thermal stress and spontaneous PTB, future studies should investigate long-term effect across the entire pregnancy periods with the extended DLNM to identify other potential critical windows of susceptibility.

5. Conclusion

We find that prenatal exposure to acute heat but not cold stress relative to no thermal stress elevated the risk of spontaneous PTB. However, both heat and cold stresses elevated the risk in the more vulnerable subpopulations. Given the expected increasing events of climate change extremes in the coming years (IPCC, 2021) and the potential impacts on birth outcomes, we call on the public health officers, antenatal care providers, and obstetricians to help communicate the potential risk to pregnant women (Giudice et al., 2021). The provision of thermal adaptation or mitigation strategies and resources may help reduce the risk of spontaneous PTB, particularly for higher-risk pregnant women. In addition to an improved healthcare system, an appropriate climate change policy is required. Several comparative studies had indicated the suitability and relevance of thermophysiological metrics as compared to ambient temperature for medical and preventive medicine given that thermophysiological metrics capture the total thermal environment and human thermophysiological responses (Blazejczyk et al., 2012; Bröde et al., 2013; Kampmann et al., 2012; Staiger et al., 2019). Future studies should consider human thermophysiological indices such as UTCI which is now gaining high application in scientific research and recommendations among clinicians, epidemiologists, and specialists in public health and thermal stress management (Krüger, 2021; Nazarian and Lee, 2021; Romaszko et al., 2022; Staiger et al., 2019; Vanos et al., 2020).

Data Availability

The UTCI data is open access from the Copernicus Climate Data Store (https://doi.org/10.24381/cds.553b7518). The birth data cannot be made publicly available due to the data access agreement, but it can be requested from the Department of Health, Western Australia (https://ww2.health.wa.gov.au/Articles/J_M/Midwives-Notification-System).

Credit Author Contributions

SDN, GAT, BM, and GP: Conceptualisation, Methodology, Investigation, Writing—Critical Review and Editing, Project Administration. SDN: Data curation, Formal analysis, Writing—Original draft preparation. All authors have read and approved the final version of the manuscript.

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Ethical Approval

This study was approved by the Human Research Ethics Committees of the Western Australia Department of Health (#2016/51) and Curtin University (#HRE2020-0523). The participants' informed consent was waived, particularly due to the implausibility of obtaining retrospective consent for de-identified secondary data.

Declaration of competing interests

The authors declare no competing interests.

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Tables

Table 1. The number of spontaneous PTB by year, season, type, and fetal and maternal sociodemographic characteristics in Western Australia, 2000-2015 (N=15,576).

Variable	**Characteristics**	**n (%)**
Year	2000-2004	4,162 (26.7)
	2005-2009	5,101 (32.7)
	2010-2015	6,313 (40.5)
Season	Transition	7,793 (50.0)
	Winter	3,963 (25.4)
	Summer	3,820 (24.5)
PTB type	Extremely PTB (20-27 weeks)	889 (5.7)
	Very PTB (28-31 weeks)	1,194 (7.7)
	Moderate PTB (32-36 weeks)	13,493 (86.6)
PTB type at extreme ends	Periviable birth (20-26 weeks)	709 (4.6)
	Late PTB (34-36 weeks)	11,905 (76.4)
Fetal sex	Male	8,752 (56.2)
	Female	6,824 (43.8)
Prenatal smoking	Non-smoker	11,805 (75.8)
	Smoker	3,771 (24.2)
Marital status	Married/de facto	12,710 (81.6)
	Unmarried*	2,866 (18.4)
Delivery age (years)	≤19	1,196 (7.7)
	20–34	11,476 (73.7)
	≥35	2,904 (18.6)
Race/ethnicity	Caucasian	11,155 (71.6)
	Non-Caucasian	4,421 (28.4)
Socioeconomic status	High	5,506 (35.3)
	Low	10,070 (64.7)

*Never married/separated/divorced/widowed/unknown. PTB, preterm birth

Table 2. The cumulative relative risks of spontaneous PTB for different UTCI percentiles relative to the median (13.8 °C) in Western Australia, 2000-2015.

Lag days	1st (0.7 °C) RR (95% CI)	5th (4.2 °C) RR (95% CI)	25th (9.7 °C) RR (95% CI)	75th (18.9 °C) RR (95% CI)	95th (26.4 °C) RR (95% CI)	99th (31.2 °C) RR (95% CI)
0	0.99 (0.99, 1.00)	0.99 (0.99, 1.00)	1.00 (1.00, 1.00)	1.00 (1.00, 1.00)	1.01 (1.01, 1.01)	1.01 (1.01, 1.02)
0-1	0.99 (0.99, 0.99	0.99 (0.99, 0.99)	1.00 (0.99, 1.00)	1.01 (1.01, 1.01)	1.02 (1.02, 1.02)	1.03 (1.02, 1.03)
0-2	0.99 (0.98, 0.99)	0.99 (0.99, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.02 (1.02, 1.03)	1.04 (1.03, 1.04)
0-3	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.03 (1.02, 1.03)	1.04 (1.04, 1.05)
0-4	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.03 (1.03, 1.04)	1.05 (1.04, 1.06)
0-5	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.03 (1.03, 1.04)	1.05 (1.04, 1.06)
0-6	0.99 (0.98, 0.99)	0.99 (0.98, 0.99)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)	1.03 (1.03, 1.04)	1.05 (1.04, 1.06)
0-13	0.95 (0.94, 0.96)	0.97 (0.96, 0.98)	0.99 (0.98, 0.99)	1.01 (1.01, 1.02)	1.02 (1.02, 1.03)	1.03 (1.02, 1.04)
0-21	0.78 (0.77, 0.80)	0.85 (0.84, 0.86)	0.95 (0.94, 0.95)	1.04 (1.03, 1.04)	1.04 (1.03, 1.05)	1.02 (1.00, 1.04)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

Table 3. The estimated interaction effects as ratio of relative risks (RRRs) and 95% confidence intervals (95% CI) of spontaneous preterm birth, relative to the indicated reference subgroup for acute cumulative exposure (lag 0-6) to 1st percentile of UTCI (cold stress) and 99th percentile of UTCI (heat stress) relative to median UTCI (no thermal stress) in Western Australia, 2000-2015.

Subgroup	1st percentile of UTCI RRR (95% CI)	99th percentile of UTCI RRR (95% CI)
Winter (ref Transition)	0.83 (0.81, 0.85)	0.87 (0.85, 0.89)
Summer (ref Transition)	0.90 (0.89, 0.92)	0.82 (0.80, 0.83)
Extremely PTB (ref Moderate PTB)	0.94 (0.93, 0.95)	1.50 (1.47, 1.52)
Very PTB (ref Moderate PTB)	1.35 (1.34, 1.36)	0.95 (0.94, 0.96)
Male (ref Female)	1.02 (1.01, 1.03)	1.15 (1.14, 1.17)
Smoker (ref Non-smoker)	0.91 (0.90, 0.92)	1.19 (1.17, 1.21)
Unmarried (ref Married)	0.57 (0.57, 0.58)	1.23 (1.21, 1.24)
non-Caucasian (ref Caucasian)	1.10 (1.09, 1.12)	1.07 (1.05, 1.08)
Low (ref High) SES	0.94 (0.93, 0.95)	0.89 (0.85, 0.94)
≤ 19 (ref 20-34) years	0.80 (0.79, 0.81)	1.46 (1.44, 1.47)
≥ 35 (ref 20-34) years	0.87 (0.87, 0.88)	1.01 (1.00, 1.02)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth; SES, Socioeconomic status.

Figures

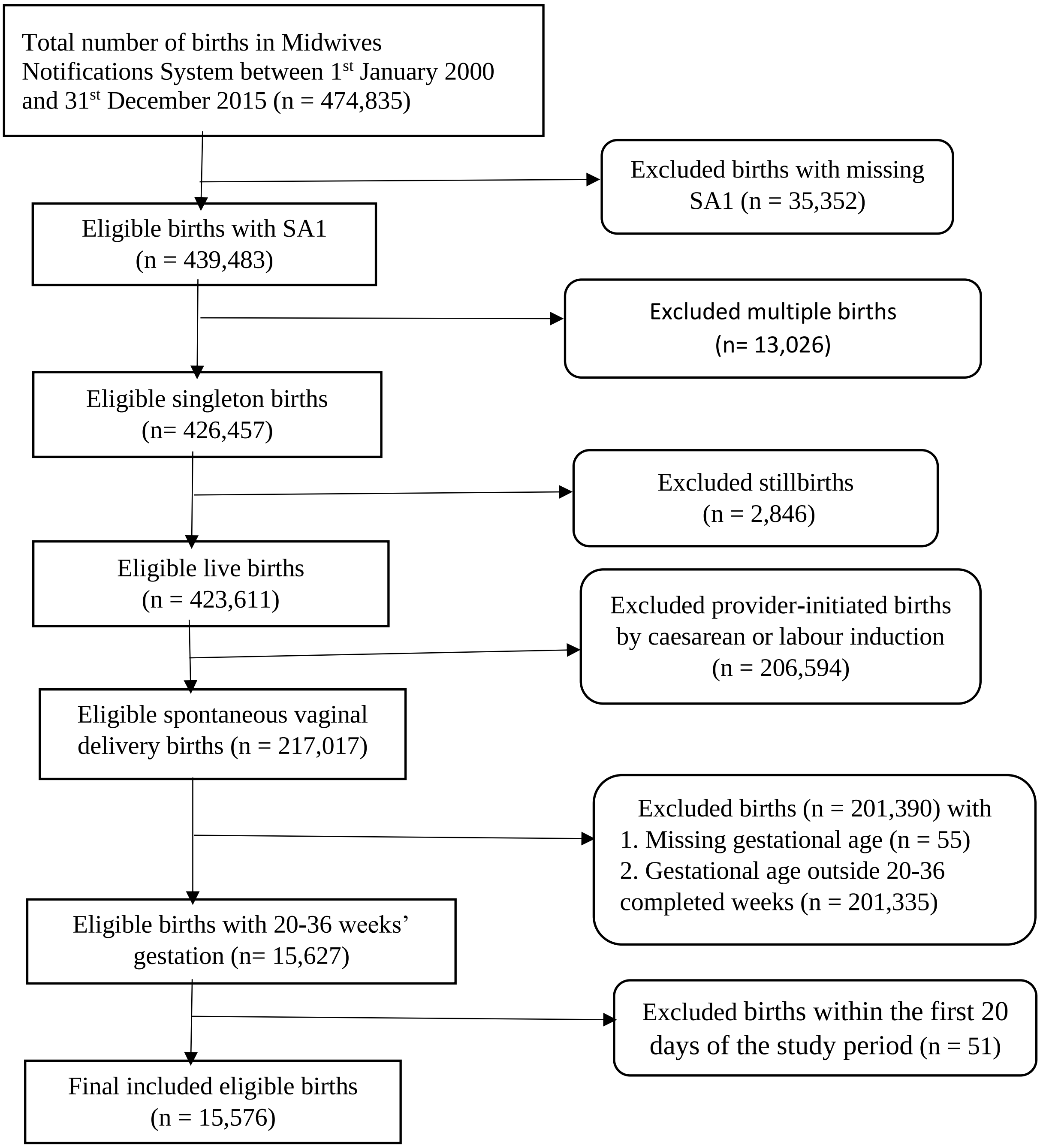

Figure 1. Flow chart of the selection of the eligible spontaneous vaginal delivery preterm births included in this study, Western Australia, 2000-2015. Note, SA1; statistical area level 1

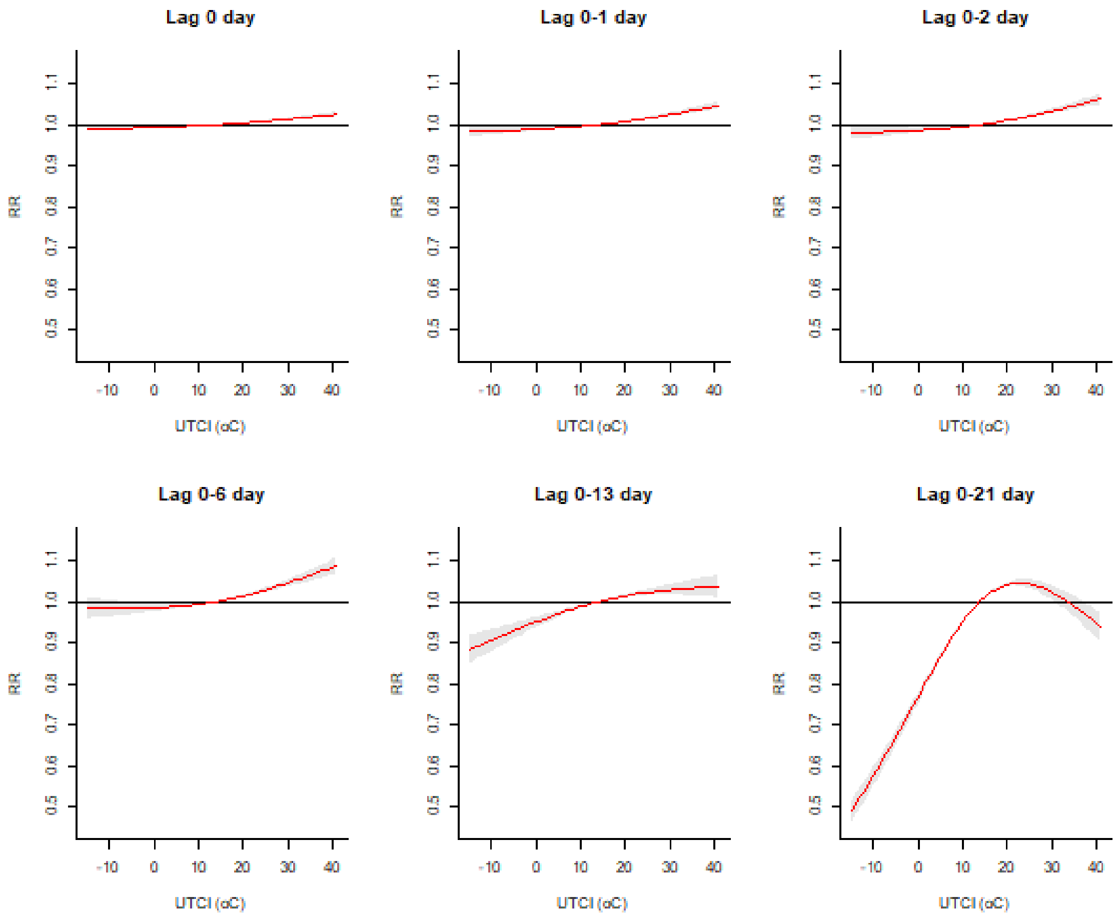

Figure 2. Exposure-response curves of daily UTCI and cumulative relative risk of spontaneous PTB at different lag structures using median UTCI of 13.8 ºC as reference. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals. Note: UTCI, Universal Thermal Climate Index in degree Celsius.

SUPPLEMENTARY MATERIALS

Tables

Table S1. The descriptive statistics of daily mean UTCI (ºC), Western Australia, 2000-2015.

Variable	Subgroup	Min	Mean (SD)	P1	P25	Median	P75	P99	Max
	All	-15.4	14.5 (6.7)	0.7	9.7	13.8	18.9	31.2	41.9
Season	Transition	-15.4	14.6 (5.7)	1.5	10.9	14.1	17.9	30.2	40.2
	Winter	-12.6	8.4 (4.1)	-1.3	5.9	8.5	10.9	20.3	31.9
	Summer	-1.3	20.5 (5.3)	9.5	16.5	20.2	24.2	33.3	41.9
Year	2000-2004	-11.0	14.1 (6.6)	0.5	9.4	13.5	18.6	30.7	41.9
	2005-2009	-15.4	14.0 (6.8)	0.2	9.3	13.4	18.5	31.1	41.3
	2010-2015	-10.2	15.1 (6.8)	1.5	10.3	14.5	19.7	31.7	41.1

Note: UTCI, Universal Thermal Climate Index in degree Celsius; SD, standard deviation; P1, P25, P75, and P99 are respective percentiles.

Table S2a. The cumulative relative risks of spontaneous PTB stratified by season for 1st and 99th percentiles relative to overall median UTCI (13.8 ˚C) in Western Australia, 2000-2015.

Lag days	1st percentile of UTCI RR (95% CI)			99th percentile RR (95% CI)		
	Transition	Winter	Summer	Transition	Winter	Summer
0	1.01 (1.01, 1.02)	0.97 (0.97, 0.98)	0.99 (0.99, 0.99)	1.04 (1.03, 1.04)	0.99 (0.99, 0.99)	1.02 (1.02, 1.03)
0-1	1.02 (1.02, 1.03)	0.95 (0.94, 0.96)	0.98 (0.98, 0.99)	1.07 (1.06, 1.08)	0.98 (0.98, 0.99)	1.03 (1.02, 1.04)
0-2	1.03 (1.03, 1.04)	0.93 (0.92, 0.94)	0.97 (0.97, 0.98)	1.09 (1.08, 1.10)	0.98 (0.97, 0.99)	1.03 (1.02, 1.04)
0-3	1.04 (1.03, 1.05)	0.91 (0.90, 0.92)	0.97 (0.96, 0.97)	1.11 (1.10, 1.13)	0.98 (0.97, 0.99)	1.02 (1.00, 1.03)
0-4	1.04 (1.03, 1.05)	0.90 (0.88, 0.91)	0.96 (0.95, 0.97)	1.13 (1.12, 1.14)	0.99 (0.97, 1.00)	1.00 (0.98, 1.01)
0-5	1.05 (1.03, 1.06)	0.88 (0.87, 0.90)	0.96 (0.95, 0.96)	1.14 (1.12, 1.15)	0.99 (0.98, 1.00)	0.97 (0.96, 0.99)
0-6	1.05 (1.03, 1.06)	0.87 (0.86, 0.89)	0.95 (0.94, 0.96)	1.15 (1.13, 1.16)	1.00 (0.98, 1.01)	0.94 (0.93, 0.96)
0-13	0.99 (0.98, 1.01)	0.84 (0.82, 0.86)	0.92 (0.91, 0.93)	1.12 (1.10, 1.15)	1.15 (1.07, 1.12)	0.73 (0.71, 0.75)
0-21	0.84 (0.83, 0.86)	0.84 (0.81, 0.87)	0.86 (0.85, 0.88)	1.09 (1.06, 1.12)	1.24 (1.20, 1.28)	0.65 (0.63, 0.67)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

Table S2b. The cumulative relative risks of spontaneous PTB stratified by season for 1st and 99th percentiles relative to season-specific median UTCI in Western Australia, 2000-2015.

	1st percentile, median UTCI			99th percentile, median UTCI		
Lag days	Transition (1.5 ºC, 14.1 ºC) RR (95% CI)	Winter (-1.3 ºC, 8.5 ºC) RR (95% CI)	Summer (9.5 ºC, 20.2 ºC) RR (95% CI)	Transition (30.2 ºC, 14.1 ºC) RR (95% CI)	Winter (20.3 ºC, 8.5 ºC) RR (95% CI)	Summer (33.3 ºC, 20.2 ºC) RR (95% CI)
0	1.01 (1.01, 1.02)	0.97 (0.97,0.98)	0.98 (0.98, 0.98)	1.04 (1.03, 1.04)	0.99 (0.99, 1.00)	1.01 (1.00, 1.01)
0-1	1.02 (1.02, 1.03)	0.95 (0.95, 0.96)	0.96 (0.96, 0.97)	1.07 (1.06, 1.08)	0.99 (0.98, 1.00)	1.01 (1.00, 1.02)
0-2	1.03 (1.02, 1.04)	0.93 (0.93, 0.94)	0.95 (0.94, 0.96)	1.09 (1.08, 1.10)	0.99 (0.98, 1.00)	1.00 (0.99, 1.01)
0-3	1.04 (1.03, 1.05)	0.92 (0.91, 0.93)	0.94 (0.93, 0.95)	1.11 (1.10. 1.13)	0.99 (0.98, 1.01)	0.99 (0.97, 1.00)
0-4	1.04 (1.03, 1.05)	0.91 (0.90, 0.92)	0.93 (0.92, 0.94)	1.13 (1.11, 1.14)	1.00 (0.98, 1.02)	0.97 (0.95, 0.98)
0-5	1.05 (1.03, 1.06)	0.90 (0.89, 0.91)	0.92 (0.91, 0.94)	1.14 (1.12, 1.15)	1.01 (0.99, 1.03)	0.94 (0.92, 0.96)
0-6	1.05 (1.03, 1.06)	0.89 (0.88, 0.91)	0.92 (0.90, 0.93)	1.14 (1.13, 1.16)	1.02 (1.00, 1.04)	0.91 (0.89, 0.93)
0-13	0.99 (0.97, 1.01)	0.89 (0.87, 0.91)	0.89 (0.87, 0.91)	1.12 (1.10, 1.15	1.17 (1.14, 1.21)	0.71 (0.69, 0.73)
0-21	0.84 (0.82, 0.86)	0.94 (0.91, 0.97)	0.80 (0.78, 0.83)	1.09 (1.06, 1.12)	1.39 (1.33, 1.45)	0.61 (0.58, 0.63)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

Table S3. The cumulative relative risks of spontaneous PTB stratified by type and sex for 1st percentile of UTCI (cold stress) and 99th percentile of UTCI (heat stress) relative to median UTCI (no thermal stress) in Western Australia, 2000-2015.

Lag days	1st percentile of UTCI RR (95% CI)			99th percentile of UTCI RR (95% CI)		
	Extremely PTB	Very PTB	Moderate PTB	Extremely PTB	Very PTB	Moderate PTB
0	0.94 (0.93, 0.94)	1.08 (1.08, 1.08)	0.99 (0.99, 0.99)	1.13 (1.13, 1.13)	0.99 (0.99, 1.00)	1.01 (1.01, 1.01)
0-1	0.89 (0.89, 0.90)	1.15 (1.15, 1.16)	0.98 (0.98, 0.99)	1.25 (1.24, 1.26)	0.99 (0.98, 0.99)	1.02 (1.01, 1.02)
0-2	0.87 (0.87, 0.88)	1.21 (1.20, 1.21)	0.98 (0.97, 0.98)	1.35 (1.34, 1.36)	0.99 (0.98, 0.99)	1.02 (1.02, 1.03)
0-3	0.87 (0.86, 0.87)	1.25 (1.24, 1.26)	0.97 (0.97, 0.98)	1.43 (1.42, 1.44)	0.99 (0.98, 0.99)	1.03 (1.02, 1.04)
0-4	0.87 (0.87, 0.88)	1.28 (1.27, 1.29)	0.97 (0.96, 0.98)	1.48 (1.47, 1.50)	0.99 (0.98, 0.99)	1.03 (1.02, 1.04)
0-5	0.89 (0.88, 0.89)	1.30 (1.29, 1.31)	0.97 (0.96, 0.98)	1.52 (1.51, 1.53)	0.98 (0.98, 0.99)	1.03 (1.02, 1.04)
0-6	0.91 (0.90, 0.92)	1.31 (1.30, 1.32)	0.97 (0.96, 0.97)	1.54 (1.52, 1.55)	0.98 (0.97, 0.99)	1.03 (1.02, 1.04)
0-13	1.04 (1.02, 1.05)	1.26 (1.24, 1.27)	0.93 (0.91, 0.94)	1.45 (1.43, 1.47)	0.85 (0.84, 0.86)	1.02 (1.01, 1.04)
0-21	0.59 (0.58, 0.60)	1.32 (1.29, 1.34)	0.76 (0.75, 0.77)	1.66 (1.63, 1.69)	0.45 (0.44, 0.46)	1.05 (1.03, 1.07)
Lag days	Male	Female		Male	Female	
0	0.98 (0.98, 0.99)	1.00 (1.00, 1.01)		1.01 (1.01, 1.01)	1.02 (1.02, 1.02)	
0-1	0.98 (0.97, 0.98)	1.01 (1.00, 1.01)		1.03 (1.02, 1.03)	1.03 (1.02, 1.03)	
0-2	0.97 (0.97, 0.98)	1.00 (1.00, 1.01)		1.04 (1.04, 1.05)	1.03 (1.02, 1.04)	
0-3	0.97 (0.97, 0.98)	1.00 (0.99, 1.01)		1.06 (1.05, 1.07)	1.02 (1.01, 1.03)	
0-4	0.98 (0.97, 0.99)	0.99 (0.99, 1.00)		1.08 (1.07, 1.09)	1.01 (1.00, 1.02)	
0-5	0.99 (0.98, 0.99)	0.98 (0.98, 0.99)		1.10 (1.09, 1.11)	0.99 (0.98, 1.00)	
0-6	0.99 (0.99, 1.00)	0.97 (0.97, 0.98)		1.12 (1.11, 1.13)	0.97 (0.96, 0.98)	
0-13	1.00 (0.99, 1.01)	0.90 (0.89, 0.91)		1.24 (1.22, 1.25)	0.82 (0.80, 0.83)	
0-21	0.74 (0.72, 0.75)	0.85 (0.84, 0.86)		1.20 (1.18, 1.22)	0.82 (0.81, 0.84)	

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

Table S4. The cumulative relative risks of spontaneous PTB stratified by maternal smoking and marital statuses, and of race/ethnicity for 1st percentile of UTCI (cold stress) and 99th percentile of UTCI (heat stress) relative to median UTCI (no thermal stress) in Western Australia, 2000-2015.

Maternal variable	Lag days	1st percentile of UTCI RR (95% CI)		99th percentile of UTCI RR (95% CI)	
Smoking status		Non-smoker	Smoker	Non-smoker	Smoker
	0	0.99 (0.99, 1.00)	0.99 (0.99, 0.99)	1.01 (1.01, 1.01)	1.03 (1.03, 1.04)
	0-1	0.99 (0.99, 0.99)	0.98 (0.98, 0.99)	1.01 (1.01, 1.02)	1.07 (1.06, 1.07)
	0-2	0.99 (0.99, 1.00)	0.97 (0.97, 0.98)	1.02 (1.01, 1.02)	1.10 (1.09, 1.10)
	0-3	0.99 (0.99, 1.00)	0.96 (0.95, 0.97)	1.01 (1.01, 1.02)	1.13 (1.12, 1.13)
	0-4	1.00 (0.99, 1.00)	0.95 (0.94, 0.95)	1.01 (1.00, 1.02)	1.15 (1.14, 1.16)
	0-5	1.00 (0.99, 1.01)	0.93 (0.92, 0.94)	1.01 (1.00, 1.02)	1.17 (1.16, 1.18)
	0-6	1.01 (1.00, 1.02)	0.92 (0.91, 0.92)	1.00 (0.99, 1.01)	1.19 (1.18, 1.21)
	0-13	1.01 (0.99, 1.02)	0.80 (0.79, 0.81)	0.97 (0.95, 0.98)	1.24 (1.22, 1.26)
	0-21	0.81 (0.80, 0.83)	0.69 (0.68, 0.71)	0.99 (0.97, 1.01)	1.09 (1.07, 1.11)
Marital status		Married	Unmarried	Married	Unmarried
	0	1.01 (1.01, 1.01)	0.92 (0.92, 0.92)	1.00 (1.00, 1.00)	1.07 (1.07, 1.07)
	0-1	1.02 (1.02, 1.02)	0.85 (0.85, 0.86)	1.00 (1.00, 1.01)	1.13 (1.12, 1.13)
	0-2	1.03 (1.03, 1.04)	0.79 (0.79, 0.80)	1.00 (1.00, 1.01)	1.18 (1.17, 1.18)
	0-3	1.04 (1.04, 1.05)	0.74 (0.74, 0.75)	1.00 (1.00, 1.01)	1.21 (1.20, 1.22)
	0-4	1.06 (1.05, 1.06)	0.70 (0.69, 0.70)	1.01 (1.00, 1.01)	1.23 (1.22, 1.24)
	0-5	1.07 (1.06, 1.08)	0.66 (0.65, 0.66)	1.01 (1.00, 1.02)	1.24 (1.23, 1.25)
	0-6	1.08 (1.07, 1.09)	0.62 (0.62, 0.63)	1.01 (1.00, 1.02)	1.24 (1.23, 1.25)
	0-13	1.10 (1.09, 1.11)	0.48 (0.47, 0.48)	1.02 (1.00, 1.03)	1.07 (1.06, 1.09)
	0-21	0.88 (0.87, 0.90)	0.44 (0.43, 0.45)	1.06 (1.04, 1.08)	0.87 (0.85, 0.89)
Race/ethnicity		Caucasian	Non-Caucasian	Caucasian	Non-Caucasian
	0	0.97 (0.97, 0.98)	1.05 (1.04, 1.05)	1.01 (1.00, 1.01)	1.03 (1.03, 1.03)
	0-1	0.96 (0.95, 0.96)	1.08 (1.07, 1.08)	1.01 (1.01, 1.02)	1.05 (1.05, 1.06)
	0-2	0.95 (0.94, 0.95)	1.10 (1.09, 1.10)	1.02 (1.01, 1.03)	1.07 (1.06, 1.08)
	0-3	0.94 (0.94, 0.95)	1.10 (1.09, 1.11)	1.02 (1.01, 1.03)	1.08 (1.08, 1.09)
	0-4	0.94 (0.94, 0.95)	1.10 (1.09, 1.10)	1.02 (1.02, 1.03)	1.09 (1.08, 1.10)
	0-5	0.95 (0.94, 0.96)	1.08 (1.07, 1.09)	1.03 (1.02, 1.04)	1.10 (1.09, 1.11)
	0-6	0.96 (0.95, 0.96)	1.06 (1.05, 1.07)	1.03 (1.02, 1.04)	1.10 (1.09, 1.11)
	0-13	0.99 (0.98, 1.00)	0.85 (0.84, 0.86)	1.02 (1.01, 1.04)	1.06 (1.04, 1.07)
	0-21	0.78 (0.76, 0.79)	0.79 (0.78, 0.80)	1.02 (1.00, 1.04)	1.02 (1.00, 1.03)
Area-level SES		High	Low	High	Low
	0	1.02 (1.02, 1.02)	0.98 (0.97, 0.98)	1.05 (1.04, 1.05)	0.99 (0.99, 1.00)
	0-1	1.04 (1.03, 1.04)	0.96 (0.96, 0.96)	1.08 (1.08, 1.09)	0.99 (0.99, 0.99)
	0-2	1.04 (1.04, 1.05)	0.95 (0.95, 0.96)	1.11 (1.10, 1.12)	0.99 (0.98, 1.00)
	0-3	1.05 (1.04, 1.05)	0.95 (0.94, 0.95)	1.13 (1.12, 1.13)	0.99 (0.98, 1.00)
	0-4	1.04 (1.04, 1.05)	0.95 (0.94, 0.96)	1.13 (1.12, 1.14)	0.99 (0.99, 1.00)
	0-5	1.04 (1.03, 1.04)	0.95 (0.95, 0.96)	1.13 (1.12, 1.14)	1.00 (0.99, 1.01)
	0-6	1.02 (1.02, 1.03)	0.96 (0.95, 0.97)	1.12 (1.11, 1.13)	1.00 (0.99, 1.01)
	0-13	0.87 (0.86, 0.88)	1.01 (0.99, 1.02)	1.02 (1.01, 1.04)	1.04 (1.03, 1.06)
	0-21	0.68 (0.67, 0.69)	0.85 (0.83, 0.86)	1.08 (1.06, 1.10)	0.99 (0.97, 1.01)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth; SES, Socioeconomic status.

Table S5. The cumulative relative risks of spontaneous PTB stratified by maternal age at delivery for 1st percentile of UTCI (cold stress) and 99th percentile of UTCI (heat stress) relative to median UTCI (no thermal stress) in Western Australia, 2000-2015.

Lag days	1st percentile of UTCI RR (95% CI)			99th percentile of UTCI RR (95% CI)		
	≤ 19	20-34	≥ 35	≤ 19	20-34	≥ 35
0	0.99 (0.99, 0.99)	1.00 (1.00, 1.00)	0.97 (0.97, 0.97)	1.11 (1.11, 1.11)	0.99 (0.99, 1.00)	1.06 (1.06, 1.06)
0-1	0.98 (0.97, 0.98)	1.00 (1.00, 1.00)	0.95 (0.95, 0.95)	1.21 (1.20, 1.21)	0.99 (0.99, 0.99)	1.10 (1.10, 1.11)
0-2	0.95 (0.95, 0.96)	1.00 (1.00, 1.01)	0.93 (0.93, 0.94)	1.29 (1.28, 1.30)	0.99 (0.98, 1.00)	1.12 (1.11, 1.13)
0-3	0.92 (0.92, 0.93)	1.01 (1.00, 1.01)	0.92 (0.91, 0.93)	1.36 (1.35, 1.37)	0.99 (0.99, 1.00)	1.11 (1.11, 1.12)
0-4	0.89 (0.89, 0.90)	1.01 (1.01, 1.02)	0.91 (0.90, 0.92)	1.41 (1.40, 1.42)	1.00 (0.99, 1.01)	1.09 (1.08, 1.10)
0-5	0.86 (0.85, 0.86)	1.02 (1.01, 1.03)	0.90 (0.89, 0.91)	1.45 (1.44, 1.46)	1.01 (1.00, 1.02)	1.06 (1.05, 1.07)
0-6	0.82 (0.81, 0.83)	1.02 (1.02, 1.03)	0.89 (0.89, 0.90)	1.47 (1.46, 1.48)	1.01 (1.00, 1.02)	1.02 (1.01, 1.03)
0-13	0.61 (0.61, 0.62)	1.03 (1.02, 1.05)	0.80 (0.79, 0.81)	1.39 (1.38, 1.41)	1.06 (1.05, 1.08)	0.76 (0.75, 0.77)
0-21	0.57 (0.56, 0.58)	0.89 (0.90, 0.90)	0.51 (0.50, 0.52)	1.28 (1.26, 1.30)	1.00 (1.00, 1.02)	0.92 (0.91, 0.94)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; PTB, preterm birth

Table S6. The cumulative relative risks of spontaneous PTB for 1st and 99th percentiles relative to median UTCI (13.8 °C) with alternative degrees of freedom in Western Australia, 2000-2015.

	3 *df* for both predictor and lag space		3 *df* for predictor and 4 *df* for lag space	
Lag days	1st (0.7 ^{0}C) RR (95% CI)	99th (31.2 ^{0}C) RR (95% CI)	1st (0.7 ^{0}C) RR (95% CI)	99th (31.2 ^{0}C) RR (95% CI)
0	1.00 (0.99, 1.00)	1.02 (1.01, 1.02)	1.01 (1.00, 1.01)	1.07 (1.07, 1.08)
0-1	0.99 (0.99, 1.00)	1.03 (1.02, 1.04)	1.01 (1.00, 1.01)	1.10 (1.09, 1.11)
0-2	0.99 (0.98, 1.00)	1.04 (1.03, 1.05)	1.00 (0.99, 1.01)	1.10 (1.09, 1.11)
0-3	0.99 (0.98, 0.99)	1.05 (1.04, 1.06)	0.99 (0.99, 1.00)	1.08 (1.07, 1.09)
0-4	0.99 (0.98, 0.99)	1.06 (1.05, 1.07)	0.99 (0.98, 0.99)	1.07 (1.06, 1.08)
0-5	0.99 (0.98, 0.99)	1.06 (1.05, 1.07)	0.98 (0.97, 0.99)	1.05 (1.04, 1.06)
0-6	0.99 (0.98, 0.99)	1.06 (1.05, 1.07)	0.98 (0.97, 0.99)	1.04 (1.03, 1.06)
0-13	0.96 (0.95, 0.97)	1.04 (1.02, 1.05)	0.96 (0.95, 0.98)	1.06 (1.04, 1.08)
0-21	0.84 (0.83, 0.86)	0.96 (0.94, 0.98)	0.85 (0.83, 0.86)	0.97 (0.95, 0.99)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; df, degree of freedom; PTB. Preterm birth.

Table S7. The cumulative relative risks of spontaneous PTB for 1st and 99th percentiles, relative to mean and an average of ‘no thermal stress’ range UTCI in Western Australia, 2000-2015.

	Mean UTCI (14.5 ^{0}C)		Average of standard no thermal stress range (17.5 ^{0}C)	
Lag days	1st percentile (0.7 ^{0}C) RR (95% CI)	99th percentile (31.2 ^{0}C) RR (95% CI)	1st percentile (0.7 ^{0}C) RR (95% CI)	99th percentile (31.2 ^{0}C) RR (95% CI)
0	0.99 (0.99, 1.00)	1.01 (1.01, 1.02)	0.99 (0.99, 0.99)	1.01 (1.01, 1.01)
0-1	0.99 (0.98, 0.99)	1.03 (1.02, 1.03)	0.98 (0.98, 0.99)	1.02 (1.02, 1.03)
0-2	0.99 (0.98, 0.99)	1.04 (1.03, 1.04)	0.98 (0.97, 0.99)	1.03 (1.02, 1.04)
0-3	0.98 (0.98, 0.99)	1.04 (1.03, 1.05)	0.98 (0.97, 0.99)	1.04 (1.03, 1.04)
0-4	0.98 (0.98, 0.99)	1.05 (1.04, 1.05)	0.98 (0.97, 0.99)	1.04 (1.03, 1.05)
0-5	0.98 (0.98, 0.99)	1.05 (1.04, 1.06)	0.98 (0.97, 0.99)	1.04 (1.03, 1.05)
0-6	0.98 (0.98, 0.99)	1.05 (1.04, 1.06)	0.98 (0.97, 0.99)	1.04 (1.03, 1.05)
0-13	0.95 (0.94, 0.96)	1.03 (1.01, 1.04)	0.94 (0.93, 0.96)	1.02 (1.01, 1.03)
0-21	0.78 (0.76, 0.79)	1.01 (0.99, 1.03)	0.76 (0.75, 0.77)	0.99 (0.97, 1.00)

Note: UTCI, Universal Thermal Climate Index in degree Celsius

Figures

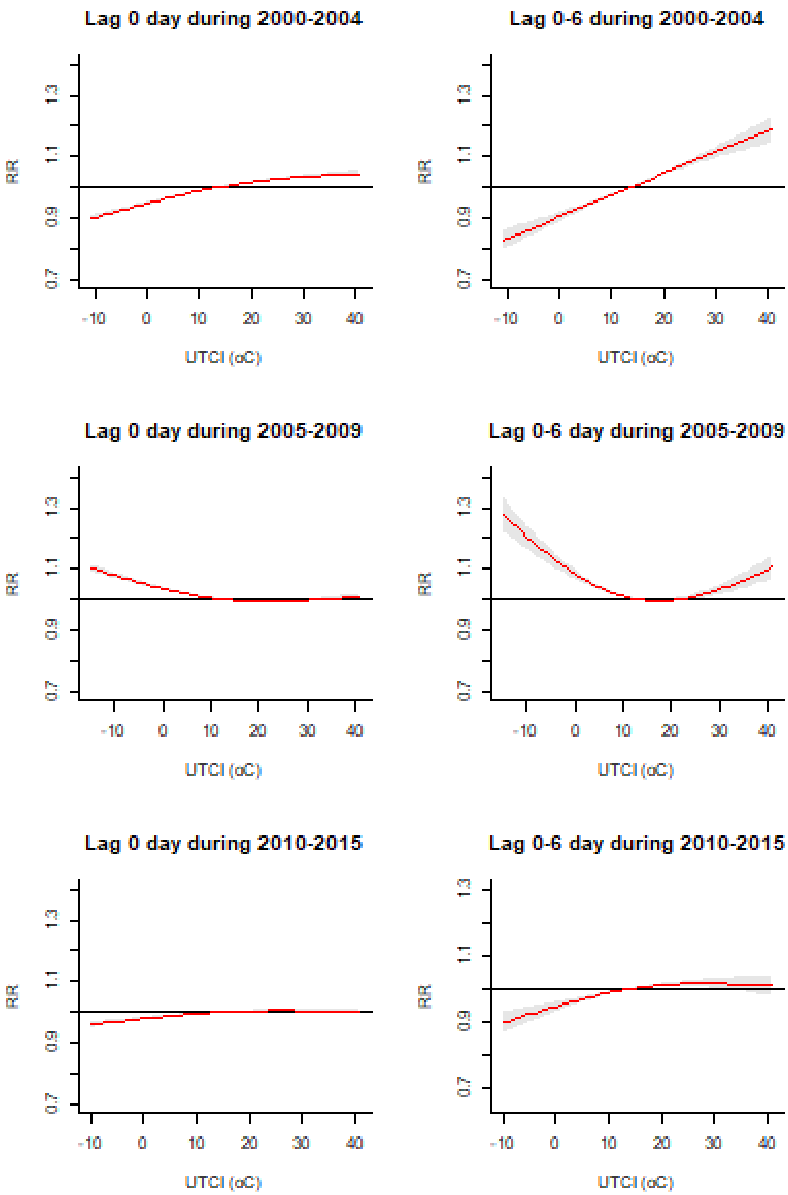

Figure S1. Year-grouped exposure-response curves of daily UTCI and immediate and six days cumulative relative risk of spontaneous PTB using year-specific median UTCI of each year as a reference. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals. Note: UTCI, Universal Thermal Climate Index in degree Celsius.

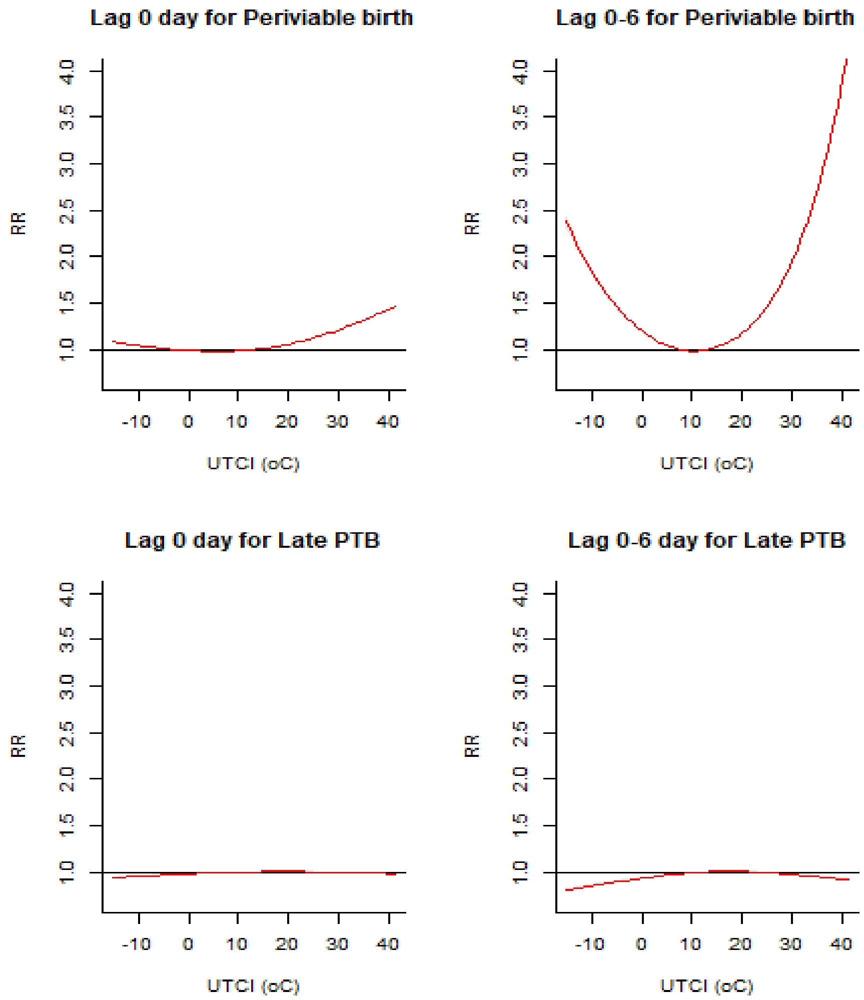

Figure S2. Exposure-response curves of daily UTCI and immediate and six days cumulative relative risk of spontaneous Periviable birth and late PTB using median UTCI of 13.8 °C as reference. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals. Note: UTCI, Universal Thermal Climate Index in degree Celsius.