Maternal acute thermophysiological stress and stillbirth in Western Australia, 2000-2015: a space-time-stratified case-crossover analysis

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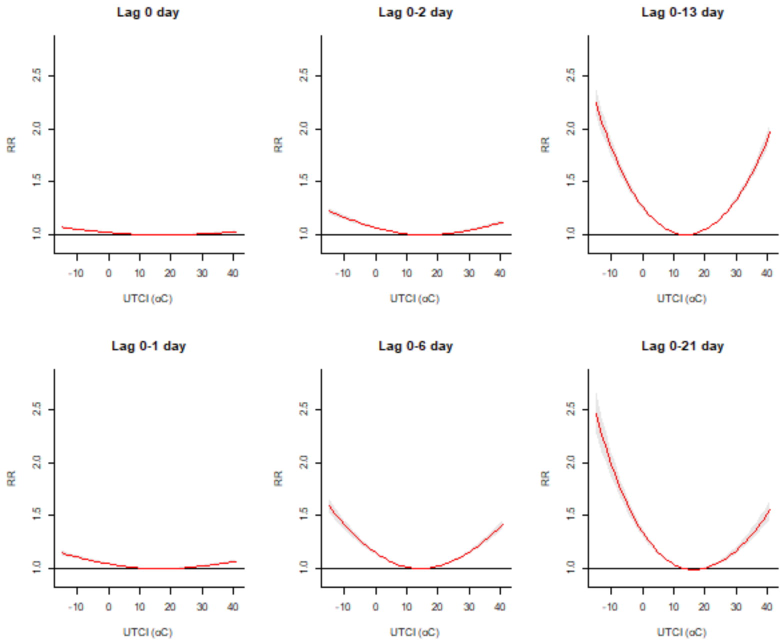
Highlights

• We conducted a space-time-stratified case-crossover analysis.
• Stillbirth risk increased with the intensity and duration of thermal stress episodes.
• Both acute cold and heat stresses positively associated with stillbirth.
• The risk of stillbirth was stronger with heat than cold stress.
• Stillbirth risk varied substantially by fetal and maternal sociodemographic factors.

Graphical Abstract



Abstract

Background: The extreme thermal environment driven by climate change disrupts thermoregulation in pregnant women and may threaten the survival of the developing fetus.
Objectives: To investigate the acute effect of maternal exposure to thermophysiological stress (measured with Universal Thermal Climate Index, UTCI) on the risk of stillbirth and modification of this effect by sociodemographic disparities.
Methods: We conducted a space-time-stratified case-crossover analysis of daily UTCI and 2,835 singleton stillbirths between 1st January 2000 and 31st December 2015 across multiple small areas in Western Australia. Distributed lag non-linear models were combined with conditional quasi-Poisson regression to investigate the effects of the UTCI exposure from the preceding 6 days to the day of stillbirth. We also explored effect modification by fetal and maternal sociodemographic factors.
Results: The median UTCI was 13.9 ^{o}C (representing no thermal stress) while the 1st and 99th percentiles were 0.7 ^{o}C (slight cold stress) and 31.7 ^{o}C (moderate heat stress), respectively. Relative to median UTCI, we found positive associations between acute maternal cold and heat stresses and higher risks of stillbirth, increasing with the intensity and duration of the thermal stress episodes. The cumulative risk from the preceding 6 days to the day of stillbirth was stronger in the 99th percentile (RR= 1.19, 95% CI: 1.17, 1.21) than the 1st percentile (RR= 1.14, 95% CI: 1.12, 1.15), relative to the median UTCI. The risks were disproportionately higher in term and male stillborn fetuses, smoking, unmarried, ≤19 years old, non-Caucasian, and low socioeconomic status mothers.

Discussion: Acute maternal exposure to both cold and heat stresses may contribute to the risk of stillbirth and be exacerbated by sociodemographic disparities. The findings suggest public health attention, especially for the identified higher-risk groups. Future studies should consider the use of a human thermophysiological index, rather than surrogates such as ambient temperature.

Keywords: Universal Thermal Climate Index, Heat stress, Cold stress, Climate change, Temperature, Stillbirth.

Introduction

With nearly two million stillbirths occurring annually worldwide, stillbirth causes substantial psychosocial burdens for families and economic burdens for countries (UN IGME, 2020). Several risk factors have been associated with stillbirth, but a high proportion of the causes of stillbirth remain unexplained (Flenady et al., 2016; Lawn et al., 2016). The biological mechanisms of stillbirth are also yet to be established. A better understanding of the causal pathways is indispensable towards the global goal of reducing stillbirth to zero or fewer than 12 per 1000 live births in every country by 2030 (Flenady et al., 2016; UN IGME, 2020).

The increasing climate change events such as extreme temperatures have potential disproportionate impacts on health outcomes of vulnerable populations such as pregnant women and developing fetuses (Hughes et al., 2016; Lee et al., 2019). Pathophysiologic evidence from animal studies indicated that maternal exposure to extreme temperatures (heat or cold stress) disrupt thermoregulation, cause hyper- or hypothermia and oxidative stress that affect placental and fetal physiology, leading to adverse pregnancy outcomes (Edwards et al., 2003; van Wettere et al., 2021).

Recent epidemiologic studies are showing a strong association between maternal exposure to heat and cold stress and the higher risk of stillbirth with multiple temperature metrics (Chersich et al., 2020; Sexton et al., 2021). However, defining heat or cold stress from ambient temperature with or without relative humidity (Sexton et al., 2021; Vanos et al., 2020) has been reported as an oversimplification of the net heat load of human exposure (Vanos et al., 2020). This approach does not account for the heat balance between the actual thermal environment and human physiological and behavioural responses (Nazarian and Lee, 2021; Vanos et al., 2020). Also, the exposure assessments were mostly derived from ground-based meteorological monitors that are distant from where people reside (Nazarian and Lee, 2021; Sexton et al., 2021). Consequently, the findings may be unrealistic with high uncertainty which impedes timely and cost-effective decision-making (Lee et al., 2019; Vanos et al., 2020). The multiple temperature metrics also hinders objective comparison of findings across studies (Jendritzky et al., 2012; Romaszko et al., 2022). Some recent studies have recommended exposure assessment with human thermophysiological indices at high spatiotemporal resolution (Nazarian and Lee, 2021; Staiger et al., 2019; Vanos et al., 2020). Four principal thermophysiological indices that have been recommended to date include Universal Thermal Climate Index (UTCI), Physiological Equivalent Temperature (PET), Perceived Temperature, and rational Standard Effective Temperature (SET) (Staiger et al., 2019). Among these indices, UTCI best represents specific climatic conditions at a location and is most sensitive to changes in ambient thermal stimuli as similar to the human body (Blazejczyk et al., 2012; Bröde et al., 2013). There are growing applications of UTCI (Krüger, 2021). However, a recent systematic review reported underutilisation of UTCI in thermal stress-related studies in epidemiology and medical sciences, despite the prognostic potential of UTCI to support climate change-related public health and clinical interventions. UTCI was utilised in only a few studies on mortality and cardiovascular diseases (Romaszko et al., 2022). So far, only one known study on pregnancy outcomes used UTCI and calculated UTCI with meteorological parameters from one synoptic station (Khodadadi et al., 2022), which would have introduced increasing exposure misclassification with distance from the station.

Stillbirth remains a major public health concern in high-income countries (HICs), including Australia (Flenady et al., 2016; Flenady et al., 2020). Compared with other HICs, Australia's late-gestation (> 28 weeks) stillbirth rate in 2015 was 2.7 per 1,000 births which was found to be 30% higher than other best-performing HICs such as Iceland and Denmark (Flenady et al., 2016; Flenady et al., 2020). Annually, Australia records over 2,000 stillbirths which translate to at least six women experiencing this traumatic event daily (Flenady et al., 2020). About 40% of Australia's stillbirths occurring in late gestation were unexplained (Flenady et al., 2020). Given severe climate change events in Australia

(Hughes et al., 2016), maternal exposure to heat or cold stress during late gestation may explain some fraction of the unexplained causes of stillbirths. Three previous Australian studies, all from Brisbane, Queensland found a positive association between extreme ambient temperatures and stillbirth. However, there were some inconsistencies: higher risk in both low and high temperatures at the second trimester (Li et al., 2018), higher risk in early than late pregnancy exposure to a heatwave in warm months (Wang et al., 2019), and higher risk in the last four weeks of gestation (Strand et al., 2011). Also, none of these studies examined the acute effect of the exposure leading up to the day of fetal death as reported in other HICs through a time-stratified case-crossover design (Auger et al., 2017; Basu et al., 2016; Rammah et al., 2019). Furthermore, due to the geoclimatic variations, acclimatisation, and mitigation strategies, even findings at specific geographic locations within the same country cannot necessarily be generalised to different climatic and sociodemographic conditions. Therefore, geoclimatic-specific studies that reflect local level variation can be more beneficial (Sexton et al., 2021).

We aimed to address the above limitations by using a spatiotemporally resolved UTCI rather than ambient air temperature to investigate the associations between maternal exposure to acute heat and cold stresses and stillbirth in Western Australia (WA). This study hypothesised that maternal exposure to both heat and cold thermophysiological stress on and up to 6 days before stillbirth was associated with higher risk of stillbirth, and that such associations were further higher among sociodemographically susceptible groups.

2. Methods

This study was reported following the REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines (Benchimol et al., 2015).

2.1 Study design

We conducted a space-time-stratified case-crossover design (Wu et al., 2021). A case-crossover design is a case-only self-matched approach in which a case serves as its control and therefore eliminates within-person time-invariant confounders such as sociodemographic factors (Maclure, 2017; Mostofsky et al., 2018). Time-varying confounders are also controlled by a referent selection strategy that matches on a series of 'control or referent times' to the 'case or index time' (Janes et al., 2005). Furthermore, the time-stratified self-matching can be implemented at multiple small-area levels for assigning the exposure at a fine spatiotemporal scale to reduce exposure misclassification (Armstrong et al., 2014; Lu et al., 2020; Vicedo-Cabrera et al., 2020). We used a time-stratified case-crossover design at a small area level to control for seasonal and long-term trends by matching case and control days within a day of the week, month, and a year within the same small area in the study location (Armstrong et al., 2014; Vicedo-Cabrera et al., 2020; Wu et al., 2021). A maximum lag of 21 days was used to eliminate the potential displacement of acute effect or the 'mortality displacement', defined as the reduction in the risk at longer lags which cancel out the higher risk associated with the acute exposure effect (Bhaskaran et al., 2013; Gasparrini et al., 2015).

2.2 Study population and case identification

WA is the largest state in Australia, covering 2.6 million km², with a total population of 2.7 million and diversified climatic zones (ABS, 2021). This study used a retrospective birth cohort of all births in WA between 1st January 2000 to 31st December 2015, selected from the Midwives Notification System. The Midwives Notification System is a statutory health data collection of all births with at least 20 weeks' of completed final gestation or at least 400 g birth weight if the gestational length is unknown (GoWA, 2021). The system contains individual-level information for mothers and children along with maternal residential address at the time of delivery at statistical area level 1 (SA1). SA1s are the second smallest geographical unit defined in Australia (ABS, 2011). A total of 474,835 births occurred during the study period. We sequentially excluded the births with missing SA1 (n = 35,352), multiple births (n = 13,026), and live births (n = 423,611). Given that we considered a maximum of 21 lag days, we excluded births less than 21 days of the end of the study period to allow sufficient follow-up time (n = 11). The final sample consisted of 2,835 singleton stillbirths in 2,041 SA1, representing 6.0 per 1,000 births in this study. Stillbirth was defined as neonates born with no sign of life at or after ≥ 20 weeks' completed gestation (Flenady et al., 2020; Li et al., 2018; Strand et al., 2011; Wang et al., 2019). We also defined subgroups based on the following information: fetal sex (male or female), gestational age (preterm if < 37 weeks' gestation or term birth), maternal age at birth delivery (≤ 19, 20–34, and ≥ 35 years), tobacco smoking status (non-smoker or smoker), and race or ethnicity (Caucasians and non-Caucasians). We also categorised birth into three seasons: summer (December-February), winter (June-August), and the transition period (remaining months). Similarly, the year of birth was trisected (2000-2004, 2005-2009, 2010-2015). The Index of Relative Socio-economic Disadvantage at a Statistical Local Area level derived by the Australian Bureau of Statistics (ABS, 2018) was assigned to the maternal residence at the time of birth and categorised into quintiles as described previously (Gebremedhin et al., 2019). We grouped quintiles 1st and 2nd as high and 3rd-5th as low socioeconomic status (SES) groups.

A known limitation in stillbirth data is the unknown time of fetal death (Auger et al., 2017). The date of stillbirth delivery is pathologically different from the time of fetal death due to the wide window period between the last evidence of fetal life and the first evidence of fetal death (Paternoster et al., 2019). The average delay time between fetal death and delivery has been reported as 48 hours with a median of fewer than 24 hours based on histologic evaluation (Gardosi et al., 1998; Genest and Singer, 1992). In HICs, 5.5–18.4% of stillbirths occur during labour (intrapartum) with the majority occurring before the onset of labour (antepartum) (Lawn et al., 2016). The antepartum stillbirth rate in Australia is 82.7% (AIHW, 2021). Therefore, as commonly reported in previous studies, we defined the day of stillbirth (case day) by deducting 2 days from the date of stillbirth delivery to correct for the estimated 48 hours average of death-to-delivery delay (Auger et al., 2017; Basu et al., 2016; Gardosi et al., 1998).

2.3 The UTCI exposure

The UTCI is an isothermal equivalent air temperature (^{o}C) that describes both atmospheric heat exchange conditions (stress) and human physiological responses (strain) based on thermophysiological and heat exchange theories (Blazejczyk et al., 2013; Jendritzky et al., 2012). UTCI was derived from the advanced Fiala multi-node model of human thermoregulation (Bröde et al., 2012; Jendritzky et al., 2012). We obtained the UTCI from the ERA5-HEAT (Human thermal comforT) dataset, a novel dataset derived by Di Napoli *et al* from the ERA5 reanalysis (Di Napoli et al., 2021). The ERA5 reanalysis is a climate dataset that combines global climate model data with quality-controlled historical in situ and satellite observations across the world to provide a global complete and consistent description of multiple climate variables (Hersbach et al., 2020). The ERA5 dataset was created by the European Centre for Medium-Range Weather Forecasts (ECMWF) at an hourly level from 1979 to date at $0.25^{\circ} \times 0.25^{\circ}$ spatial resolution. The ERA5-HEAT dataset took inputs from the following ERA5 variables: 2 metres above ground level for both air temperature and dew point temperature (relative humidity), wind speed at 10 metres above ground level, solar radiation, and thermal radiation at the surface of the Earth (Di Napoli et al., 2021). As a thermophysiological stress index, UTCI calculation requires the mean radiant temperature (MRT) as an input variable. The MRT describes the heat load experienced by a person in an outdoor environment and irradiated by solar and thermal radiation given an environment, posture, and thermal properties of clothing (Di Napoli et al., 2020; Tredre, 1965). MRT was calculated from the ECMWF numerical weather prediction model radiation outputs that accounted for changes in the Sun's position to generate global gridded MRT (Di Napoli et al 2020). The gridded UTCI was then computed by an automated operational procedure via a six-order polynomial equation from four gridded stacks: MRT and ERA5-retrieved air temperature, relative humidity, and wind speed (Bröde et al., 2012; Di Napoli et al., 2021). Further description of the gridded UTCI dataset is available elsewhere (Di Napoli et al., 2021). We obtained the daily gridded UTCI at 0.25° × 0.25° spatial resolution of the 24 hours averages between 1st January 2000 to 31st December 2015 across Australia and extracted the UTCI at the SA1 levels in WA using ArcGIS software (version 10.8.1).

2.4 Statistical analysis

We combined distributed lag non-linear model (DLNM) with conditional quasi-Poisson regression to simultaneously investigate the immediate and cumulative lagged effects of the time-varying UTCI exposure on stillbirth (Armstrong et al., 2014; Gasparrini et al., 2010; Khodadadi et al., 2022; Vicedo-Cabrera et al., 2020). The non-linear exposure–lag–response association was defined through the cross-basis term (Gasparrini, 2014; Gasparrini et al., 2010) of the UTCI predictor using natural cubic splines in both dimensions of the UTCI predictor and the lags with a maximum of 21 lag days. Spline knots were set at equally spaced values on the log scale of lags (Gasparrini, 2014; Gasparrini et al., 2010). The selection of the degrees of freedom (number of knots) for UTCI predictor and lag days was based on the minimisation of the Akaike information criterion (AIC) among different combinations (Gasparrini, 2014; Gasparrini et al., 2010). Accordingly, we selected 2 and 3 degrees of freedom for the predictor and lags, respectively. The modelling framework was specified as follows:

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

where α is the intercept; $Y_{t,s}$ is the observed number of daily stillbirths at day *t* in spatial location *s* (SA1); *cb* is the cross-basis function to model the non-linear exposure-lag-association of daily UTCI, and *holiday* is a binary indicator variable for public holidays. The factor variable *stratum* defined the same days of the week in the same month of the same year at the same SA1. We conditioned on the *stratum* through the "eliminate" function in "gnm" package to include adjusted factors that are required in the model but are not of direct interest (Armstrong et al., 2014; Turner and Firth, 2020). This also substantially improved the computational efficiency of the modelling even where there were many factor levels (Armstrong et al., 2014; Turner and Firth, 2020). This modelling framework has been applied recently (Lu et al., 2020; Vicedo-Cabrera et al., 2020), and the methodology has been previously described elsewhere (Armstrong et al., 2014; Gasparrini, 2014). The median UTCI was used as a reference to estimate the relative risks (RRs) and 95% confidence intervals (CIs) at the cold (1st and 5th percentiles), mild (25th and 75th percentiles), and heat stress (95th and 99th percentiles). We presented the results for the immediate effects of exposure on the day of fetal death (lag 0) and cumulative effects from day 0 up to preceding day N (lag 0-N) for the first six preceding days (Auger et al., 2017; Basu et al., 2016; Dastoorpoor et al., 2021; Khodadadi et al., 2022; Rammah et al., 2019). We also reported for lag 0-13 and lag 0-21, representing exposure up to the second- and third-weeks preceding stillbirth respectively (Dastoorpoor et al., 2021; Khodadadi et al., 2022). We reported cumulative effects rather than individual lag days to avoid potential spurious findings due to collinearity associated with single-lag results in distributed lag models (Basagaña and Barrera-Gómez, 2021; Bhaskaran et al., 2013).

We also calculated the attributed risk (AR) as the number of excess stillbirths per 10,000 births that could be attributable to cold and heat stress exposures (Ha et al., 2017):

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

where I_u is the background rate. This was taken as the study-specific incidence rate and calculated as from the eligible stillbirths and the total birth over the study period (0.6%). RR is the estimated RR (95% CI) for immediate (lag 0) and cumulative (lag 0-6) cold and heat stress exposures, relative to the median UTCI.

Subgroup analyses were conducted to investigate the potential modification effects of the fetal and maternal sociodemographic factors described earlier. Missing fetal sex (n = 6), gestational age (n = 29), and tobacco smoking status (n = 16) records were excluded from subgroup analyses. We reported the RR (95% CI) for the 1st and 99th percentiles, relative to the median UTCI.

We also performed several sensitivity analyses to ascertain the robustness of the main analysis to choices of the model assumptions. We changed the degrees of freedom to 3 for both UTCI predictor and lags; and then to 3 for the predictor with 4 for lags. Also, we changed the reference median UTCI to mean UTCI; and then to the average of the standard *no thermal stress* range which is 17.5 °C (Blazejczyk et al., 2013; Di Napoli et al., 2021). Due to discrepancies in the event day definition, we redefined the stillbirth date as a day death-to-delivery delay (Rammah et al., 2019) and then day of stillbirth delivery (Dastoorpoor et al., 2021; Khodadadi et al., 2022) and reanalysed the data.

All analyses were performed with R software (version 4.1.1) and the packages 'dlnm' (Gasparrini et al., 2010) and 'gnm' (Turner and Firth, 2020) were used to fit DLNM and conditional quasi-Poisson regression, respectively. Following the recent recommendations of the American Statistical Association, we reported and interpreted the RR (95% CI) without considering the 'statistically significant' threshold (Wasserstein et al., 2019).

3. Results

3.1 The UTCI exposure and birth cohort characteristics

The standard UTCI ranges were originally categorised into 10 thermal stresses levels corresponding to specific human physiological responses to the actual thermal environment (Blazejczyk et al., 2013; Di Napoli et al., 2021). Across the study period, the mean (± standard deviation) and median UTCI (interquartile range) were 14.6 °C (± 6.8 °C) and 13.9 °C (9.4 °C), respectively, both falling within the *no thermal stress* range of 9 °C to 26 °C. The 1st (0.7 °C) and the 99th (31.7 °C) percentiles were within *slight cold stress* and *moderate heat stress* levels, respectively. The largest mean UTCI was observed in summer (20.6 ± 5.4 °C), 2010-2015 (15.2 ± 6.8 °C) which also lied within the *no thermal stress* range (Table 1). Out of the total of 2,835 singleton stillbirths included in this study, 41.4% occurred during 2010-2015 and over half (51.4%) in the transition seasons. Slightly above half were males (52.1%) and the majority were preterm stillborn (80.8%). Most of the pregnant women did not smoke (78.4%), were married (83.5%), aged between 20–34 years (71.1%), and Caucasians (69.6%). More than three fifth of the births were to women who resided in low SES areas (64.3%) (Table 2).

3.2 Thermophysiological stress and stillbirth

The exposure-response association on the day of fetal death (lag 0) and the cumulative effects showed U-shaped curves, indicating that both cold and heat thermal stresses associated positively with the risk of stillbirth (Figure). Relative to the median UTCI (no thermal stress), the positive associations increased with the intensity and duration of the thermal stress episodes. The risks were stronger at the cold stress (1st and 5th percentiles) and heat stress (95th and 99th percentiles) than the 'mild' thermal stress (25th and 75th percentiles), increasing with cumulative exposures. Relative to no thermal stress (median UTCI), the risk of stillbirth for exposure to cold stress (1st percentile) and heat stress (99th percentile) were very similar on the day of stillbirth up to two preceding days and then the same at 8% higher risk on the cumulative three days (RR=1.08, 95% CI: 1.07, 1.09). Thereafter, the cumulative risks were stronger in the heat than cold stress. The cumulative risk from the 6 preceding days to the day of stillbirth was higher by 14% in the 1st percentile (RR= 1.14, 95% CI: 1.12, 1.15) but higher by 19% in the 99th percentile (RR= 1.19, 95% CI: 1.17, 1.21) as compared to the risks at the median UTCI. There was also an indication of long-term effects as observed in the higher risk in relatively prolonged cumulative lag days (0-13 and 0-21) (Table 3). Compared to the median UTCI, acute cumulative exposures for days 0 to 6 of cold and heat stress were approximately attributed to 8 (95%

CI: 7, 9) and 11 (95%CI: 10, 12) excess stillbirths per 10,000 births, respectively, using our study-specific background incidence as reference (Table 4). Both heat and cold stresses indicated lower risks during winter but higher risks during summer and transition seasons. The cumulative effect for days 0 to 6 of heat stress was 124% higher during transition (RR = 2.24, 95% CI: 2.19, 2.30) and 21% higher during summer (RR = 1.21, 95% CI: 1.18, 1.25), relative to season-specific median UTCI (Table S1). The risks were relatively elevated in earliest year 2000-2004 (Figure S).

3.3 Thermophysiological stress and stillbirth by fetal factors

The immediate and cumulative effects by gestational age showed a higher risk in the term than preterm stillbirths. Relative to the median UTCI, the risks were higher in heat stress (99th percentile) than cold stress (1st percentile) for term stillbirth but higher in cold than heat stress for preterm stillbirths. Consistent with the main findings, all the risks were higher with increasing cumulative exposure to either cold or heat thermal stress. For example, the cumulative risk for cumulative exposure in the 6 days preceding stillbirth to the 1st and 99th percentiles, relative to the median UTCI were higher by 45% (RR=1.45, 95% CI: 1.43, 1.47) and 91% (RR=1.91, 95% CI:1.88, 1.94) for term and 12% (RR=1.12, 95% CI: 1.10, 1.13) and 11% (RR=1.11, 95% CI:1.10, 1.13) for preterm stillbirths. While female fetuses were almost unaffected, male fetuses were more susceptible to both cold and heat stresses. The risks were elevated with more cumulative days of exposure and was higher in the 99th percentile than the 1st percentile, relative to the median UTCI (Table 5).

3.4 Thermophysiological stress and stillbirth by maternal sociodemographic factors

Relative to the median UTCI, there was no observable short-term effect of exposure to thermal stress among pregnant women who did not smoke during pregnancy. Conversely, both cold and heat stresses showed higher risks of stillbirth in pregnant women who smoked, increasing with duration of exposure and stronger for cold than heat stress. For example, for cumulative 0 to 6 days exposure, the risks were 142% higher in the 1st percentile (RR= 2.42, 95% CI= 2.39, 2.45) and 81% higher in the 99th percentile (RR= 1.81, 95% CI: 1.78, 1.83), relative to median UTCI among those women that smoked during pregnancy. Unmarried pregnant women experienced a higher risk of stillbirth from cold and heat stresses as compared to those identified as married and the risk was stronger in the 99th percentile than 1st percentile, relative to the median UTCI. Regarding races or ethnicity, Caucasians experienced essentially no impact for cold stress but for heat stress, example 8% higher risk (RR=1.08, 95% CI: 1.06, 1.09) for cumulative exposure in the 6 days preceding stillbirth. Relative to median UTCI during the same exposure period, non-Caucasians experienced more elevated risks of 92% higher (RR= 1.92, 95% CI: 1.90, 1.95) and 44% higher (RR=1.44, 95% CI: 1.42, 1.46) for cold and heat stresses, respectively. The immediate effect and cumulative effects for the first five preceding days were more elevated in the high than low SES women for both 1st and 99th percentiles, relative to the median UTCI. However, periods of exposure (from 6 days upward) showed more elevated risk in low than high SES groups (Table 6).

Women aged ≥ 35 years experienced no or small lower risk from exposure to cold or heat stress, but adverse associations were observed in the other subgroups and more elevated in adolescents (≤19 years) than young adults (20–34 years). Relative to the median UTCI, the risk was stronger in the 99th than 1st percentile for lag 0 to lag 0-4 but became stronger in the 1st than 99th percentiles for longer periods of exposure (Table 7).

3.4 Sensitivity analyses

Results were generally similar to that of the main analyses after changing the degrees of freedom for defining the cross-basis matrices (Table S2). Similarly, the main results showed no substantial difference when either daily mean UTCI or average of the standard no thermal stress range was used as the reference UTCI (Table S3). However, redefining the case day (day of stillbirth) as a day preceding the delivery day showed no association for the immediate and most of the shorter durations of exposure, particularly for the 1st percentile relative to the median UTCI. The results showed lower risk when the delivery day was used as the case day (Table S4).

4. Discussion

4.1 Main findings

Both mean and median UTCI were within the standard no thermal stress ranges. The 1st and 99th percentiles of UTCI were within slight cold stress and moderate heat stress ranges, respectively (Blazejczyk et al., 2013; Di Napoli et al., 2021). Relative to the median UTCI, we found positive associations between both immediate and short-term cumulative exposures to various thermal stress conditions and the risk of stillbirth in WA. The risks were particularly elevated in both the 1st percentile (cold stress) and the 99th percentile (heat stress). The risks were higher by the intensity and duration of the thermal stress episodes and were comparatively stronger in the heat than cold stress. We also observed higher risks in cumulative exposures from 13 and 21 days until stillbirth, suggesting that longer thermal stress also played a role and should be considered in future studies (Strand et al., 2011).

Our findings were consistent with previous studies that evaluated the acute exposure to extreme temperatures and the risk of stillbirth (Auger et al., 2017; Basu et al., 2016; Rammah et al., 2019). For instance, studies from the USA reported a percentage change of 10.4% (95% CI: 4.4, 16.8) (Basu et al., 2016) and 39% higher odds (OR= 1.39, 95% CI: 1.15, 1.69) (Rammah et al., 2019) of stillbirth per 10 °F increase in mean apparent temperature for cumulative average exposure of lag days 2 to 6 before the day of delivery during the warm season. Basu *et al* further reported for the cold season and found no association (Basu et al., 2016). Our results showed positive associations in both cold and heat stresses that increased with intensity and duration of exposure but were stronger in the heat than cold stress. Considering the exposure, the more comparable studies were two time-series analyses, both in Iran that also used UTCI (Khodadadi et al., 2022) and Physiological Equivalent Temperature (PET) (Dastoorpoor et al., 2021). However, in addition to the design, these studies varied from ours as the UTCI and PET were derived with meteorological factors from one synoptic meteorological station and used the delivery day as the event day (day of stillbirth). Khodadadi *et al* found higher risk of stillbirth that included the null at 99th percentile (46.4 °C) and lower risk at 1st percentile (11.6°C), relative to median UTCI (17.5 °C, no thermal stress) for acute exposures (Khodadadi et al., 2022). Compared to median PET (defined as no thermal stress), the risk of stillbirth with high PET (99th percentile) was most elevated at lag 0 but weaker at cumulative lag days and the low PET (1st percentile) showed lower risks (Dastoorpoor et al., 2021). From our sensitivity analysis that considered delivery day as the day of stillbirth, we found small lower risks in both 99th and 1st percentiles, relative to the median UTCI. However, it has been documented extensively in the literature that there is a death-to-delivery delay for which reason the time of death in stillborn fetuses will be highly inaccurate if taken as the time of stillbirth delivery (Gardosi et al., 1998; Genest and Singer, 1992; Paternoster et al., 2019). Consistent with our main findings, Li *et al* concluded that maternal exposure to both low and high ambient temperatures showed higher risks of preterm birth and stillbirth in Brisbane, Australia (Li et al., 2018). This also means that depending on the population characteristics, climatic conditions, adaptation strategies, and the level of outdoor activities during either cold or heat stress, the lower risks could be observed. The difference between our results and few previous studies, may be justified by the strength of the study design and analysis (Mostofsky et al., 2018; Wu et al., 2021), the UTCI, and spatiotemporal exposure assessment (Nazarian and Lee, 2021; Staiger et al., 2019; Vanos et al., 2020) in addition to the climatic and maternal behavioural characteristics described earlier. Furthermore, compared with other thermal indexes, including PET, the UTCI has been shown to be most appropriate and best represents specific climatic conditions at any geographical location, is very sensitive to changes in ambient thermal stimuli just as the human body, and can express even slight differences in the intensity of the thermal stimuli (Blazejczyk et al., 2012; Jendritzky et al., 2012). A recent review therefore recommended UTCI for future thermal-related studies and early warning systems (Krüger, 2021). We found that the most elevated risks were during the transition seasons and earliest year 2000-2004. During the study period there may have been continuous improvements in antenatal care services; housing conditions, which included the use of air conditioners and other mitigation strategies; and acclimatisation. These may have contributed to the lower risks in the later years as compared to the early years. However, with increasing severity of climate change and noticeable impacts on health outcomes (Hughes et al., 2016; Lee et al., 2019), risk may be expected to be higher in the most recent years. Furthermore, by the standard UTCI range, our estimated risks were for *slight cold stress* and *moderate heat stress,* relative to *no thermal stress* (Blazejczyk et al., 2013; Di Napoli et al., 2021). It is therefore more plausible to observe stronger risks and higher number of excess stillbirths in other study areas where the 1st and 99th percentiles of UTCI are in greater thermal stress ranges. Our result also indicated that sudden adaptation during transition periods for acute exposure might be difficult, leading to relatively elevated risk in this season. It is also plausible that pregnant women reduced exposure level by cautiously reducing outdoor activities or increasing the use of cooling and heating systems during winter and summer as compared with the transition season.

The finding was also consistent with the recent meta-analysis of four studies that found 24% higher odds (OR =1.24, 95% CI: 1.12, 1.36) of stillbirth during high versus low ambient temperatures with exposure period less than one week (Chersich et al., 2020). Thus, pregnant women and particularly at late gestational periods may not be able to immediately adapt or thermoregulate the acute exposure to thermal stresses, potentially elevating the risk of stillbirth (Auger et al., 2017; Chersich et al., 2020).

4.3 Potential effect modification by fetal factors

Consistent with the previous finding, our results indicated a comparatively stronger risk of stillbirth in male than in female fetuses (Basu et al., 2016). This is explainable as sex-specific maternal–placental–fetal interaction through the mechanisms of genetic, epigenetic, and hormonal effects (Al-Qaraghouli and Fang, 2017; Catalano et al., 2008). The response to environmental exposures is favoured by natural selection *in utero* (Al-Qaraghouli and Fang, 2017; Catalano et al., 2008). Compared to the female fetus, the male fetus has faster fetal development and metabolic rates that results in potentially higher allostatic load, which can be increased in the presence of environmental stressors (Catalano et al., 2008; Mondal et al., 2014). Therefore, when pregnant women are exposed to environmental stressors, the biological system could easily abort less resilient male fetuses than female fetuses to enhance survivability and liveability (Catalano et al., 2008). A systematic review and meta-analysis found an elevated risk of stillbirth in males by about 10% (Mondal et al., 2014).

Regarding gestational age, we found a stronger risk in term stillborn than preterm stillborn fetuses which is consistent with finding in Quebec, Canada (Auger et al., 2017). Conversely, a study in Brisbane, Australia found that increasing temperature associated with higher risk of stillbirth for preterm but observed no association for term stillborn (Strand et al., 2011). This study, however, analysed the association of mean temperature in the last four weeks (Strand et al., 2011) which represents chronic exposure rather than the acute exposure assessment applied in our study, and others (Auger et al., 2017; Basu et al., 2016; Dastoorpoor et al., 2021; Rammah et al., 2019). Given the ubiquity of the thermal environment, extremes in maternal thermal exposure may occur throughout the pregnancy period which puts term stillbirths at longer exposure than the preterm stillbirths. Preterm stillbirths, however, have other major competing risk factors such as malformations, chromosomal abnormalities, and congenital infections (Mondal et al., 2014) that may far exceed the impact of acute thermal stress, which thereby remains concealed. Pregnant women at term need to be more cautious and warrant closer monitoring during thermal stress episodes (Auger et al., 2017).

4.4 Potential effect modification by maternal sociodemographic factors

Some subpopulations of pregnant women such as smokers, unmarried, adolescents, and non-Caucasians were more susceptible to the acute effect of the cold or heat stress. Residing in high SES areas showed stronger risk from case day up to the previous 5 days after which the risk became stronger in low SES areas. Apart from smoking status which showed elevated risk in cold than heat stress, the observed risks were more elevated in the heat stress for all other examined sociodemographic factors. Smoking during pregnancy, which is more likely to be intensified and hazardous in cold conditions (Arku et al., 2015), has been well-documented as a contributor to pregnancy outcomes, including stillbirth (Gould et al., 2020). This could also be due to more complex interactions with age, race, and SES where the risks may be further elevated in young, non-Caucasian, unmarried and low SES mothers who are more vulnerable to smoking and at higher risk of stillbirth. Further investigation is necessary to evaluate the magnitude of such interactions. There is a tendency for reduced risky behaviours and outdoor activities among married individuals and older adults, resulting in lower risks in these subgroups as compared to their counterparts (Basu et al., 2016). Additionally, married women may also benefit from economic and psychosocial support from their partners which reduce economic and psychosocial stress, thereby also reducing their risk of stillbirth as compared to the unmarried women. For racial or ethnicity disparities, genetic and socioeconomic vulnerabilities, structural or systemic racism, low level of antenatal care utilisation, and indulgence in more risky behaviours (e.g., smoking, illicit drug or alcohol intake) were reported previously to have contributed to the added risk of stillbirth in the non-Caucasians in high-income countries (Alson et al., 2021; Basu et al., 2016; Rammah et al., 2019). Generally, climate change-related factors such as thermal stress interact with these maternal factors to exacerbate the impacts on health outcomes (Ebi et al., 2021). Several other modifiable risk factors, and maternal infections such as syphilis, hepatitis (Lawn et al., 2016), and seasonal influenza with a peak during cold weather (Wang et al., 2021) also contribute to the higher risk of stillbirth. With the projection of more severe extreme climatic events, more investment in research and appropriate thermal stress risk management actions are required to prevent the preventable climate change-related adverse health outcomes, especially among the vulnerable subpopulations (Chersich et al., 2020; Ebi et al., 2021). These may include thermal mitigation strategies such as hydration, *greening* the environment (particularly planting of shade or canopy cover trees), providing public shade structures, increasing affordability of cooling and heating technologies and other biophysical solutions, and heat warning systems.

4.2 Biological mechanisms

Evidence regarding biological pathways by which the ambient thermal environment can lead to stillbirth is accumulating. Findings from *in vivo* studies have indicated that heat or cold stress could cause hyper- or hypothermia and oxidative stress that affect placental and fetal physiology, and fetoplacental exchange of materials, leading to adverse pregnancy outcomes (Edwards et al., 2003; van Wettere et al., 2021). Human thermophysiological responses to thermal stress involve energy balance and metabolism to maintain the core body temperature within a narrow range on either side of 37°C (Blazejczyk et al., 2013; Collier et al., 2017). Thermal stress disrupts the maternal thermoregulatory mechanism, alters the *in utero* thermal environment, and causes hyperthermia or hypothermia with negative impacts on the mother and fetus (Edwards et al., 2003; Hansen, 2009). Such thermal stress and the associated thermophysiological responses can induce cellular and biochemical catalytic processes, leading to oxidative damage, cell death, and other pathophysiological responses that lead to adverse pregnancy outcomes, including stillbirth (Collier et al., 2017; Xu et al., 2019; Ziskin and Morrissey, 2011). Thermal vulnerability is also exacerbated by women's risk profiles involving maternal age, sweating capacity, cardiovascular function, respiration rate, subcutaneous fat, pH, and nutritional status (Ziskin and Morrissey, 2011) and worsened by poor maternal low sociodemographic status. Moreover, decreased surface area to body mass ratio during pregnancy reduces the ability of the body to dissipate heat to the external environment through sweating (Wells and Cole, 2002). Maternal weight gain, fetal growth, and fetal metabolic activity further increase the maternal basal metabolic rate and heat stress (Mondal et al., 2014; Wells and Cole, 2002). These increase at the late gestational period, peaking at term, and higher in male than female fetuses (Auger et al., 2017; Mondal et al., 2014). There is also impairment of placental development and function by maternal hyperthermia and severity depends on the gestational period (van Wettere et al., 2021). Another pathway is related to dehydration from increased maternal urination and sweating which could result in a low volume of blood water. Consequently, the uterine and placental blood flow reduces and affects the transport of heat, oxygen, and nutrients to the developing fetus, a precursor to fetal death. Furthermore, as a heat dissipation mechanism, asymptomatic thermal stress can theoretically increase the shunting of blood volume to the periphery, alter placental and umbilical blood perfusion, and thereby reduce the fetoplacental exchange of heat and materials (Edwards et al., 2003; Ziskin and Morrissey, 2011). Maternal heat or cold stress can also induce a 'thermal shock' response in the developing fetus (Edwards et al., 2003). Rapid cell division makes the fetus sensitive to the fetal thermal environment which is largely regulated by the mother, leading to fetal vulnerability to maternal thermal stress (Ziskin and Morrissey, 2011).

4.5 Strengths and Limitations

This study has several strengths. One major strength was the space-time-stratified case-crossover design and the analytical framework. These enabled us to significantly minimise time-invariant and known and unknown confounding factors. Unlike previous studies that used temperature or apparent temperature, we used a more robust, and physiologically relevant thermophysiological index, the UTCI with spatiotemporal variability (Jendritzky et al., 2012; Krüger, 2021; Nazarian and Lee, 2021; Vanos et al., 2020). We also examined many maternal sociodemographic effect modifiers. Furthermore, this was the first study to our knowledge that specifically investigated the acute effect of thermal stress in a few days preceding delivery and the risk of stillbirth in Australia.

We also acknowledged some limitations in this study. First, a known limitation of all stillbirth data is the lack of accurate information on the time of stillbirth and so estimated this with 48 hours (2 days) delay as mostly reported in the literature based on a histologic report (Gardosi et al., 1998; Genest and Singer, 1992). There are presently no reliable imaging techniques for the accurate estimation of the fetal or stillbirth time of death (Paternoster et al., 2019). Second, we did not have information on indoor thermal conditions or the use of air conditioning systems. Third, our exposure assessment did not account for time-location-activity patterns of pregnant women and change of residential address during pregnancy. However, the potential exposure misclassification from activity patterns would be expected to bias the estimated effects towards the null (Rammah et al., 2019). For residential mobility, we least expect this to result in minimal misclassification given that we analysed associations in short-term periods shortly before delivery (Rammah et al., 2019). Moreover, previous studies on associations between air pollutants and pregnancy outcomes found no clear evidence of the influence of maternal residential mobility during pregnancy (Edwards et al., 2022). Fourth, we did not have sufficient data to separately analyse intrapartum and antepartum stillbirths. Finally, we cannot exclude the possibility of the existence of influential effect modifiers that were not included in this study. We did not have data to adjust for any air pollutants, but this was not considered as a limitation (Auger et al., 2017). The adjustment of an air pollutant (an intermediate but not a confounder) in estimating the total effect of temperature or thermal stress on health outcomes has been discouraged and considered conceptually inappropriate (Buckley et al., 2014; Reid et al., 2012). Moreover, some previous studies examined this and reported no change in the results after the adjustment of air pollutants (Basu et al., 2016; Li et al., 2018; Rammah et al., 2019; Strand et al., 2011).

5. Conclusion

Relative to the median UTCI (no thermal stress), we observed higher risks of stillbirth for acute maternal exposures to thermal stresses. Risk increased with the intensity and duration of the thermal stress episodes and were particularly elevated for both cold stress (1^{st} percentile) and heat stress (99^{th} percentile). The impact of heat stress was stronger than cold stress. Acute exposures to cold or heat stress up to 6 preceding days, relative to no thermal stress was attributed to about 8 to 11 additional stillbirths per 10,000 births. We also found the most elevated risks during the transition period between summer and winter, and 2000-2004. The risks were disproportionately higher in term and male stillborn fetuses, smoking, unmarried, ≤19 years old, non-Caucasians, and low socioeconomic status mothers. Given the increasing frequency of climate change events, which include thermal extremes, healthcare practitioners and policymakers may want to consider thermal mitigation and adaptation strategies and improve resources for pregnant women, especially the identified higher-risk groups. This may contribute to preventing a proportion of stillbirths as well as have co-benefits in reducing other associated morbidities of pregnancy. Future studies may consider use of a human thermophysiological index, such as UTCI, as a more thermophysiologically relevant exposure (Krüger, 2021; Vanos et al., 2020).

Credit author statement

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

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Ethical approval

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

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Declaration of competing interest

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

Data Availability

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

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Tables

Table 1. 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	14.6 ± 6.8	0.7	9.7	13.9	19.1	31.7	41.9
Season	Winter	-12.4	8.5 ±4.1	-1.3	5.9	8.5	10.9	20.9	31.9
	Transition	-15.4	14.6 ± 5.8	1.5	10.9	14.1	18.0	30.8	40.2
	Summer	-0.6	20.6 ± 5.4	9.6	16.6	20.3	24.3	33.7	41.9
Year	2000-2004	-11.0	14.2 ± 6.7	0.5	9.4	13.5	18.7	31.2	41.9
	2005-2009	-15.4	14.1 ± 6.9	0.2	9.3	13.4	18.6	31.7	40.3
	2010-2015	-10.2	15.2 ± 6.8	1.5	10.3	14.6	19.8	32.0	41

Note: SD, standard deviation; P1, P25, P75, and P99 are 1st, 25th, 75th, and 99th percentiles respectively; UTCI, Universal Thermal Climate Index in degree Celsius.

Table 2. Number of stillbirths by year, season, and fetal and maternal sociodemographic characteristics included in the study, Western Australia, 2000-2015 (N= 2,835).

Variable	**Characteristics**	**n (%)**

Year	2000-2004	780 (27.5)
	2005-2009	880 (31.0)
	2010-2015	1,175 (41.4)
Season	Transition	1,456 (51.4)
	Winter	682 (24.0)
	Summer	697 (24.6)
Sex*	Male	1,476 (52.1)
	Female	1,353 (47.7)
	Unknown	6 (0.2)
Gestational age (weeks)*	Term (≥ 37)	514 (18.1)
	Preterm (< 37)	2,292 (80.8)
	Unknown	29 (1.0)
Smoking status during pregnancy*	Non-smoker	2,223 (78.4)
	Smoker	596 (21.0)
	Unknown	16 (0.6)
Marital status	Married/de facto married	2,370 (83.5)
	Unmarried[#]	465 (16.1)
Maternal age at delivery (years)	Teenagers (≤19)	180 (6.3)
	Young adults (20–34)	2,015 (71.1)
	Older adults (≥35)	640 (22.6)
Maternal race/ethnicity	Caucasian	1,974 (69.6)
	Non- Caucasian	861 (30.4)
Residential area's socioeconomic disadvantage status	Low	1,011 (35.7)
	High	1,824 (64.3)

[#]Never married/separated/divorced/widowed/unknown. *The missing records were excluded from subgroup analyses.

Table 3. The cumulative relative risks of stillbirth for different UTCI levels relative to median (13.9 °C), Western Australia, 2000-2015

Lag days	1st (0.7 ^{0}C) RR (95% CI)	5th (4.2 ^{0}C) RR (95% CI)	25th (9.7 ^{0}C) RR (95% CI)	75th (19.1 ^{0}C) RR (95% CI)	95th (26.7 ^{0}C) RR (95% CI)	99th (31.7 ^{0}C) RR (95% CI)
0	1.02 (1.02, 1.03)	1.01 (1.01, 1.02)	1.00 (1.00, 1.01)	1.00 (1.00, 1.00)	1.01 (1.00, 1.01)	1.01 (1.01, 1.02)
0-1	1.04 (1.04, 1.05)	1.03 (1.02, 1.03)	1.01 (1.01, 1.01)	1.00 (1.00, 1.00)	1.01 (1.01, 1.02)	1.03 (1.02, 1.04)
0-2	1.06 (1.05, 1.07)	1.04 (1.03, 1.04)	1.01 (1.01, 1.01)	1.00 (1.00, 1.00)	1.03 (1.02, 1.03)	1.05 (1.04, 1.06)
0-3	1.08 (1.07, 1.09)	1.05 (1.04, 1.06)	1.01 (1.01, 1.02)	1.00 (1.00, 1.01)	1.04 (1.03, 1.05)	1.08 (1.07, 1.09)
0-4	1.10 (1.09, 1.11)	1.06 (1.05, 1.07)	1.01 (1.01, 1.02)	1.01 (1.00, 1.01)	1.06 (1.05, 1.07)	1.12 (1.10, 1.13)
0-5	1.12 (1.11, 1.13)	1.07 (1.06, 1.08)	1.02 (1.01, 1.02)	1.01 (1.01, 1.01)	1.08 (1.07, 1.09)	1.15 (1.13, 1.17)
0-6	1.14 (1.12, 1.15)	1.08 (1.07, 1.09)	1.02 (1.01, 1.02)	1.02 (1.01, 1.02)	1.10 (1.09, 1.11)	1.19 (1.17, 1.21)
0-13	1.24 (1.22, 1.26)	1.13 (1.12, 1.14)	1.03 (1.02, 1.03)	1.03 (1.03, 1.04)	1.21 (1.19, 1.22)	1.41 (1.38, 1.44)
0-21	1.31 (1.28, 1.35)	1.18 (1.17, 1.20)	1.05 (1.04, 1.06)	1.00 (0.99, 1.00)	1.10 (1.08, 1.12)	1.22 (1.18, 1.25)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Table 4. The attributable risk of stillbirths per 10,000 births for exposure to 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015

Lag days	1st percentile (0.7 °C) AR (95% CI)	99th percentile (31.7 °C) AR (95% CI)
0	1 (1, 1)	1 (0, 1)
0-6	8 (7, 9)	11 (10, 12)
0-13	14 (13, 16)	24 (22, 26)
0-21	19 (17, 21)	13 (11, 15)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; AR, attributable risk

Table 5. The cumulative relative risks of stillbirth stratified by fetal gestational age and sex for 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015.

Fetal variable	Lag days	1st percentile (0.7 °C) RR (95% CI)	99th percentile (31.7 °C) RR (95% CI)

Gestational age		Term	Preterm	Term	Preterm
	0	1.03 (1.03, 1.03)	1.03 (1.02, 1.03)	1.07 (1.07, 1.08)	1.00 (1.00, 1.01)
	0-1	1.07 (1.06, 1.08)	1.05 (1.05, 1.06)	1.16 (1.15, 1.17)	1.01 (1.01, 1.02)
	0-2	1.12 (1.11, 1.13)	1.07 (1.06, 1.08)	1.26 (1.25, 1.28)	1.03 (1.02, 1.04)
	0-3	1.19 (1.18, 1.20)	1.09 (1.08, 1.10)	1.39 (1.38, 1.41)	1.04 (1.03, 1.06)
	0-4	1.26 (1.25, 1.28)	1.10 (1.09, 1.11)	1.54 (1.52, 1.56)	1.06 (1.05, 1.08)
	0-5	1.35 (1.33, 1.37)	1.11 (1.10, 1.12)	1.71 (1.69, 1.74)	1.09 (1.07, 1.10)
	0-6	1.45 (1.43, 1.47)	1.12 (1.10, 1.13)	1.91 (1.88, 1.94)	1.11 (1.10, 1.13)
	0-13	2.39 (2.35, 2.44)	1.12 (1.10, 1.14)	3.58 (3.50, 3.66)	1.25 (1.22, 1.27)
	0-21	3.32 (3.24, 3.40)	1.14 (1.11, 1.17)	3.81 (3.69, 3.94)	1.10 (1.07, 1.13)
Fetal sex		Male	Female	Male	Female
	0	1.07 (1.06, 1.07)	0.98 (0.98, 0.98)	1.06 (1.06, 1.07)	0.96 (0.96, 0.96)
	0-1	1.12 (1.11, 1.13)	0.97 (0.97, 0.98)	1.13 (1.12, 1.14)	0.93 (0.93, 0.94)
	0-2	1.16 (1.16, 1.17)	0.97 (0.97, 0.98)	1.21 (1.20, 1.22)	0.91 (0.90, 0.92)
	0-3	1.20 (1.19, 1.21)	0.98 (0.97, 0.99)	1.29 (1.28, 1.31)	0.90 (0.89, 0.91)
	0-4	1.22 (1.21, 1.23)	1.00 (0.99, 1.01)	1.38 (1.36, 1.40)	0.90 (0.89, 0.91)
	0-5	1.23 (1.22, 1.25)	1.03 (1.02, 1.04)	1.46 (1.44, 1.49)	0.90 (0.89, 0.91)
	0-6	1.24 (1.22, 1.25)	1.06 (1.05, 1.07)	1.55 (1.53, 1.57)	0.91 (0.90, 0.92)
	0-13	1.16 (1.14, 1.18)	1.38 (1.36, 1.41)	1.82 (1.78, 1.86)	1.12 (1.10, 1.15)
	0-21	1.15 (1.12, 1.18)	1.61 (1.57, 1.65)	0.98 (0.96, 1.01)	1.70 (1.65, 1.75)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Table 6. The cumulative relative risks of stillbirth stratified by maternal tobacco smoking status, marital status, race/ethnicity, and socioeconomic status for 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015.

Maternal variable	Lag days	1st percentile (0.7 °C) RR (95% CI)		99th percentile (31.7 °C) RR (95% CI)	
Smoking status		Non-smoker	Smoker	Non-smoker	Smoker
	0	0.98 (0.98,0.990	1.17 (1.17, 1.18)	0.94 (0.93, 0.94)	1.22 (1.21, 1.22)
	0-1	0.97 (0.97, 0.98)	1.36 (1.35, 1.37)	0.90 (0.89, 0.90)	1.42 (1.41, 1.43)
	0-2	0.96 (0.95, 0.97)	1.56 (1.55, 1.57)	0.88 (0.87, 0.89)	1.58 (1.57, 1.60)
	0-3	0.95 (0.94, 0.96)	1.77 (1.75, 1.78)	0.88 (0.87, 0.89)	1.71 (1.69, 1.73)
	0-4	0.95 (0.94, 0.96)	1.98 (1.96, 2.00)	0.89 (0.88, 0.91)	1.79 (1.77, 1.81)
	0-5	0.94 (0.93, 0.95)	2.20 (2.17, 2.22)	0.92 (0.91, 0.93)	1.82 (1.79, 1.84)
	0-6	0.94 (0.93, 0.95)	2.42 (2.39, 2.45)	0.96 (0.94, 0.97)	1.81 (1.78, 1.83)
	0-13	0.91 (0.90, 0.93)	4.22 (4.14, 4.30)	1.35 (1.32, 1.38)	1.25 (1.22, 1.27)
	0-21	0.82 (0.80, 0.84)	7.68 (7.49, 7.87)	1.33 (1.29, 1.37)	0.91 (0.89, 0.94)

Marital status		Married/de facto	Unmarried	Married/de facto	Unmarried
	0	1.01 (1.01, 1.02)	1.08 (1.08, 1.08)	0.97 (0.97, 0.97)	1.25 (1.24, 1.25)
	0-1	1.02 (1.02, 1.03)	1.19 (1.18, 1.19)	0.95 (0.95, 0.96)	1.49 (1.48, 1.50)
	0-2	1.03 (1.02, 1.04)	1.32 (1.31, 1.33)	0.95 (0.94, 0.96)	1.72 (1.70, 1.73)
	0-3	1.03 (1.02, 1.04)	1.49 (1.48, 1.51)	0.96 (0.95, 0.98)	1.91 (1.89, 1.93)
	0-4	1.03 (1.02, 1.04)	1.70 (1.69, 1.72)	0.99 (0.97, 1.00)	2.05 (2.02, 2.07)
	0-5	1.02 (1.01, 1.04)	1.96 (1.94, 1.98)	1.01 (1.00, 1.03)	2.14 (2.11, 2.17)
	0-6	1.02 (1.00, 1.03)	2.27 (2.24, 2.30)	1.05 (1.04, 1.07)	2.18 (2.15, 2.21)
	0-13	0.94 (0.92, 0.95)	6.35 (6.23, 6.47)	1.36 (1.33, 1.39)	1.65 (1.62, 1.69)
	0-21	0.88 (0.86, 0.90)	14.04 (13.68,14.41)	1.26 (1.28, 1.30)	1.03 (1.00, 1.06)
		Caucasians	Non-Caucasians	Caucasians	Non-Caucasians
Race or ethnicity	0	0.99 (0.99, 0.99)	1.10 (1.10, 1.10)	0.98 (0.97, 0.98)	1.09 (1.09, 1.10)
	0-1	0.98 (0.98, 0.99)	1.21 (1.20, 1.22)	0.97 (0.96, 0.98)	1.18 (1.17, 1.18)
	0-2	0.97 (0.96, 0.98)	1.33 (1.32, 1.34)	0.97 (0.96, 0.98)	1.25 (1.24, 1.26)
	0-3	0.96 (0.95, 0.97)	1.46 (1.45, 1.47)	0.99 (0.97, 1.00)	1.32 (1.30, 1.33)
	0-4	0.95 (0.94, 0.96)	1.60 (1.58, 1.62)	1.01 (1.00, 1.02)	1.37 (1.35, 1.39)
	0-5	0.93 (0.92, 0.94)	1.75 (1.73, 1.78)	1.04 (1.03, 1.06)	1.41 (1.39, 1.43)
	0-6	0.92 (0.91, 0.93)	1.92 (1.90, 1.95)	1.08 (1.06, 1.09)	1.44 (1.42, 1.46)
	0-13	0.81 (0.79, 0.82)	3.50 (3.44, 3.57)	1.36 (1.33, 1.39)	1.42 (1.40, 1.45)
	0-21	0.67 (0.65, 0.69)	6.47 (6.31, 6.63)	1.19 (1.15, 1.23)	1.19 (1.16, 1.22)
Area-level SES		Low	High	Low	High
	0	1.04 (1.03, 1.04)	1.01 (1.01, 1.01)	1.07 (1.07, 1.07)	0.97 (0.97, 0.98)
	0-1	1.07 (1.06, 1.07)	1.02 (1.02, 1.03)	1.13 (1.12, 1.13)	0.97 (0.96, 0.97)
	0-2	1.09 (1.08, 1.10)	1.04 (1.03, 1.05)	1.16 (1.15, 1.17)	0.98 (0.97, 0.99)
	0-3	1.11 (1.10, 1.12)	1.06 (1.05, 1.07)	1.19 (1.17, 1.20)	1.02 (1.00, 1.03)
	0-4	1.12 (1.11, 1.13)	1.08 (1.07, 1.09)	1.19 (1.18, 1.21)	1.07 (1.05, 1.08)
	0-5	1.13 (1.11, 1.14)	1.11 (1.10, 1.12)	1.19 (1.17, 1.21)	1.13 (1.11, 1.15)
	0-6	1.13 (1.12, 1.14)	1.14 (1.12, 1.15)	1.18 (1.16, 1.19)	1.20 (1.19, 1.22)
	0-13	1.09 (1.07, 1.11)	1.35 (1.33, 1.38)	1.02 (1.00, 1.04)	1.79 (1.75, 1.83)
	0-21	1.06 (1.03, 1.08)	1.48 (1.45, 1.52)	1.14 (1.11, 1.17)	1.31 (1.27, 1.35)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; SES, Socioeconomic status

Table 7. The cumulative relative risks of stillbirth stratified by maternal age for 1st and 99th percentiles relative to median UTCI (13.9 °C), Western Australia, 2000-2015.

Lag days	1st percentile (0.7 °C) RR (95% CI)			99th percentile (31.7 °C) RR (95% CI)		
	≤19	20-34	≥35	≤19	20-34	≥35
0	1.11 (1.10, 1.11)	1.02 (1.01, 1.02)	1.00 (1.00, 1.00)	1.22 (1.21, 1.22)	1.07 (1.07, 1.08)	0.76 (0.76, 0.77)
0-1	1.23 (1.22, 1.24)	1.03 (1.03, 1.04)	0.99 (0.99, 1.00)	1.43 (1.42, 1.44)	1.14 (1.14, 1.15)	0.62 (0.61, 0.62)
0-2	1.37 (1.36, 1.38)	1.05 (1.04, 1.06)	0.98 (0.98, 0.99)	1.61 (1.59, 1.62)	1.22 (1.21, 1.23)	0.52 (0.51, 0.52)
0-3	1.54 (1.53, 1.56)	1.07 (1.06, 1.08)	0.97 (0.96, 0.98)	1.75 (1.73, 1.77)	1.30 (1.28, 1.31)	0.46 (0.45, 0.46)
0-4	1.74 (1.72, 1.75)	1.08 (1.07, 1.10)	0.95 (0.94, 0.96)	1.85 (1.83, 1.88)	1.38 (1.36, 1.39)	0.42 (0.41, 0.42)
0-5	1.95 (1.93, 1.98)	1.10 (1.09, 1.12)	0.93 (0.92, 0.94)	1.92 (1.89, 1.94)	1.45 (1.43, 1.47)	0.40 (0.39, 0.40)
0-6	2.20 (2.17, 2.23)	1.12 (1.11, 1.14)	0.91 (0.90, 0.92)	1.95 (1.92, 1.97)	1.53 (1.51, 1.55)	0.38 (0.38, 0.39)
0-13	4.25 (4.17, 4.33)	1.25 (1.23, 1.28)	0.77 (0.76, 0.79)	1.87 (1.83, 1.91)	1.88 (1.84, 1.92)	0.41 (0.40, 0.42)
0-21	4.60 (4.49, 4.72)	1.34 (1.31, 1.37)	0.73 (0.71, 0.75)	3.26 (3.17, 3.35)	1.58 (1.53, 1.62)	0.30 (0.29, 0.31)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Figures

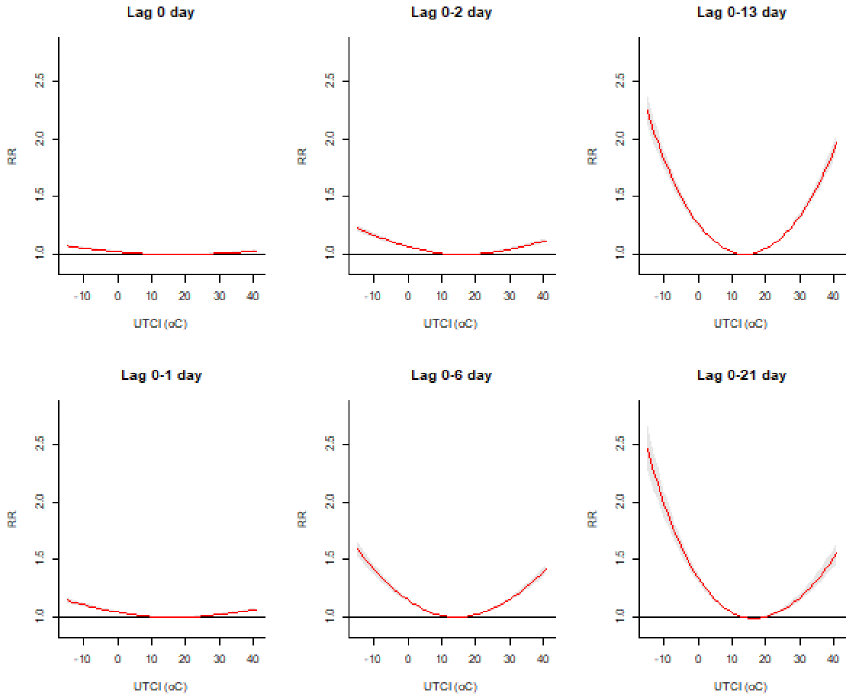

Figure. Exposure-response curves of daily UTCI and cumulative relative risk of stillbirths, relative to median UTCI of 13.9 ºC on the event day and up to different preceding days. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals (CIs). Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Supplemental materials

Table S1. The cumulative relative risks of stillbirth 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)	Winter (-1.3 ºC, 8.5 ºC)	Summer (9.6 ºC, 20.3 ºC)	Transition (30.8 ºC, 14.1 ºC)	Winter (20.9 ºC, 8.5 ºC)	Summer (33.7 ºC, 20.3 ºC)
0	1.12 (1.12, 1.13)	0.88 (0.88, 0.89)	1.04 (1.03, 1.05)	1.22 (1.21, 1.22)	0.82 (0.81, 0.83)	0.99 (0.98, 1.00)
0-1	1.23 (1.22, 1.24)	0.78 (0.78, 0.79)	1.06 (1.05, 1.07)	1.44 (1.42, 1.45)	0.69 (0.67, 0.70)	1.00 (0.98, 1.01)
0-2	1.33 (1.32, 1.35)	0.70 (0.69, 0.71)	1.06 (1.05, 1.08)	1.65 (1.62, 1.67)	0.58 (0.57, 0.60)	1.02 (1.00, 1.04)
0-3	1.42 (1.40, 1.44)	0.64 (0.63, 0.65)	1.04 (1.03, 1.06)	1.84 (1.81, 1.87)	0.50 (0.49, 0.52)	1.05 (1.03, 1.08)
0-4	1.49 (1.46, 1.51)	0.58 (0.57, 0.60)	1.01 (0.99, 1.03)	2.00 (1.97, 2.04)	0.44 (0.43, 0.46)	1.10 (1.07, 1.13)
0-5	1.54 (1.52, 1.57)	0.54 (0.53, 0.55)	0.97 (0.95, 0.99)	2.14 (2.09, 2.19)	0.40 (0.38, 0.41)	1.15 (1.12, 1.18)
0-6	1.58 (1.55, 1.61)	0.51 (0.50, 0.52)	0.92 (0.89, 0.94)	2.24 (2.19, 2.30)	0.36 (0.35, 0.37)	1.21 (1.18, 1.25)
0-13	1.62 (1.58, 1.66)	0.46 (0.44, 0.47)	0.56 (0.54, 0.58)	2.28 (2.21, 2.36)	0.27 (0.25, 0.28)	1.53 (1.47, 1.59)
0-21	1.72 (1.66, 1.78)	0.93 (0.89, 0.98)	0.40 (0.38, 0.42)	1.96 (1.88, 2.05)	0.40 (0.37, 0.43)	0.87 (0.82, 0.92)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Table S2. The cumulative relative risks of stillbirth for 1st and 99th percentiles relative to median UTCI (13.9 °C) with alternative degrees of freedom, Western Australia, 2000-2015.

Lag days	3 *df* for both predictor variable and lag spaces		3 *df* for predictor variable and 4 *df* for lag spaces	
	1st percentile (0.7 ºC) RR (95% CI)	99th percentile (31.7 ºC) RR (95% CI)	1st percentile (0.7 ºC) RR (95% CI)	99th percentile (31.7 ºC) RR (95% CI)
0	1.01 (1.00, 1.01)	1.04 (1.04, 1.05)	1.01 (1.01, 1.02)	1.14 (1.13, 1.14)
0-1	1.02 (1.01, 1.02)	1.09 (1.08, 1.10)	1.02 (1.01, 1.03)	1.21 (1.20, 1.23)
0-2	1.02 (1.01, 1.03)	1.14 (1.12, 1.15)	1.03 (1.02, 1.04)	1.24 (1.23, 1.26)
0-3	1.03 (1.02, 1.04)	1.19 (1.17, 1.20)	1.03 (1.02, 1.05)	1.26 (1.24, 1.27)
0-4	1.04 (1.03, 1.05)	1.24 (1.22, 1.26)	1.04 (1.03, 1.05)	1.27 (1.25, 1.28)
0-5	1.05 (1.03, 1.06)	1.29 (1.27, 1.31)	1.05 (1.03, 1.06)	1.29 (1.27, 1.31)
0-6	1.06 (1.04, 1.07)	1.34 (1.32, 1.37)	1.05 (1.04, 1.07)	1.32 (1.30, 1.34)
0-13	1.15 (1.13, 1.18)	1.56 (1.52, 1.60)	1.15 (1.13, 1.18)	1.63 (1.59, 1.67)
0-21	1.38 (1.34, 1.42)	1.22 (1.18, 1.26)	1.38 (1.34, 1.42)	1.24 (1.20, 1.28)

Note: UTCI, Universal Thermal Climate Index in degree Celsius; *df*, degree of freedom

Table S3. The cumulative relative risks of stillbirth for 1st and 99th percentiles, relative to mean and an average of 'no thermal stress' range UTCI, Western Australia, 2000-2015.

Lag days	Mean UTCI (14.6 ºC) as reference		Average of the 'no thermal stress' range (17.5 ºC) as reference	
	1st percentile (0.7 ºC) RR (95% CI)	99th percentile (31.7 ºC) RR (95% CI)	1st percentile (0.7 ºC) RR (95% CI)	99th percentile (31.7 ºC) RR (95% CI)
0	1.02 (1.02, 1.03)	1.01 (1.01, 1.02)	1.02 (1.02, 1.03)	1.01 (1.01, 1.02)
0-1	1.04 (1.04, 1.05)	1.03 (1.02, 1.04)	1.04 (1.04, 1.05)	1.03 (1.02, 1.04)
0-2	1.06 (1.05, 1.07)	1.05 (1.04, 1.06)	1.06 (1.05, 1.07)	1.05 (1.04, 1.06)
0-3	1.08 (1.07, 1.09)	1.08 (1.07, 1.09)	1.08 (1.07, 1.09)	1.08 (1.07, 1.09)
0-4	1.10 (1.09, 1.11)	1.12 (1.10, 1.13)	1.10 (1.09, 1.11)	1.11 (1.10, 1.13)
0-5	1.12 (1.11, 1.13)	1.15 (1.13, 1.17)	1.11 (1.10, 1.13)	1.15 (1.13, 1.16)
0-6	1.14 (1.12, 1.15)	1.19 (1.17, 1.21)	1.13 (1.11, 1.15)	1.18 (1.16, 1.20)
0-13	1.24 (1.22, 1.26)	1.40 (1.37, 1.43)	1.22 (1.20, 1.24)	1.38 (1.35, 1.41)
0-21	1.32 (1.29, 1.35)	1.22 (1.19, 1.26)	1.32 (1.29, 1.36)	1.23 (1.19, 1.26)

Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Table S4. The cumulative relative risks of stillbirth for 1st and 99th percentiles relative to median UTCI (13.9 °C) with alternative definitions of case day, Western Australia, 2000-2015*.

Case day	Lag days	1st percentile (0.7 °C) RR (95% CI)	99th percentile (31.7 °C) RR (95% CI)
1 day before delivery	0	1.00 (0.99, 1.00)	0.99 (0.99, 0.99)
	0-1	0.99 (0.99, 1.00)	0.99 (0.98, 1.00)
	0-2	0.99 (0.99, 1.00)	1.00 (0.99, 1.01)
	0-3	1.00 (0.99, 1.01)	1.01 (1.00, 1.02)
	0-4	1.00 (0.99, 1.01)	1.03 (1.02, 1.05)
	0-5	1.00 (0.99, 1.01)	1.06 (1.04, 1.07)
	0-6	1.01 (1.00, 1.02)	1.09 (1.07, 1.10)
	0-13	1.04 (1.02, 1.06)	1.29 (1.27, 1.32)
	0-21	1.02 (1.00, 1.05)	1.19 (1.15, 1.22)
On the delivery day	0	0.96 (0.95, 0.96)	0.98 (0.97, 0.98)
	0-1	0.92 (0.92, 0.93)	0.97 (0.96, 0.97)
	0-2	0.90 (0.89, 0.90)	0.96 (0.95, 0.97)
	0-3	0.88 (0.87, 0.89)	0.97 (0.96, 0.98)
	0-4	0.86 (0.85, 0.87)	0.98 (0.96, 0.99)
	0-5	0.85 (0.84, 0.87)	0.99 (0.98, 1.01)
	0-6	0.85 (0.84, 0.86)	1.01 (1.00, 1.03)
	0-13	0.85 (0.83, 0.86)	1.21 (1.19, 1.24)
	0-21	0.77 (0.75, 0.79)	1.27 (1.24, 1.31)

*Total included stillbirths = 2,836 (increased by one), Note: UTCI, Universal Thermal Climate Index in degree Celsius.

Figures

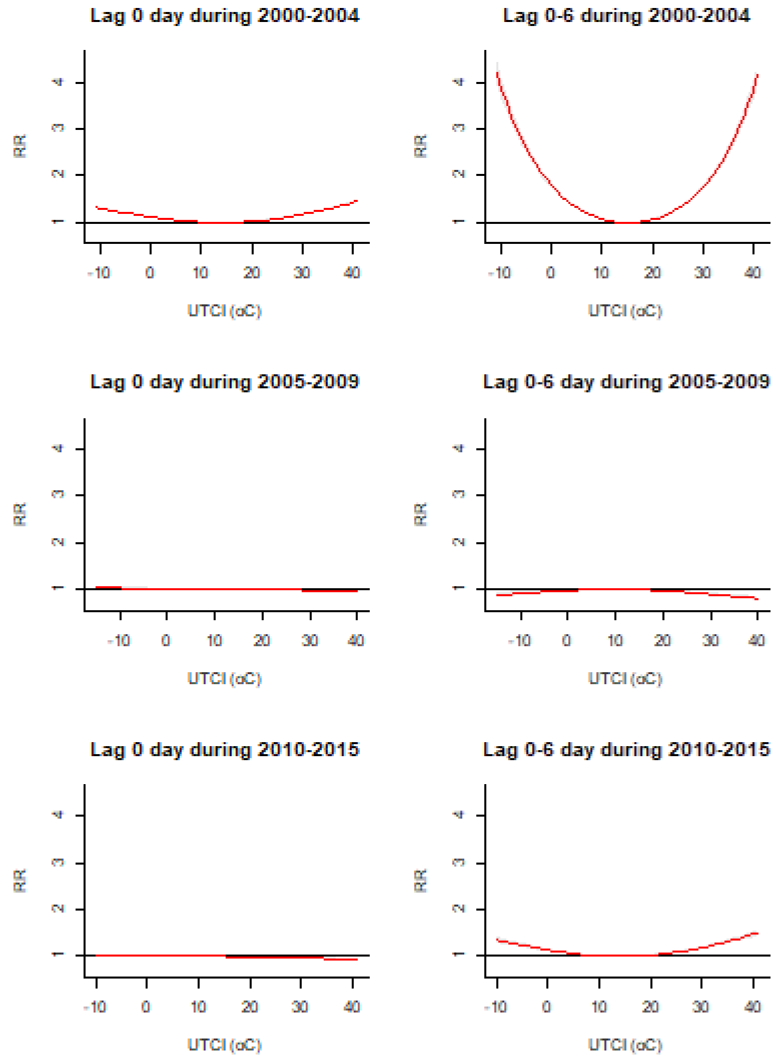

Figure S. Temporal exposure-response curves of daily UTCI and immediate and six days cumulative relative risk of stillbirth using year-specific median UTCI of each year as reference. Solid red lines represent point estimates, and the whiskers represent 95% confidence intervals (CIs). Note: UTCI, Universal Thermal Climate Index in degree Celsius.