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Original Contribution

Identifying critical periods of susceptibility for maternal exposure to biothermal stress and the risks of stillbirth and spontaneous preterm birth in Western Australia

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Abstract

A few studies investigated critical periods of temperature and the risks of stillbirth and preterm birth. This study aimed to identify critical periods of composite biothermal stress (Universal Thermal Climate Index, UTCI) for stillbirth and spontaneous preterm birth (sPTB). From the Midwives Notification System, 415 271 singleton births between January 1, 2000, and December 31, 2015, were linked to spatiotemporal UTCI in Western Australia. Covariate-adjusted weekly and monthly distributed lag nonlinear Cox regression from 12 weeks before conception to birth was performed. Relative to median exposure (14.2 °C), extreme UTCI levels (1st-10th and 90th-99th centiles) were associated with higher hazards of stillbirth and sPTB, especially stronger at lower than higher exposures. Critical susceptible periods at 1st centile (10.2 °C) exposure were found during gestational weeks 21 to 42, with the strongest hazard of 1.14 (95% CI, 1.03-1.27) in the 42nd week for stillbirth, and during gestational weeks 26 to 36, with the strongest hazard of 1.09 (95% CI, 1.06-1.12) in the 36th week for sPTB. Monthly exposure showed a similar pattern but with greater magnitude. Mid to late gestation showed critical susceptible periods of biothermal stress on the birth outcomes, suggesting further studies and timely climate-related health care interventions.

Key words: temperature; climate change; Universal Thermal Climate Index; birth outcomes; heat stress; cold stress; Sustainable Development Goals.

Introduction

Preterm birth (PTB, born before 37 gestational weeks) and stillbirth (born with no signs of life at or after 28 weeks' gestation according to the World Health Organization's definition) are global public health concerns with health, psychological, and economic burdens.[1,2] Global estimates indicated 13.4 million PTBs in 2020[1] and 2.0 million stillbirths in 2015.[2] In Australia, PTBs increased slightly from 8.4% in 2010 to 8.7% in 2017,[3] with over 2000 stillbirths (at least 20 weeks' gestation) occurring annually.[4] Despite well-known risk factors, many cases of PTB or spontaneous PTB (sPTB) and stillbirth have unexplained causes and unclear biological mechanisms for prevention strategies.[5-7] In particular, two-thirds of all PTBs are sPTBs with no known risk factors to establish causality,[8] suggesting a focused investigation of sPTBs for nontraditional risk factors. Clinicians now recognize nontraditional risk factors like environmental exposures, including climate change events such as extreme ambient temperatures.[9,10]

Extreme ambient temperatures (heat or cold stress), such as those that could arise from climate change, disrupt maternal thermoregulatory capacity and cause hypo- or hyperthermia and oxidative stress, which affect placental and fetal growth and physiology, leading to adverse birth outcomes such as PTB or sPTB and stillbirth.[11-13] Identifying critical susceptible periods is essential for elucidating pathophysiologic mechanisms and public health interventions. Previous studies often investigated short-term effects or trimester-average exposure effects.[13] This may not identify precise sensitive periods due to inherent bias in the modeling approach, as demonstrated in a simulation study.[14] A novel approach called distributed lag linear and nonlinear modeling (DLNM) has been proposed.[14-16] Unlike the trimester-average effect estimates, DLNM simultaneously accounts for both the intensity and timing of past exposure to obtain unbiased estimates at finer temporal scales (eg, weekly, monthly).[14-16] To the best of our knowledge, only 2 known previous studies applied DLNM for fine temporal long-term effects of ambient temperature and PTB[17,18] and none for stillbirth.

Previous studies often assessed ambient temperature using proximity to monitoring stations, which could result in exposure misclassification and exclusion of more vulnerable populations

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lacking monitoring stations.[19,20] Moreover, to enhance the thermophysiologic relevance of thermal-health investigations, composite biothermal metrics that integrate the actual thermal environment (air temperature, solar radiation, relative humidity, and wind speed) and physiological processes have recently been recommended.[21-23] The Universal Thermal Climate Index (UTCI), the most advanced biothermal metric that closely simulates the human thermophysiologic responses,[23-25] has been widely used and recommended in medical, epidemiologic, and thermal-health warning systems, as well as for forecasting, as reviewed elsewhere.[26,27] Short-term UTCI exposure and birth outcomes have been reported,[28-30] but there is no known literature applying the robust DLNM approach with a long-term UTCI assessment to identify critical susceptible periods for stillbirth and PTB or sPTB.

This study aimed to use spatiotemporal UTCI to examine the time-varying associations between biothermal stress and stillbirth and sPTB risks in Western Australia to identify critical susceptible periods and vulnerable subpopulations.

Methods

The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines were followed.[31]

Study design and population

This population-based retrospective cohort study analyzed deidentified Midwives Notification System (MNS) birth records in Western Australia from January 1, 2000, to December 31, 2015. MNS is the electronic system for birth delivery registration in Western Australia and records all births with ≥20 completed gestational weeks or ≥400 g fetal weight if the gestational age is unknown.[32] These data include various sociodemographic and clinical information and maternal residential addresses as statistical area level 1 (SA1, the second smallest geographical unit in Australia with a median of 19 hectares and an average population of 400 individuals)[33] at the time of birth delivery. The study started with 474 835 births but excluded births with missing SA1 (n = 35 352), gestational age (n = 1021), and sex (n = 5); multiple births (n = 13 018); gestational age outside the range of 22 to 42 weeks' gestation (n = 1412) by considering both periviability[34] and postterm periods[35] with complications[36]; and births to postmenopausal mothers over 50 years old (n = 7).[37] To mitigate the potential fixed-cohort bias, we further excluded pregnancies with conception dates less than 22 weeks before the beginning of the cohort (n = 7310) and more than 42 weeks before the cohort ended (n = 1434).[38,39] Births with incorrect SA1 or SA1 with missing exposures were excluded (n = 5). The final sample included 415 271 (87.5%) singleton births with 22 to 42 weeks' gestation for the stillbirth analysis but 400 867 (84.4%) for the sPTB analysis, as 14 404 births with provider initiated (induced or cesarean section) PTB were excluded from the main sPTB analysis (Figure S1).

Outcomes assessment

Stillbirth was defined as a baby born with no sign of life at ≥20 weeks' gestation[4,32] and sPTB as a baby born before 37 weeks' gestation with spontaneous onset of labor and vaginal delivery.[5] Gestational age was determined based on the best available clinical estimates from ultrasonography or the last menstrual period if ultrasound was unavailable.

Covariates

Several covariates were selected a priori as potential confounders based on biological and epidemiologic evidence[17-20,40] and data availability. These included sex (male or female), year of conception (1999 = 1 to 2015 = 17), season of conception (autumn, March-May; winter, June-August; spring, September-November; summer, December-February), maternal age, race/ethnicity (Caucasian or non-Caucasian), marital status (married or unmarried), smoking during pregnancy (nonsmoker or smoker), parity (nulliparous or multiparous), and remoteness (urban or rural). The area-level Index of Relative Socio-economic Disadvantage in the local government area (ranges from <1.5 to over 370 000 km^2 with a population of <100 to over 220,00 people in Western Australia), derived by the Australian Bureau of Statistics,[41] was categorized into tertiles to define high, moderate, and low socioeconomic status (SES). Very few births without SES (n = 22), smoking status (n = 14), and remoteness indicator (n = 143) were assigned a separate category as "unknown."

Spatiotemporal UTCI exposure assessment

UTCI is an equivalent air temperature (°C) that integrates the total ambient thermal environment under reference human physiologic processes.[24,42,43] Details on UTCI were provided elsewhere.[24,42,43] Briefly, UTCI was calculated as a 6-order polynomial equation from mean radiant temperature, air temperature, relative humidity at 2 m above ground level, and wind speed at 10 m above ground level, with reference to human physiologic processes. UTCI has 10 standard categories with values +9 °C to +26 °C, defined as *no thermal stress*, and values below and above this range are defined as cold and heat stresses, respectively, with increasing intensity up to extreme cold and heat stresses.[24,42,43] Daily gridded UTCI of the 24-hour averages at a spatial resolution of 0.25° × 0.25° (∼ 27 km at the equator) was obtained from the Copernicus Climate Data Store[42] between January 1, 1999, and December 31, 2015, and processed at the SA1 level using ArcGIS software (version 10.8.1). For each birth, daily UTCI exposure was assigned from 12 weeks preconception (84 days) to birth, based on dates of conception and birth, and the maternal residential address.[40,44,45] Weekly (7-day average) exposures were calculated from 12 weeks preconception (–11 to 0 weeks) until birth. Monthly exposure from 3 months (90 days) of preconception to birth was also calculated. Cumulative exposures such as trimesters (1-13, 14-26, and 27 to birth delivery gestational weeks), preconception to birth, entire pregnancy (conception to birth), and preconception (average of 12 weeks before pregnancy) were also calculated.

Statistical analyses

Cox proportional hazard regression, incorporating DLNM, was conducted, treating gestational age as the time axis and using binary birth outcomes to estimate the weekly- and monthly-specific effects of UTCI exposure on the hazards of stillbirth and sPTB.[17,40,45,46] A cross-basis matrix was constructed to define the exposure–lag-response association using the R package "dlnm"[15,16] to perform the Cox regression using the R package "survival."[47] Linear exposure-response and nonlinear exposure-response with lag-response functions using natural cubic splines with combinations of 2 to 7 degrees of freedom (*df*) with knots at equally spaced values were explored.[15,16] The maximum weekly exposure period (lag period) was set at 54 weeks for stillbirth (12 weeks preconception up to 42 gestational weeks) and 48 weeks for sPTB (12 weeks preconception up to 36 gestational weeks). Based on the lowest Akaike information criterion (AIC) and visual inspections to adequately capture the exposure–lag-response associations for better model interpretability without overfitting, the optimal *df* of exposure and lag period used for the final analyses were 6 and 4, respectively.[15,16,48] The Schoenfeld residual test was first performed to check the assumptions of the Cox regression to specify time interaction terms by covariate and exposure where the proportional hazard assumption was violated.[17,40,49] The fitted model was used to estimate the adjusted hazard ratios (HRs) and 95% CIs at the "extreme" (1st, 99th centiles), "severe" (5th, 95th centiles), and "moderate" (10th, 90th centiles) exposures, using the median (50th centile) UTCI as reference. Exposure periods in which 95% CIs did not include the null were identified as critical susceptible periods. Monthly-specific associations were also examined.

Furthermore, the cumulative exposures described above were evaluated using standard Cox regression models without lag periods. Based on the lowest AIC, the *df* used for natural splines were 2 for preconception and entire pregnancy, 5 for the 3 trimester-average exposures for stillbirth, 3 for preconception and entire pregnancy, and 2 for the 3 trimester-average exposures for sPTB. Cumulative preconception and entire pregnancy exposures were included together in 1 model, and all 3 trimester exposures were included together in another model to minimize bias in the effect estimates.[14,39] All models were adjusted for the potential confounders described above. Maternal age was modeled as a continuous variable using natural splines with 3 *df*.

Effect modifications were explored through stratified analyses by year of birth (2000-2007 and 2000-2015), infant sex, race or ethnicity, maternal age (<35 and ≥35 years), SES, remoteness, smoking status, parity, and pregnancy complications (yes or no for placental abruption, preeclampsia, gestational diabetes, premature rupture of membrane, threatened miscarriage, threatened preterm birth, asthma, and urinary tract infection). These analyses used cumulative exposure from preconception to birth.

Several sensitivity analyses were performed to ascertain the stability of the weekly-specific results. (1) Mean rather than median UTCI was used as the reference.[17] (2) The *df* in the natural cubic spline was decreased by 1 for both exposure and lag period in constructing the cross-basis matrices (ie, 5 and 3 *df*). (3) The *df* in the natural cubic spline was increased by 1 for both exposure and lag period in constructing the cross-basis matrices (ie, 7 and 5 *df*). (4) The birth cohort was restricted to only live singleton births (n = 413 348 births) and PTBs (6.9%) as in previous studies[17,18] instead of sPTBs. (5) Weekly exposures from conception to birth were analyzed without preconception exposures.

All statistical analyses were performed using the statistical software R 4.2.1 (R Development Core Team 2020). Following the recent recommendations by the American Statistical Association, the HRs (95 % CI) results were reported and interpreted without considering any 'statistically significant' threshold.[50]

Results

This study included 415 271 singleton births, of whom 1923 (0.5%), 15 524 (3.9%), and 14 404 (3.5%) were stillbirths, sPTBs, and provided-initiated (induced or cesarean) PTBs, respectively. A little above half of the births were male (51.2%), and most were born to mothers who were 20 to 34 years old (75.3%), Caucasians (78.3%), married (87.3%), multiparous (58.1%), nonsmokers (85.3%), and urban residents (61.9%) (Table 1). The average UTCI exposure from preconception to birth has approximately an equal mean (14.5 ± 2.5 °C) and median (14.2 °C). The specific average exposures for preconception, pregnancy, and each trimester were similar to the overall preconception up to birth (Table 2, Table S1).

Maternal exposure to different thresholds of lower and higher weekly exposures with reference to the median UTCI (14.2 °C) showed positive associations with stillbirth (Figure S2). Especially, the HRs for low exposures at the 1st (10.2 °C) to 10th (12.8 °C) centiles of UTCI showed critical susceptible periods, with most elevated hazards at the 1st centile of UTCI during the 21st to 42nd gestational weeks, which increased toward birth, with the strongest hazard of 1.14 (95% CI, 1.03-1.27) during the 42nd gestational week (Figure 1, Table S2). Although with slightly higher magnitude and wider confidence intervals, monthly UTCI exposure showed almost similar patterns to weekly UTCI exposure. The strongest hazard of stillbirth was 1.24 (95% CI, 1.05-1.47) during the 10th gestational month at the 5th centile exposure as compared with the median UTCI (Figure S3). For cumulative exposures, exposure at the 1st centile as compared with the median showed the strongest hazards of 1.28 (95% CI, 1.07-1.52) in the preconception period and 1.33 (95% CI, 1.13-1.55) for the entire pregnancy period. Trimester-specific exposures showed critical susceptible periods in the first and third trimesters, especially at the 1st centile of UTCI, which was stronger but less precise in the first trimester, 1.58 (95% CI, 1.18-2.11), than in the third trimester, 1.33 (95% CI, 1.04-1.72). Cumulative exposures at high thresholds generally showed very small lower or essentially no hazard of stillbirth (Table 3).

For sPTB, critical susceptible periods were found for lower (1st to 10th centiles) exposures during the 26th to 36th gestational weeks, which increased with gestation and higher (99th centile) exposure during the preconception weeks and 13th to 24th gestational weeks. The strongest hazard was 1.09 (95% CI, 1.06-1.12) in the 36th gestational week at the 1st exposure centile (Figure 2, Figure S4, Table S3). The monthly UTCI exposure showed almost similar patterns to the weekly exposure. In addition to increasing critical susceptible periods during late pregnancy (seventh to ninth gestational months), lower exposure thresholds also showed small critical lower hazards in the 3rd preconception month. Higher exposures, particularly at the 99th centile, showed critical susceptibility in the third preconception month and during the fourth to sixth gestational months but critical lower hazards during the eighth to ninth gestational months. The monthly hazard was strongest at the 1st centile exposure, 1.22 (95% CI, 1.14-1.30), and lowest at the 99th centile exposure, 0.88 (95% CI, 0.82-0.94), both occurring in the ninth gestational month (Figure S5). Cumulatively, exposure at the 1st centile as compared to median UTCI showed the strongest hazard of 1.10 (95% CI, 1.01-1.20) for the preconception period and 1.22 (95% CI, 1.13-1.32) for the entire pregnancy. Exposure at the 99th centile as compared to the median UTCI showed the strongest hazard of 1.31 (95% CI, 1.13-1.52) in the second trimester (Table 3).

Stratified analyses suggested effect modifications, mostly at the 1st centile relative to the median exposure (Table S4). At the 1st centile exposure, the adjusted HRs were more elevated in the early years of 2000 to 2007 for both stillbirth and sPTB. The hazard was higher in female births for stillbirth and in male births for sPTB, and the hazard was higher in Caucasians for stillbirth and in non-Caucasians for sPTB. The hazard was higher in births whose mothers were <35 years old for stillbirth but no clear difference for sPTB, as well as higher in low/moderate area-level SES for stillbirth but high SES for sPTB. Higher hazards were found in rural areas for both stillbirth and sPTB at higher 1st centile exposure. Mothers who did not smoke during pregnancy were at a higher hazard of stillbirth, but smokers showed a higher hazard of sPTB. Nulliparous mothers showed a higher hazard of both stillbirth and sPTB. Mothers with complicated pregnancies were at a higher

Table 1. Maternal characteristics of included singleton births in Western Australia, 2000-2015 ($n = 415\,271$).

Characteristics	n (%)	Characteristics	n (%)
Stillbirth		*Smoking status*	
No	413 348 (99.5)	No	354 235 (85.3)
Yes	1923 (0.5)	Yes	61 022 (14.7)
Birth status		Unknown	14 (0.0)
Term	385 343 (92.8)	*Remoteness*	
Provider-initiated PTB	14 404 (3.5)	Urban	257 158 (61.9)
sPTB	15 524 (3.9)	Rural	157 970 (38.0)
Sex		Unknown	143 (0.0)
Male	212 562 (51.2)	SES	
Female	202 709 (48.8)	High	138 417 (33.3)
Maternal age (years)		Moderate	138 416 (33.3)
≤19	19 033 (4.6)	Low	138 416 (33.3)
20-34	312 880 (75.3)	Unknown	22 (0.0)
≥35	83 358 (20.1)	*Season of conception*	
Race		Autumn	100 889 (24.3)
Caucasian	325 340 (78.3)	Winter	105 588 (25.4)
Non-Caucasian	89 931 (21.7)	Spring	104 824 (25.2)
Marital status		Summer	103 970 (25.0)
Married	362 575 (87.3)		
Unmarried	52 696 (12.7)		
Parity			
Nulliparity	173 932 (41.9)		
Multiparty	241 339 (58.1)		

Abbreviations: PTB; preterm birth; SES, socioeconomic status; sPTB, spontaneous preterm birth.

hazard of stillbirth, while those with uncomplicated pregnancies showed a slightly higher hazard of sPTB (Table S4).

The sensitivity analyses did not change substantially, suggesting the stability of the results under varying modeling conditions and assumptions. The weekly identified critical susceptible or lower hazard periods were consistent with the main results (Figures S6-S11).

Discussion

Main findings

Both lower (1st-10th centile) and higher (99th centile) exposures as compared to median exposure showed positive associations with stillbirth and sPTB. Except for the 99th centile exposure, higher biothermal exposures (90th and 95th centiles) showed essentially no association with birth outcomes. The association was most elevated for 1st centile exposure, with increasing critical susceptible periods from mid to late pregnancy for both stillbirth (21st-42nd gestational weeks) and sPTB (26th-36th gestational weeks). The results of monthly UTCI exposure were consistent with those of the weekly exposure, with a greater magnitude but lower precision of HR. The 99th centile exposure additionally showed increased susceptibility in the third preconception month and decreased hazard in late gestational months for sPTB. Trimester-specific hazards were strongest in the first trimester for stillbirth and in the second trimester for sPTB at 1st and 99th centiles of exposure, respectively. Compared with weekly or monthly exposures, the trimester-average exposures were less precise and less sensitive to the specific gestational time window of susceptibility.[14,16]

Two recent studies employed DLNM Cox regression to investigate weekly ambient temperature and the hazard of PTB.[17,18] The first study analyzed 4101 live singleton births, of whom 5.7% were PTB in Guangzhou, China, with weekly mean ambient temperature from conception up to birth. Compared with the mean temperature, a higher hazard of PTB was found at higher (95th centile) exposure during the 4th to 8th and 22nd to 27th gestational weeks. Lower exposure (5th centile) was associated with lower hazards of PTB, with a critical lower hazard ("protective") period during the 2nd to 10th and 20th to 26th gestational weeks.[17] We found that both higher and lower exposures, particularly lower exposures, were associated with higher hazards of sPTB. The second study analyzed 5347 live singleton births

Table 2. Descriptive statistics of the average UTCI (°C) during 12 weeks preconception through to gestational weeks at delivery exposure periods for included singleton births in Western Australia, 2000-2015 ($n = 415\,271$).

Exposure periods	Minimum	Mean ± SD	Median	P1	P5	P10	IQR	P90	P95	P99	Maximum
Preconception to pregnancy	7.3	14.5 ± 2.5	14.2	10.2	11.9	12.8	1.2	15.4	17.4	26.1	31.2
Preconception	1.4	14.4 ± 5.2	14.0	5.8	7.6	8.2	8.8	20.9	22.0	29.5	35.8
Pregnancy	4.9	14.6 ± 2.9	14.2	9.6	11.3	11.9	2.9	16.7	18.3	26.7	34.1
First trimester	1.7	14.6 ± 5.2	14.2	5.9	7.7	8.3	8.8	20.9	22.0	29.6	36.0
Second trimester	1.6	14.6 ± 5.2	14.2	6.1	7.8	8.5	8.7	20.9	22.0	29.8	36.1
Third trimester	−1.1	14.5 ± 5.2	14.0	5.6	7.7	8.3	8.7	20.8	22.0	29.7	35.7

Abbreviations: IQR, interquartile range = P75-P25; P1 to P99, 1st to 99th centiles; UTCI, Universal Thermal Climate Index.

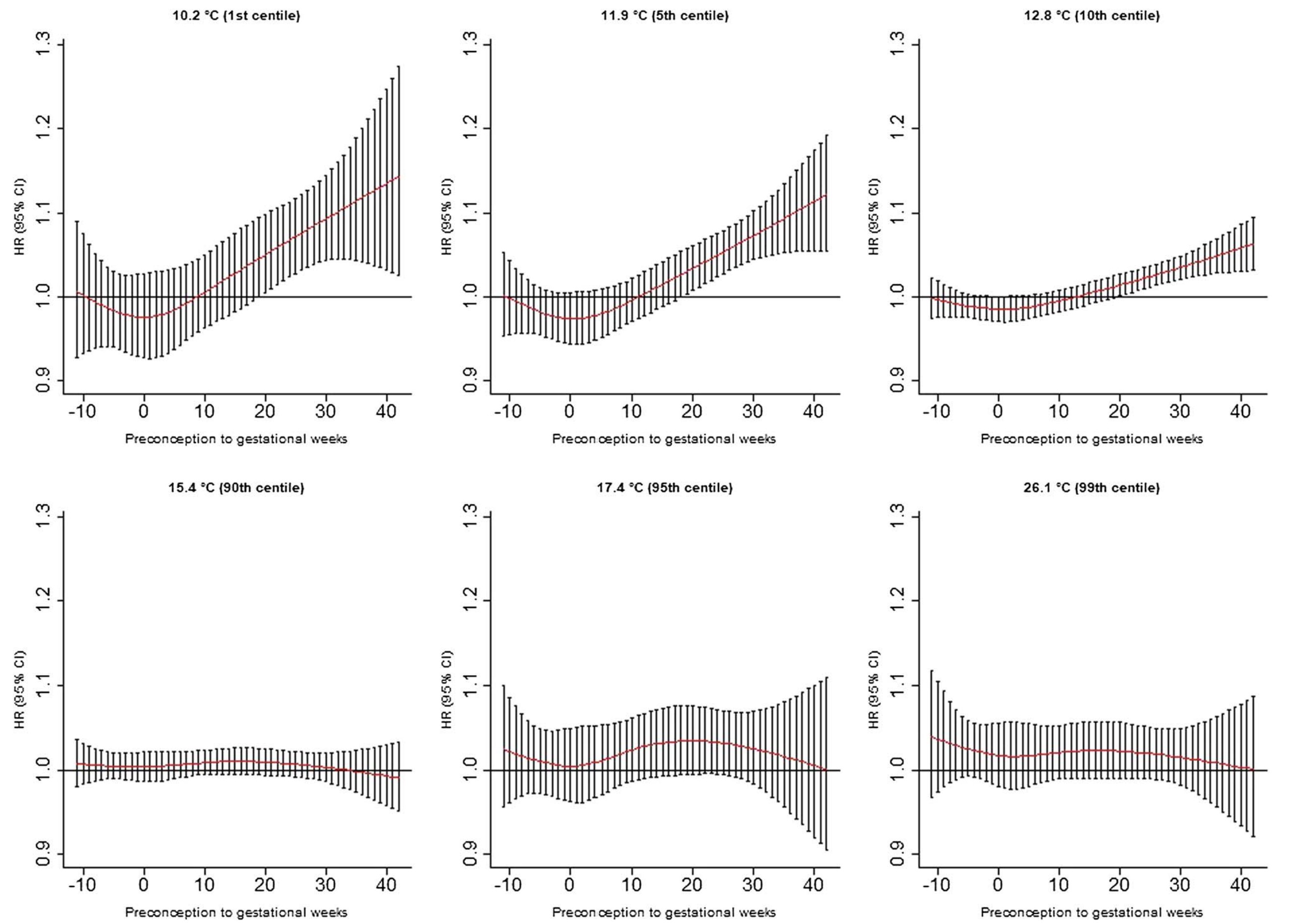

Figure 1. Adjusted hazard ratios of stillbirth associated with weekly-specific UTCI over 12-week preconception (–11 to 0) through to gestational week at delivery (1 to 42) at different thresholds of UTCI using the median of 14.2 °C as a reference in Western Australia, 2000-2015. Solid horizontal red lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were fitted from distributed lag nonlinear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. HR, hazard ratio; UTCI, Universal Thermal Climate Index.

with 4.3% of PTBs and examined the association between mean temperature during the first 26 weeks of gestation and the last 30 days before birth in France.[18] Those authors found early pregnancy (fourth to ninth gestational weeks) and 10 to 4 days before delivery as critical susceptible periods only at the 1st centile exposure as compared with the median exposure.[18] In contrast, we found late pregnancy weeks (26th-36th gestational weeks) for sPTB at the 1st centile as compared with the median exposure. However, the short-term effect reported by Hough et al[18] fell within the critical susceptible periods reported here and other previous studies that investigated short-term ambient temperature and PTB, as reviewed elsewhere.[13,51] Our sensitivity analysis that included only live singleton births and PTBs, as in those studies,[17,18] showed consistent results with sPTB. However, to minimize live-birth bias, future studies should include all eligible births regardless of stillbirth status and data on all pregnancy losses if possible.[39] The live-birth bias may arise from collider stratification due to unmeasured factors influencing both stillbirth and PTB or from the depletion of susceptible groups, particularly larger for sociodemographically vulnerable groups.[39,52] The differences in exposure metric in particular and population characteristics (genetics, lifestyle, adaptation or acclimatization, and mitigation strategies) may explain differing critical periods found in the previous studies.[17,18] There is no known related study for stillbirth, but similar to sPTB, our results suggest mid to late gestational weeks as plausible critical susceptible periods for both lower and higher exposures, aligning with existing research that mainly focussed on short-term effects.[13] Further long-term effect investigations across diverse geodemographic areas using weekly or monthly biothermal metrics and the DLNM approach can help establish the critical susceptible periods, offering valuable insights to better understand the biological mechanisms and timely climate-related health care and policy strategies.[14,16,22,40]

An unexpected finding was the additional small “protective effect” of the higher exposures toward the end of pregnancy at the 95th and 99th centiles of monthly exposure for sPTB. Pregnant women may reduce higher exposures, particularly in late pregnancy, by staying indoors with the co-benefits of taking sufficient rest and reducing other environmental exposures (eg, air pollution), using air conditioning, and taking other perinatal precautions seriously, potentially explaining this effect. The finding could also be due to other artifactual factors or several biases from exposure misclassification, selection, confounding, and information biases given that pregnancy outcomes are complex with naturally multifactorial interplays.[39] The selective survival due to fewer ongoing pregnancies at later gestational lags may introduce truncation or informative censoring bias as well as edge effects, model extrapolation, or sparse data instability at extreme exposures and longer lags, especially when the outcome events are low. Thus, while biological or behavioral adaptations in

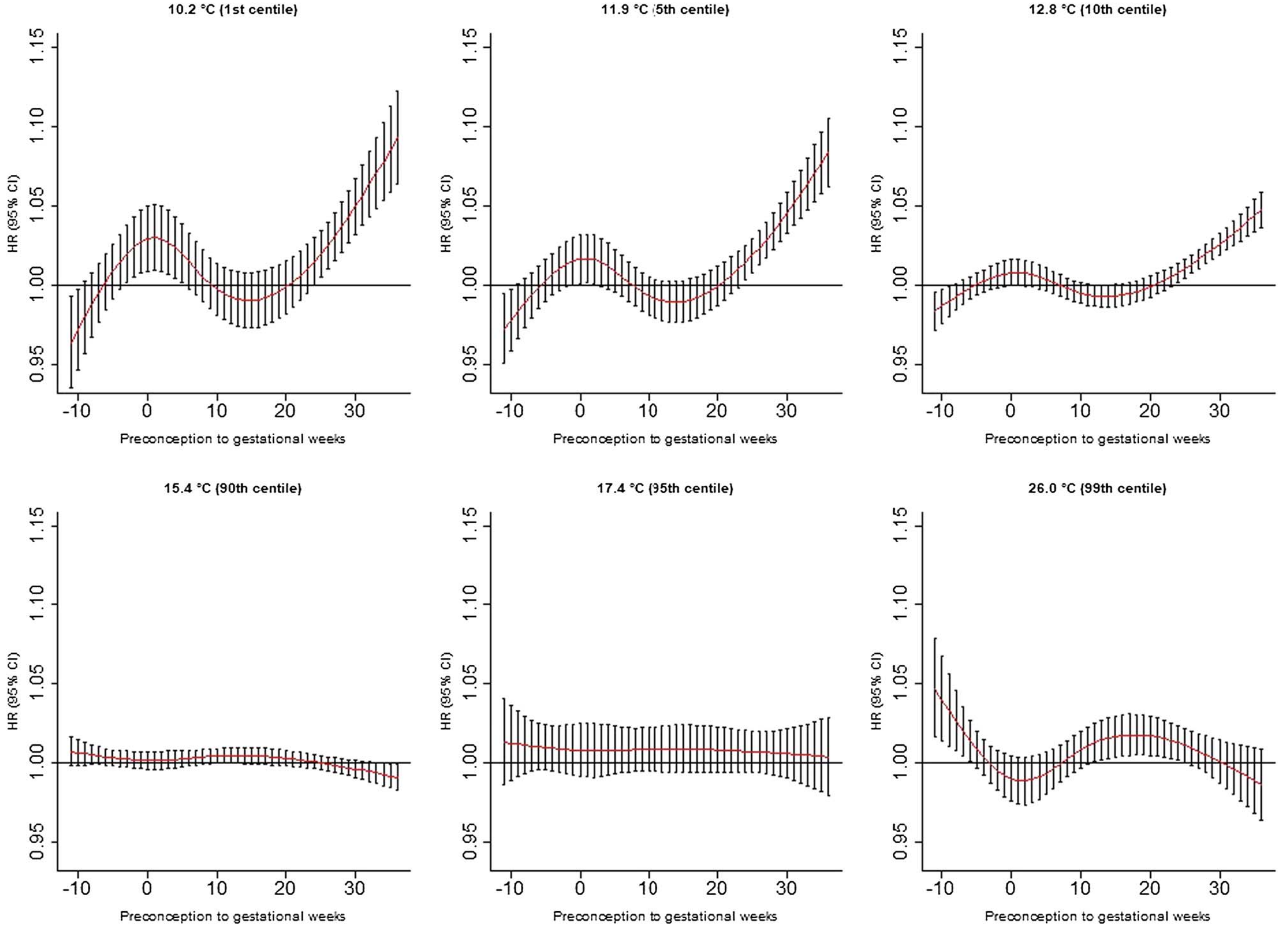

Figure 2. Adjusted hazard ratios of sPTB associated with weekly-specific UTCI over 12-week preconception (−11 to 0) through to gestational week at delivery (1 to 36) at different thresholds of UTCI using the median of 14.2 °C as a reference in Western Australia, 2000-2015. Solid horizontal red lines represent point estimates, and the vertical bars represent 95% confidence intervals. Models were fitted from distributed lag nonlinear Cox proportional hazards models with adjustment for infant sex, maternal age, race or ethnicity, marital status, smoking status, parity, remoteness, socioeconomic status, and year and season of conception. HR, hazard ratio; sPTB, spontaneous preterm birth; UTCI, universal thermal climate index.

late gestation cannot be ruled out, the "protective effect" pattern likely reflects methodological artefacts rather than a true causal effect and have to be interpreted with cautions. Further studies are required to explain this observation.

Cumulative preconception exposure was associated with higher hazards of both stillbirth and sPTB, as found in 2 Chinese studies for PTB.[53,54] Further investigations are required to explore this overlooked critical period of gametogenesis for intervention.[55] This period can be affected by environmental exposures and is now gaining attention in air pollution–perinatal epidemiology.[56]

The observed higher exposure-outcome associations for both birth outcomes in early years than in later years could be attributed to positive behavioral changes, adaptation or acclimatization, climate mitigation strategies, and improved health care services in later years. Lower exposure levels particularly showed slightly elevated hazard in certain vulnerable subpopulations, which varied between the birth outcomes but were consistently higher in nulliparity and residing in rural areas for both stillbirth and sPTB. While the differences between birth outcomes for the subgroup-specific effects require further investigations, it is worth noting that most of the identified more vulnerable groups for stillbirth, including mothers <35 years old, low/moderate SES, rural areas, nulliparity, and complicated pregnancies, were expected. Young mothers who are possibly nulliparous are more likely to engage in outdoor activities, increasing their extreme biothermal exposures. Those residing in rural and low/moderate SES areas might not have adequate health care services and climate-mitigation strategies or resources, together with other indirect challenges (eg, poor nutrition, infections) associated with rurality and low/moderate SES. Pregnancy complications are established risk factors for adverse birth outcomes and have been associated with extreme temperatures previously.[57] Some unexpected subgroup-specific findings, such as slightly higher hazards in nonsmokers than smokers for stillbirth, could be due to several sources of bias, including unmeasured confounding, measurement errors, and selection bias (eg, early losses of at-risk pregnancies).[39,58]

A healthy climate promotes healthy health and birth outcomes. Extreme temperatures or biothermal stress (heat or cold stress) contribute to climate change. To address climate change–related risks on pregnancy or birth outcomes, various resilient strategies are required, aligning with the Sustainable Development Goals (SDGs) 3, 7, and 13.[59] These involve reducing outdoor activities or seeking protection (cool or warm areas, wearing appropriate clothing) during cold or heat stress periods, greening the environment, creating thermal-resilient health systems and infrastructure, and involving health practitioners in climate advocacy, education, awareness creation, and policy development.[9,10,13] Transitioning to "clean" renewable energy sources that are not based on fossil fuels, in line with SDG 7,[59] and fostering climate

Table 3. The exposure-response association between maternal cumulative UTCI exposures over 12 weeks preconception through to pregnancy and trimester-specific periods as compared with median 14.2 °C and the hazard ratios (95% CIs) of stillbirth and sPTB at various percentiles of the exposure in Western Australia, 2000-2015.

Exposure period	UTCI centile	Stillbirth HR (95% CI)	sPTB HR (95% CI)
Preconception to birth	P1	1.28 (1.07-1.52)	1.07 (0.98-1.17)
	P99	0.91 (0.72-1.15)	0.97 (0.89-1.05)
Preconception	P1	1.28 (1.03-1.60)	1.10 (1.01-1.20)
	P99	1.16 (0.85-1.59)	0.93 (0.83-1.05)
Pregnancy	P1	1.33 (1.13-1.55)	1.22 (1.13-1.32)
	P99	0.91 (0.68-1.21)	1.08 (0.97-1.20)
First trimester	P1	1.58 (1.18-2.11)	1.15 (1.06-1.26)
	P99	0.97 (0.66-1.42)	0.93 (0.83-1.05)
Second trimester	P1	1.08 (0.81-1.43)	0.97 (0.90-1.05)
	P99	0.91 (0.59-1.42)	1.31 (1.13-1.52)
Third trimester	P1	1.33 (1.04-1.72)	1.22 (1.12-1.32)
	P99	1.17 (0.81-1.70)	0.86 (0.77-0.97)

Abbreviations: HR-hazard ratio; P1 and P99, 1st and 99th centiles; sPTB, spontaneous preterm birth; UTCI, Universal Thermal Climate Index.
The model was adjusted for infant sex, maternal age, race or ethnicity, marital status, parity, maternal smoking, remoteness, area-level socioeconomic status, and year and season of conception.

justice are critical for ensuring healthy pregnancy outcomes and healthy future generations.[9,10] Building an effective and efficient mass public transport infrastructure to reduce private transportation is another important climate change mitigation strategy. This has substantial co-benefits, such as large reductions in greenhouse gas emissions, air and noise pollution, traffic injuries and fatalities, and congestion.[60]

Potential pathophysiological mechanisms

Extensive evidence on plausible pathophysiological mechanisms linking maternal exposure to cold and heat stress to adverse birth outcomes, including stillbirth and PTB or sPTB, has been reported in a recent umbrella review.[13] Briefly, biothermal stress can cause hypo- or hyperthermia, triggering various biological and biochemical responses such as oxidative stress, cell death, and abnormal intracellular heat shock proteins (HSPs), especially HSP 60 and 70. These impact placental growth and physiology and fetoplacental transport systems, affecting fetal growth and development. An abnormal increase in neuroendocrine and inflammatory activities and activation of the fetal hypothalamic-pituitary-adrenal axis induce labor prematurely. All these induced responses lead to fetal death or stillbirth and sPTB, especially when biothermal stress occurs in mid to late gestation.[11,12,61-63] Preconception, a period of organogenesis when women may be unaware of pregnancy, is also a critical period for teratogenic effects, where environmental exposures can potentially induce epigenetic alterations, and has also been associated with changes in reproductive hormones, inflammation, and oxidative stress, leading to adverse pregnancy outcomes.[55]

Strengths and limitations

This study has several strengths. To our knowledge, this is the first study using a thermophysiologically relevant metric (UTCI)[23-25] for long-term assessment of the exposure and the risk of stillbirth and sPTB or PTB. The spatiotemporal exposure assessment reduced exposure misclassification as compared to the conventional use of simple models or proximity to monitoring stations.[19,20] This study also benefits from the application of DLNM Cox regression, which accounted for both intensity and timing of past exposures and time-to-event, enabling more precise identification of fine temporal susceptible periods as compared to the usual trimester-based periods.[14-16] Given the limited studies on the long-term effect of ambient temperature on PTB with this novel methodology[17,18] and no known related previous evidence on stillbirth, our findings contribute important epidemiologic evidence for intervention strategies and understanding pathophysiologic mechanisms. Compared to the 2 comparative studies,[17,18] the included cohort in our study was the largest with detailed information to distinguish between induced and spontaneous PTB.

However, there are some limitations of this study. Exposure assessment at fine spatial resolution (SA1 level) can also introduce misclassification due to limited information on exposures in nearby areas such as parks, shopping centers, and local-level community centers that people access daily.[40] Maternal residential mobility may affect the accuracy of the exposure assessment and has been reported to be disproportional by maternal characteristics.[64,65] Thus, when practically possible, epidemiologic studies should integrate residential mobility into environmental exposure assessments.[64] The inability to account for daily activity patterns, time spent outdoors or indoors, and use of air conditioning may lead to exposure misclassification. Although it is challenging for large-scale studies, personalized activity/real-time exposure assessment may be helpful. The study did not compare the results of UTCI with ambient temperature. However, several evaluative and comparative studies concluded that UTCI is the state-of-the-science and more useful biothermal metric for thermal-health outcomes, warning systems, and forecasting.[23-25,66,67] This biothermal metric has been applied in many studies reviewed previously.[26,27] The area-level SES as a proxy for individual SES could introduce misclassification bias of the SES. Certain covariates or potential confounding factors, such as maternal alcohol or illicit drug intake, nutritional status, infection (eg, seasonal influenza), maternal weight, and physical activity during pregnancy, were not included due to lack of data. Some of these factors were partly controlled through socioeconomic and remoteness variables. Pregnancy is multifactorial and time-limited with severe cohort attritions (eg, no information on early pregnancy loss). Therefore, several potential sources of bias in environmental-perinatal epidemiology, such as residual confounding, selection, and information biases, as well as potential exposure misclassification, could have implications for the interpretations of the findings.[39]

Conclusion

We found nonlinear time-varying associations of biothermal stress from preconception to birth with the hazards of stillbirth and spontaneous preterm birth with sociodemographic disparities. Mid to late gestational weeks were potential critical susceptible exposure periods, especially stronger at lower than higher exposures. Cumulative preconception exposure also showed positive associations with both birth outcomes. The identified potential susceptible periods require further investigation and clinical or public health attention to promote healthy pregnancy outcomes. Given the public health burden of adverse birth outcomes, addressing even small relative risks associated with biothermal stress can have substantial impacts at the population level. Future studies could also benefit from the novel approaches (UTCI and DLNM) utilized in this study.

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Supplementary material

Supplementary material is available at the *American Journal of Epidemiology* online.

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Conflict of interest

The authors declare no conflicts of interest.

Data availability

The birth data used in this study cannot be made available publicly due to the data access agreement. The data were obtained from the Department of Health, Western Australia after approval by the Human Research Ethics Committees of the Western Australia Department of Health (#2016/51) and Curtin University (#HRE2020-0523). Interested researchers with appropriate approvals can request the data directly from the Department of Health, Western Australia at https://ww2.health.wa.gov.au/Articles/J_M/Midwives-Notification-System.
The exposure data (UTCI) is freely available at the European Centre for Medium-Range Forecasts Copernicus Climate Data Store at https://cds.climate.copernicus.eu/datasets/derived-utci-historical?tab=overview.

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