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Prenatal exposure to long-term heat stress and stillbirth in Ghana: A within-space time-series analysis

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ABSTRACT

Introduction: Few studies examined the association between prenatal long-term ambient temperature exposure and stillbirth and fewer still from developing countries. Rather than ambient temperature, we used a human thermophysiological index, Universal Thermal Climate Index (UTCI) to investigate the role of long-term heat stress exposure on stillbirth in Ghana.
Methods: District-level monthly UTCI was linked with 90,532 stillbirths of 5,961,328 births across all 260 local districts between 1st January 2012 and 31st December 2020. A within-space time-series design was applied with distributed lag nonlinear models and conditional quasi-Poisson regression.
Results: The mean (28.5 ± 2.1 °C) and median UTCI (28.8 °C) indicated *moderate heat stress.* The Relative Risks (RRs) and 95% Confidence Intervals (CIs) for exposure to lower-moderate heat (1st to 25th percentiles of UTCI) and strong heat (99th percentile) stresses showed lower risks, relative to the median UTCI. The higher-moderate heat stress exposures (75th and 90th percentiles) showed greater risks which increased with the duration of heat stress exposures and were stronger in the 90th percentile. The risk ranged from 2% (RR = 1.02, 95% CI 0.99, 1.05) to 18% (RR = 1.18, 95% CI 1.02, 1.36) for the 90th percentile, relative to the median UTCI. Assuming causality, 19 (95% CI 3, 37) and 27 (95% CI 3, 54) excess stillbirths per 10,000 births were attributable to long-term exposure to the 90th percentile relative to median UTCI for the past six and nine months, respectively. Districts with low population density, low gross domestic product, and low air pollution which collectively defined rural districts were at higher risk as compared to those in the high level (urban districts).
Discussion: Maternal exposure to long-term heat stress was associated with a greater risk of stillbirth. Climate change-resilient interventional measures to reduce maternal exposure to heat stress, particularly in rural areas may help lower the risk of stillbirth.

1. Introduction

A fetal death of at least 28 weeks' gestation or at least 1000 g birth weight if the gestational length is unknown is defined by World Health Organisation (WHO) as stillbirth (UN, 2020). Between 2000 and 2019, the world recorded 48 million stillbirths and 84% of these were from low-and-middle-income countries (LMICs) with Sub-Saharan Africa (SSA) as the highest contributor (UN, 2020). The human-induced

Abbreviations: WHO, World Health Organisation; UTCI, Universal Thermal Climate Index; LMICs, Low-and-middle-income countries; SSA, Sub-Saharan Africa; CHIM, Health Information Management; DHIMS, District Health Information Management System; GHS, Ghana Health Service; GMHS, Ghana Maternal Health Survey; GDP, Gross Domestic Production; MRT, Mean Radiant Temperature; DLNM, Distributed Lag Nonlinear Model; AIC, Akaike information criterion.

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climate change crisis (IPCC, 2021), particularly extreme ambient temperatures and air pollution are adding to the usual risk factors of stillbirth (Giudice et al., 2021; Nyadanu et al., 2022a).

Establishing causality with certainty is challenging, yet many coherent biological pathways explain the plausible impacts of extreme ambient temperatures on stillbirth. These include the impacts of hyperthermia, dehydration, thermally-induced oxidative stress on placental growth and physiology, and maternal-fetal transport of materials such as nutrients, water, oxygen, and removal of fetal metabolic wastes (Ayinzat et al., 2021; Berestoviy et al., 2021; Edwards et al., 2003). A recent systematic review that included 12 studies from seven countries found an association between extreme ambient temperatures and stillbirth (Sexton et al., 2021). The review included only one study from the most vulnerable settings, LMICs which was based on a cross-sectional analysis of the 2007 Ghana Maternal Health Survey (GMHS) at larger geographic units (Asamoah et al., 2018) with notable exposure misclassification due to varying temperatures at different locations across the country. A recent cross-sectional retrospective study in 14 LMICs also linked gridded daily temperature to a demographic health survey and reported acute or short-term effects of ambient temperature on stillbirth and preterm birth (McElroy et al., 2022). However, there is currently no study from an LMIC that has applied a longitudinal design, and no study from this region that has ascertained stillbirth by clinical diagnosis and investigated chronic or long-term effects of the exposure. Moreover, given the wide differences in thermal variability, adaptation and mitigation strategies, a geodemographic-specific assessment of the impact of thermal stress on stillbirth will be more relevant for contextually and targeted interventions (Sexton et al., 2021).

The ambient thermal environment is a combination of the air temperature, solar radiation, relative humidity, and the air velocity (Staiger et al., 2019; Vanos et al., 2020). Thus, using only ambient temperature as a surrogate of thermal stress cannot be considered as adequate characterisation of the human thermal exposure (Matzarakis, 2021; Vanos et al., 2020). However, thermal stress-related epidemiologic studies, in general, use ambient temperature rather than a human thermophysiological index. This limitation has been raised recently with a recommendation for a change to the human thermophysiological indices to improve the reliability, robustness, comparability, and physiological relevance of the findings (Staiger et al., 2019; Vanos et al., 2020). The human body only feel the impact of all climatic factors collectively as human physiologic systems do not have specific sensors to detect and differentially respond to a single climatic factor such as air temperature (Matzarakis, 2021). Also,the thermal stress imposed on a person is a result of the total thermal environment together with activity or metabolic heat production and behaviours such as clothing worn (Staiger et al., 2019; Vanos et al., 2020). The use of air temperature metric in measuring relationships between thermal stress and health outcomes is partly due to lack of access to the necessary meteorological data and computational complexities to characterise the total thermal environment to produce more valid thermal-health outcomes and projections (Staiger et al., 2019; Urban et al., 2021; Vanos et al., 2020). It is, therefore, expected that thermophysiological indices instead of air temperature will become the thermal indices of preference as the necessary climatic variables and operational procedures for easy computation are becoming increasingly available (Nazarian and Lee, 2021; Staiger et al., 2019; Urban et al., 2021; Vanos et al., 2020). Four of several thermophysiological indices were evaluated to be appropriate (Staiger et al., 2019) and Universal Thermal Climate Index (UTCI) was proven most suitable (Blazejczyk et al., 2012; Bröde et al., 2013; Kampmann et al., 2012). Regardless of climate zone, seasons, and personal characteristics, UTCI has a prognostic potential to describe the actual thermal environment and human thermophysiological response in different climates (Blazejczyk et al., 2012; Bröde et al., 2013; Romaszko et al., 2022). UTCI is useful to examine both the impacts of the ambient thermal environment (heat or cold stress) on health outcomes and as thermal stress warning systems to support public health interventions and climate governance (Krüger, 2021; Romaszko et al., 2022).

Using a single ambient temperature or apparent temperature (temperature and relative humidity) or inappropriate thermal metric to predict related health outcomes can result in less realistic projections for either under or overspending of the limited resources of the health system (Staiger et al., 2019; Vanos et al., 2020). For instance, among three thermal metrics (Apparent Temperature, Net Effective Temperature, and UTCI) assessed in Spain and Portugal, the relative risk of cardiovascular morbidity was lowest with UTCI (Santurtún et al., 2020). This was explained by the fact that UTCI, which also integrates the individual's physiological characteristics while taking into account the thermal environmental influences, may smooth out any overestimations present in the other two indices (Santurtún et al., 2020). Analysis of daily mortality data from 21 cities across nine European countries found strong correlation between the results of the UTCI and air temperature for heat stress but larger differences between the results of UTCI and air temperature for cold stress due to the role of wind in the definition of UTCI (Urban et al., 2021). Another study examined daily minimum and maximum temperatures and UTCI and concluded that UTCI serve as a more useful tool to predict the risk of mortality (Romaszko et al., 2017). A recent systematic review revealed that UTCI is now gaining attention among epidemiologists, clinicians, and public health professionals (Romaszko et al., 2022). While a few studies have utilised UTCI to investigate mortality, emergency department visits, and cardiovascular diseases (Romaszko et al., 2022), only three studies have so far reported UTCI in perinatal epidemiology (Khodadadi et al., 2022; Nyadanu et al., 2022b, 2022c). Further epidemiologic studies with UTCI had been recommended (Romaszko et al., 2022), particularly from LMICs, including Ghana where related evidence is currently limited.

Environmental exposures often show effects that delayed (lagged) in time which requires accounting for the time structure of the effect in assessing the exposure–response relationship (Gasparrini et al., 2010). A modelling framework known as Distributed Lag Nonlinear Model (DLNM) was developed to flexibly describe the potential nonlinear exposure-response relationship together with the lagged effects, defined as exposure-lag-response associations (Gasparrini, 2014; Gasparrini et al., 2010). Some previous studies employed this robust novel methodology by combining the DLNM with time-series to investigate exposure-lag-response associations (Cheng et al., 2021; Jegasothy et al., 2022; Khodadadi et al., 2022). Based on these contexts, we aimed to link fine spatiotemporal UTCI to the clinically diagnosed stillbirths at small area levels and implemented a within-space time-series DLNM to examine the exposure-lag-response association between prenatal exposure to long-term heat stress and stillbirth in Ghana.

2. Methods

The REporting of studies Conducted using Observational Routinely collected health Data (RECORD) guidelines was followed in reporting the results (Benchimol et al., 2015).

2.1. Study design

A previously applied DLNM time-series design (Cheng et al., 2021; Jegasothy et al., 2022; Khodadadi et al., 2022) was extended to include spatial variation, resulting in a within-space time-series DLNM analysis. Specifically, we matched the variations within districts nested within regions to control by design for measured and unmeasured known and unknown, spatially varying confounders. The seasonal and long-term trends, potential temporal autocorrelation, and overdispersion were also controlled.

2.2. Study population and birth data

Ghana is a coastal SSA country in West Africa and located at 8° 00′ N and 2° 00′ W. Ghana's population from the 2021 census was 30.8 million at a growth rate of 2.1% with a population density of 129 persons/km^2 (GSS, 2021). As a tropical humid monsoon climatic region, Ghana has a dry winter characterised by dust (harmattan) and rainy summer seasons. The average temperature is 26.1 °C in the southern and 28.9 °C in the northern and could rise above 40 °C in the north-eastern parts of the country. About 2.3% of pregnancies end up in stillbirths (GSS, 2018) but the prevalence varies geographically from 2.1 to 3.2% (Agbozo et al., 2016; Ha et al., 2012; Nonterah et al., 2020).

Ghana is organised into 16 geopolitical regions which are subdivided into 260 non-overlapping local districts. From the recent 2021 census, the average population size per district was 118,130 persons (GSS, 2021). The local district is the lowest level of health service management and policy implementation. As a common challenge in most LMICs or SSA countries, including Ghana, nationwide individual-level electronic birth records are currently unavailable (Froen et al., 2016). Previous studies in LMICs, therefore, used population-based surveys to investigate the association between heat stress and stillbirth (Asamoah et al., 2018; McElroy et al., 2022), despite the inherent limitations of the survey datasets, especially for reporting pregnancy and adverse pregnancy outcomes such as stillbirth (Kwesiga et al., 2021; McClure, 2020). Recently in Ghana, however, district health directorates collate health information from public and private health facilities monthly and transfer the data remotely to the Centre for Health Information Management (CHIM) of the Ghana Health Service (GHS) using the District Health Information Management System version 2 (DHIMS2) (GHS, 2018). We obtained district-level monthly stillbirths – defined as fetal death in pregnancies that lasted for at least seven months - from the CHIM of GHS across the 260 districts from 1st January 2012 to 31st December 2020.

2.3. Universal Thermal Climate Index exposure and other covariates

The primary exposure, UTCI is an isothermal equivalent air temperature (°C) of the reference condition causing the same human physiological response to the actual thermal environmental condition (combination of air temperature, wind speed, relative humidity, and radiation) (Blazejczyk et al., 2013; Bröde et al., 2012; Jendritzky et al., 2012). For interpretation and application of UTCI across the different climatic zones and human physiological responses, non-meteorological variables, and the thermal properties of clothing (insulation, vapour resistance, air permeability) are critical and included in defining the reference conditions. The reference conditions are 4 km/h walking speed, 2.3 MET ($\simeq$135 W m^{-2}) rate of metabolic heat production, wind speed of 0.5 m/s at 10 m above the ground level, mean radiant temperature equal to air temperature (that is no additional thermal radiation), and relative humidity of 50% (with vapour pressure capped at 20 hPa for air temperature above 29 °C) (Bröde et al., 2012). UTCI is derived from the advanced Fiala multi-node model of human heat balance that fully accounts for heat transfer and exchange (Blazejczyk et al., 2013; Jendritzky et al., 2012). We used the UTCI from the global hourly gridded historical dataset of human thermal comfort indices derived from ERA5 reanalysis (ERA5-HEAT, Human thErmAl comforT) (Di Napoli et al., 2021). ERA5 dataset is the fifth global climate reanalysis produced by the European Centre for Medium-Range Weather Forecasts (Hersbach et al., 2020). The UTCI calculation involved two major steps. First, the solar and thermal radiation fluxes at the surface of the Earth were extracted from ERA5 with numerical weather prediction models and used to calculate the mean radiant temperature (MRT) (Di Napoli et al., 2020). Second, the MRT, and ERA5-retrieved 2 m above ground level for both air temperature and relative humidity, and wind speed at 10 m above ground level were used as inputs into a six-order polynomial equation to derive the global gridded UTCI (except for Antarctica) for each hour on regular latitude-longitude grids at 0.25° × 0.25° spatial resolution from 1979 to present (Di Napoli et al., 2021). Further details on the operational procedures for deriving the UTCI were described elsewhere (Bröde et al., 2012; Di Napoli et al., 2021). We obtained 24-h averages of the gridded UTCI over Ghana between 1st January 2011 and 31st December 2020 and processed them with ArcGIS software (version 10.8.1). Data for 2011 were included to allow for a lag period before the first observation in January 2012. District-level monthly mean UTCI was calculated.

We also obtained the following annual global gridded datasets as covariates: between 2012 and 2019 at approximately 1 km × 1 km spatial resolution for fine particulate matter air pollution ($PM_{2.5}$) estimates version V4. GL.03 (Hammer et al., 2020) and ambient population (24 h average population modelling that fully exploited the potential activity space of people throughout the day and night rather than merely a residential area) (Rose et al., 2020). Between 2010 and 2015 at a spatial resolution of 5 arc-min (approximately 10 km at the equator) for total Gross Domestic Production (Purchasing Power Parity) (hereon GDP) in constant 2011 international United States dollars were also obtained (Kummu et al., 2018). District-specific values were extracted with ArcGIS software (version 10.8.1). For each covariate, linear interpolation was performed using the 'imputeTS' package (Moritz and Bartz-Beielstein, 2017) to extrapolate to 2020. Data between 2012 and 2020 were used for the analysis. The ambient population was divided by the district area to obtain the population density. Overall means were also computed to dichotomise the districts into low (≤median) or high (>median) subgroups for each covariate.

2.4. Statistical analysis

2.4.1. Main analyses

The DLNM was combined with conditional quasi-Poisson regression for simultaneous investigation of the immediate, delayed, and cumulative effects of UTCI on stillbirth (Gasparrini, 2014; Gasparrini et al., 2010). The model was specified as

$$\log\left[E\left(Y_{t,i,s}\right)\right] = \alpha + cb(\mathrm{UTCI}) + \mathrm{Month} + ns(\mathrm{time}, df) + \mathrm{cov}, \mathrm{offset} = \log(\mathrm{total\ birth}) \quad (1)$$

where $Y_{t,i,s}$ is the observed number of stillbirths in month t for a year i at district s; α is the intercept; *cb* is the cross-basis function to define the nonlinear exposure–lag–response association using the 'dlnm' R package (Gasparrini et al., 2010). The *cb* was specified through natural cubic splines in both the UTCI predictor and the lag dimensions with the maximum lag of 9 months to capture preconception periods or gestational ages that might extend to the 10th month. Equally spaced spline knots were placed at the log scale of lags. The choice of optimum degrees of freedom (*df*) was informed by the minimisation of the Akaike information criterion (AIC) (Gasparrini, 2014; Gasparrini et al., 2010). Several combinations of 2–5 *df* were investigated following the previous studies (Cheng et al., 2021; Jegasothy et al., 2022; Khodadadi et al., 2022; McElroy et al., 2022) and practical recommendations (Perperoglou et al., 2019). Finally, 5 and 3 dfs were selected to model the exposure-response and lag-response associations, respectively. The *Month* is the month factor variable (1, 2, 3, ….., 12) to control for annual seasonality. The *ns (time, df)* is a natural spline of time in a continuous number of months over the study period with 36 *df* (4 per year based on the lowest AIC) to control for long-term temporal trends. The *cov* is the covariates as percentages of fetal sex (male and female) and maternal age at delivery (10–19, 20–34, and ≥35 years), and natural splines with 2 *df* to flexibly model the continuous variables GDP and population density. To control for unobserved and unmeasured spatially varying confounding effects, we fitted the conditional quasi-Poisson regression using the "gnm" R package by including a conditional factor *stratum*, indicating the variation in the same district in the same region through the "eliminate" function (Turner and Firth, 2020). We estimated the

Relative Risks (RRs) and 95% Confidence Intervals (CIs) at the 1st, 10th, 25th, 75th, 90th, and 99th percentiles, relative to median UTCI. Because of the potential temporal collinearity or autocorrelation in individual lag effect estimates which could lead to spurious findings (Basagaña and Barrera-Gómez, 2021), we reported immediate (lag 0) and cumulative effects (lag 0-N, where N = 1, 2, …., 9 months) as the main results (Basu et al., 2016; Cheng et al., 2021; Khodadadi et al., 2022).

We also calculated the number of excess stillbirths per 10,000 births attributable to heat stress by estimating the Attributed Risk (AR) following (Ha et al., 2017) as

$$AR = I_u(RR - 1) \quad (2)$$

Two measures for I_u (the background incidence of stillbirth) were used: our study-specific incidence (1.5%) and the prevalence rate from the GMHS 2017 (2.3%) (GSS, 2018). We used the RR (95% CI) for the UTCI threshold (which was 90th percentile from the main analysis) that showed the most consistent higher risks across the exposure periods to estimate the AR.

Stratified analyses for the dichotomised subgroups for seasons (wet summer or rainy season: April–November and dry winter or harmattan season: December–March), population density, GDP, and air pollution) were also performed using the UTCI threshold at the 90th percentile. For stratification analysis by season, we excluded the factor month to avoid over-adjustment. The estimated risks between the subgroups were compared by performing the Altman and Bland test of interaction (Altman and Bland, 2003; Hutchon, 2005).

2.4.2. Sensitivity analyses

A series of sensitivity analyses were performed to ascertain the robustness of the main results. We included GDP and population density as linear terms. $PM_{2.5}$ (a mediator) was not included in the main analysis for estimating the *total effect* (overall effect) of thermal stress because temperature contributes to the formation of particulate matter as recommended (Buckley et al., 2014; Gronlund et al., 2020). But $PM_{2.5}$ was included to ascertain the *direct effect* of UTCI in which any variation in the $PM_{2.5}$ mediator was eliminated (Gronlund et al., 2020; Igelström et al., 2022) by including the annual $PM_{2.5}$ as natural splines with 2 *df*. The reference UTCI was changed to 26 °C (upper value for *no thermal stress* range) (Blazejczyk et al., 2013) which was the closest to our median UTCI. Because the earliest final gestational age of stillbirth was 28 weeks, the maximum lag was changed to seven months. The *dfs* were changed to 4 and 3 for the predictor and lag space dimensions, respectively. We replaced the *ns (time, df)* with a year index factor variable (1, 2, 3, …, 9) to control for long-term trends as inter-annual variability. We also excluded the month factor and included only *ns (time, df)* as previous acute effect studies on daily exposure-lag-association considered this to have accounted for both seasonal and long-term trends (Cheng et al., 2021; Jegasothy et al., 2022; Khodadadi et al., 2022).

All statistical analyses were performed utilising R statistical software (version 4.1.1) (R, 2021). Results were interpreted in the context of human thermophysiology without considering statistical significance as recommended by the American Statistical Association (Wasserstein et al., 2019).

3. Results

3.1. Characteristics of the birth cohorts, exposure, and covariates

The cohort consisted of 5,961,328 births of which 90,532 (1.5%) were stillbirths. Slightly above half of the births were male (mean = 51%) and majority (mean = 72%) were born by young adults (20–34 years). The overall mean (28.5 ± 2.1 °C) and median UTCI (28.8 °C), as well as that of specific subgroups, indicated *moderate heat stress*. From the minimum to the 10th percentile of UTCI were in *no thermal stress* range. UTCI above the median fell within the *moderate heat stress* range, except in the 99th percentile which indicated *strong heat stress* (Table 1 and Table S1) according to the standard ten categories of UTCI that range from extreme cold stress to extreme heat stress (Blazejczyk et al., 2013). The overall average (mean ± standard deviation) for GDP was 281.8 ± 778.6 per million US dollars for population density of 1225 ± 4114 persons per km^2 with $PM_{2.5}$ concentration of 59.7 ± 9.2 μg/m^3 (Table 1). The geographical distribution revealed that most of the districts had an average of fewer than 10 stillbirths per 1000 births. Almost all districts were exposed to UTCI of 27.6 °C to 30.2 °C which is within the moderate heat stress threshold (Fig. 1). Both UTCI and stillbirth varied temporally in somewhat similar pattern over the study period (Fig. 2).

3.2. Thermophysiological stress exposures and risk of stillbirth

The unadjusted (that is included only UTCI exposure) cumulative effect of UTCI on stillbirth indicated a rise-and-fall pattern (Fig. S1). Similar patterns were found for adjusted (that is additionally included confounding factors) cumulative exposure-lag-response associations with better precision than unadjusted effect estimates. Compared to the monthly median UTCI, we found lower risks of stillbirth at both ends of UTCI distribution but higher risk within 29 °C–32 °C (Fig. 3). The range from no thermal stress up to lower levels of moderate heat stress thresholds (1st to below the 75th percentile of UTCI) showed lower risks of stillbirth as compared to the median thermal stress. The higher-moderate heat stress exposure levels (that is the 75th to 90th percentiles of UTCI), relative to median thermal stress showed higher risks and increased with the duration of heat exposure episodes from the month of birth up to the past nine months. These ranged from 1% (RR = 1.01, 95% CI 1.00, 1.03) to 14% (RR = 1.14, 95% CI 1.06, 1.22) for the 75th percentile (29.9 °C) and 2% (RR = 1.02, 95% CI 0.99, 1.05) to 18% (RR = 1.18, 95% CI 1.02, 1.36) for the 90th percentile (30.8 °C), relative to the median UTCI (28.8 °C). However, the relative risk began to decrease at the 95th percentile and became almost 'protective' at the 99th

Table 1
Descriptive statistics of the births, environmental exposures, and sociodemographic conditions across the 260 districts in Ghana, 2012–2020.

Variables	Mean	SD	Median	Min	P25	P75	Max	IQR*
Births (N = 5,961,328)	212.3	345.6	162.0	1.00	86.0	266.0	45929.0	180.0
Stillbirths (N = 90,532)	3.2	5.4	2.0	0.00	0.0	4.0	111.0	4.0
Male (%)	50.9	5.7	50.9	0.0	47.9	53.8	100.0	5.9
Female (%)	49.0	5.7	49.1	0.0	46.1	52.1	100.0	6.0
Teen:10–19 years (%)	13.0	5.7	13.0	0.0	9.4	16.4	65.3	7.0
Young adult: 20–34 years (%)	72.1	6.3	72.2	0.0	68.5	75.9	96.4	7.4
Adult: ≥35 years (%)	14.0	4.5	13.9	0.0	11.2	16.7	77.6	5.5
UTCI (°C)	28.5	2.0	28.8	19.6	27.2	29.9	35.2	2.7
$PM_{2.5}$ (μg/m^3)	59.7	9.2	59.6	38.4	52.8	67.8	81.4	15.0
GDP (per million US dollars)	281.8	778.6	50.5	0.8	24.8	106.8	5132.5	82.0
Population density (persons/km^2)	1224.9	4113.8	141.5	8.0	78.0	318.0	39070.0	240.0

Note. SD, standard deviation; UTCI, Universal Thermal Climate Index; P25 and P75, 25th and 75th percentiles; *IQR, Interquartile range = P75–P25; GDP, Gross Domestic Production (Purchasing Power Parity); US, United States; $PM_{2.5}$; fine particulate matter at aerodynamic diameter ≤2.5 μm.

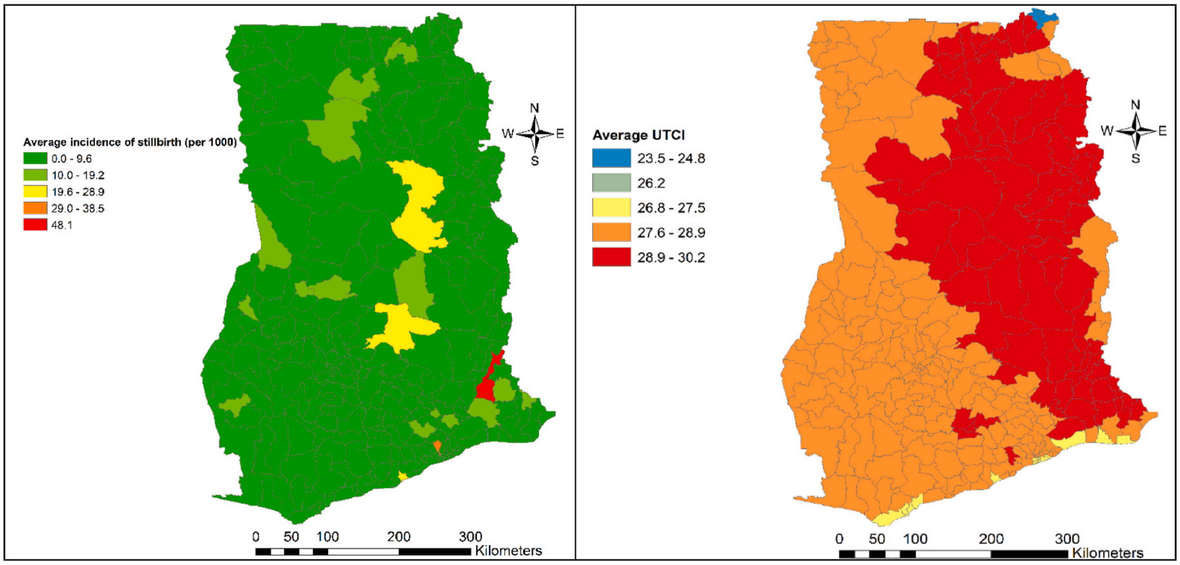

Fig. 1. Geographical distribution of the overall average incidence of stillbirth (per 1000 births) and the UTCI (°C) across the 260 districts in Ghana during 2012–2020. Mapping was based on equal interval classification method in ArcGIS. Note: UTCI, Universal Thermal Climate Index. The base map was obtained from https://data.humdata.org/dataset/ghana-administrative-boundaries.

percentile (strong heat stress, 33.2 °C) relative to the median UTCI (Table 2). Although with lower magnitudes of effects, almost similar patterns were observed for the adjusted individual lag effects. The most elevated risk of 3% higher (RR = 1.03, 95% CI 1.01, 1.05) was consistently found for the first to third months before the month of stillbirth delivery (third trimester) for the 90th percentile, relative to the median UTCI (Table S2). There were 19 (95% CI 3, 37) excess stillbirths per 10,000 births attributable to long-term heat stress exposure at the 90th percentile, relative to the median UTCI for the past six months and 27 (95% CI 3, 54) for the past nine months based on 1.5% baseline rate of stillbirth (Table 3).

3.3. Thermophysiological stress and risk of stillbirth by subgroups

Relative to the season-specific median UTCI, the risk was slightly greater in winter than in summer (Table S2). Comparing the risk between the two seasons indicated that the risk in the month of stillbirth (lag 0) and up to eight preceding months (lag 0–8) were 4% (RRR = 1.04, 95% CI 0.95, 1.14) and 11% (RRR = 1.11, 95% CI 0.72, 1.69) greater, respectively, in winter as compared to summer exposure at the 90th percentile relative to the median UTCI (Table 4). The stratification analyses also showed slightly greater risk in districts with low population density, low GDP, and low $PM_{2.5}$ concentration than the risks in the high subgroup categories (Table S3). The comparative test of interaction showed that the risks in low as compared to high population density areas for exposure to the 90th percentile relative to median UTCI increased from the month of stillbirth at 4% (RRR = 1.04, 95% CI 0.97, 1.11) to the nine months preceding the month of stillbirth at 29% (RRR = 1.29, 95% CI 0.93, 1.79). A similar observation was found in low relative to high GDP areas at 2% (RRR = 1.02, 95% CI 0.95, 1.09) in the month of stillbirth to 63% (RRR = 1.63, 95% CI 1.16, 2.28) in up to nine preceding months. Low relative to high $PM_{2.5}$ concentrations also indicated the same pattern, but the greatest risk was found in the six preceding months (RRR = 1.21, 95% CI, 0.95, 1.55). However, all except GDP included the null in the confidence intervals (Table 4).

3.4. Sensitivity analyses

Adjustment for annual $PM_{2.5}$ had a negligible influence on the effect estimates (Fig. S2). The results of all sensitivity analyses under varying modelling conditions or assumptions were consistent with the results from the main analysis but with comparatively lower precision (Figs. S3–S9).

4. Discussion

4.1. Thermophysiological stress and risk of stillbirth

Using nearly 6 million births in Ghana with monthly district-level clinically determined stillbirths (1.5%), we investigated the immediate, delayed, and cumulative effects of heat stress on stillbirths. We found that long-term exposure to moderate heat stress showed a higher risk of stillbirth. Our findings also suggested possible effects of heat stress during the preconception period as shown in lag 0–9 and lag 9 months (that is from the last 9 months before the month of stillbirth). The risk was slightly greater during the dry and dusty winter season (harmattan) than during the wet rainy summer season.

Our findings, based on the use of a UTCI to describe the impact of thermophysiological stress, were unique as compared to previous findings based on ambient temperature metrics (Sexton et al., 2021). Our findings were consistent with a few of the 12 previous studies included in a recent systematic review that reported an association between long-term ambient temperature exposures and stillbirth (Sexton et al., 2021). The magnitudes of the effect estimates were, however, incomparable across studies as each study used different temperature metrics and thresholds. For instance, Ha et al. (2017) reported 3.71 times higher odds of stillbirth (OR = 3.71, 95% CI: 3.07, 4.47) for exposure to heat (>90th percentile) as compared to mild (10th −90th percentile) mean temperatures in the United States. Wang et al. (2019) combined the 90th and 95th percentiles of maximum temperatures over two, three, and four days for six heatwave definitions in Brisbane, Australia. The authors found the most elevated hazard ratio of 1.52 (HR = 1.52, 95% CI 1.11, 2.09) in the 8th gestational month for their greatest heatwave definition. Other studies compared minimum-prevalence temperature to estimate the risks at given thresholds (Li et al., 2018; Weng et al., 2018). The previous studies included in the systematic review were from temperate and subtropical regions and reported higher relative risks for both heat and cold temperatures across the pregnancy period (Sexton et al., 2021). We reported only heat stress because our study area is tropical with UTCI ranging from no thermal stress to strong heat stress on the standard scale (Blazejczyk et al., 2013; Di Napoli et al., 2021). There was only one previous study on long-term effects from SSA country, which was also

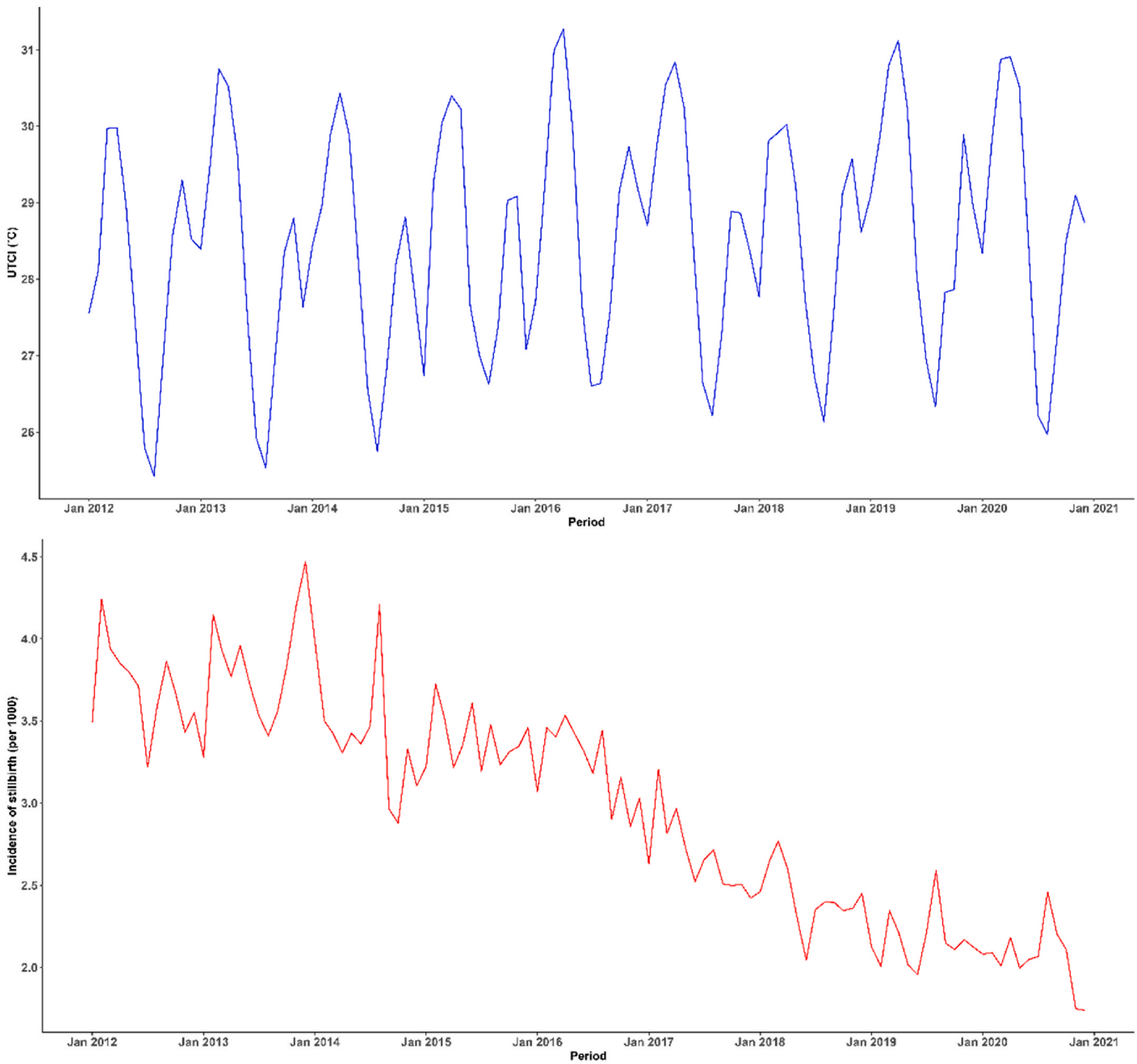

Fig. 2. Average monthly variations of UTCI and stillbirth rate across the 260 districts in Ghana from January 2012 to December 2020.

conducted in Ghana. This study found 12% higher odds of miscarriage or stillbirth per degree increase in annual mean wet-bulb globe temperature (OR = 1.12, 95% CI 0.90, 1.39) after adjusting for maternal age but the association diminished (OR = 1.00, 95% CI 0.80, 1.25) after additional adjustment for gravidity (Asamoah et al., 2018). This may be because high gravidity is a marker of recurrent pregnancy loss. Our findings showed stronger magnitude of effects, which may be due to differences in the study designs. The previous study was a cross-sectional analysis of maternal self-reported outcomes from a survey dataset, considered pregnancy loss with miscarriage and stillbirth together as one outcome, and assessed exposure at relatively larger geographic units (i.e. regions) with notable exposure misclassification. Moreover, the potential for spatial confounding effects was not accounted for in their analysis.

The individual month exposure-response associations did not show a higher risk at the early stages of pregnancy which was consistent with findings reported in the United States (Ha et al., 2017) but contrary to those from a study in Brisbane, Australia that found higher effects of heat exposure in early as compared to late pregnancy (Wang et al., 2019). Differences in exposure assessment and outcome definition, acclimatisation, and behavioural interventions by pregnant women in the context of the climatic conditions could account for these contrasting findings. However, considering the transient nature of the heat exposure and abrupt stillbirth outcome, the risk is more likely to be stronger in late pregnancy. This is partly due to fact that the late pregnancy period has more advanced physiological changes with greater difficulty for maternal thermoregulation as compared to the early pregnancy period (Wells and Cole, 2002). Contrary to Ha et al. (2017), we also found possible higher effects of stillbirth in preconception periods, a crucial period for gametogenesis and placental development where the negative impacts from environmental stressors such as heat stress can be profound (Keikha et al., 2022). For the thresholds in the no thermal stress or

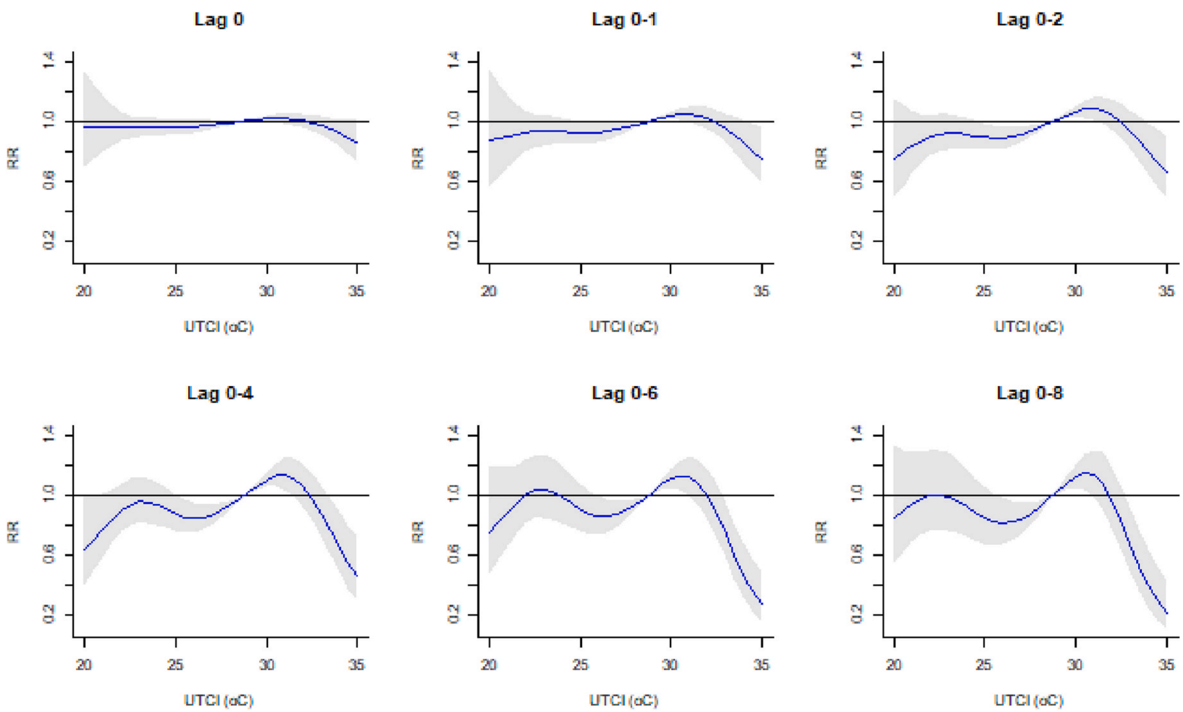

Fig. 3. Cumulative exposure-response curves of monthly UTCI and stillbirth at different lag months, relative to the median UTCI (28.8 °C).

Table 2
The estimated cumulative relative risks (RRs) and 95% confidence intervals (95% CIs) of stillbirth at different percentiles of UTCI, relative to the median UTCI (28.8 °C) in Ghana, 2012–2020.

Lag months	1st (23.0 °C)	10th (25.8 °C)	25th (27.2 °C)	75th (29.9 °C)	90th (30.8 °C)	95th (31.6 °C)	99th (33.2 °C)
0	0.96 (0.89, 1.03)	0.96 (0.92, 1.01)	0.98 (0.95, 1.00)	1.01 (1.00, 1.03)	1.02 (0.99, 1.05)	1.01 (0.97, 1.05)	0.96 (0.90, 1.02)
0–1	0.93 (0.84, 1.04)	0.92 (0.86, 0.99)	0.95 (0.91, 0.99)	1.03 (1.01, 1.06)	1.05 (1.00, 1.10)	1.04 (0.97, 1.11)	0.93 (0.83, 1.04)
0–2	0.92 (0.81, 1.04)	0.88 (0.81, 0.96)	0.92 (0.87, 0.96)	1.06 (1.03, 1.09)	1.08 (1.02, 1.15)	1.07 (0.98, 1.16)	0.91 (0.79, 1.06)
0–3	0.93 (0.81, 1.07)	0.86 (0.77, 0.95)	0.89 (0.84, 0.94)	1.08 (1.04, 1.12)	1.11 (1.04, 1.20	1.09 (0.99, 1.21)	0.88 (0.74, 1.06)
0–4	0.96 (0.82, 1.12)	0.84 (0.75, 0.95)	0.88 (0.82, 0.94)	1.10 (1.05, 1.14)	1.13 (1.04, 1.23)	1.10 (0.98, 1.24)	0.83 (0.67, 1.02)
0–5	1.00 (0.84, 1.19)	0.85 (0.74, 0.97)	0.87 (0.81, 0.94)	1.10 (1.05, 1.15)	1.13 (1.04, 1.24)	1.09 (0.95, 1.24)	0.75 (0.59, 0.95)
0–6	1.04 (0.85, 1.27)	0.86 (0.73, 1.00)	0.88 (0.80, 0.96)	1.10 (1.05, 1.16)	1.13 (1.02, 1.25)	1.06 (0.92, 1.23)	0.67 (0.51, 0.88)
0–7	1.04 (0.82, 1.31)	0.85 (0.71, 1.02)	0.87 (0.79, 0.96)	1.10 (1.04, 1.16)	1.12 (1.00, 1.26)	1.04 (0.89, 1.23)	0.62 (0.46, 0.84)
0–8	0.99 (0.76, 1.28)	0.81 (0.66, 0.99)	0.85 (0.76, 0.95)	1.11 (1.05, 1.19)	1.14 (1.00, 1.29)	1.06 (0.88, 1.27)	0.61 (0.44, 0.86)
0–9	0.88 (0.65, 1.18)	0.74 (0.59, 0.92)	0.81 (0.71, 0.91)	1.14 (1.06, 1.22)	1.18 (1.02, 1.36)	1.10 (0.89, 1.36)	0.65 (0.45, 0.94)

Table 3
The cumulative monthly attributed risks (ARs) and 95% confidence intervals (95% CIs) per 10,000 births at 90th percentile of UTCI (30.8 °C), relative to median UTCI (28.8 °C) in Ghana, 2012–2020.

Lag months	AR (95% CI)[a]	AR (95% CI)[b]
0	2.8 (−1.5, 7.2)	4.3 (−2.4, 11.1)
0–1	7.0 (−0.1, 14.5)	10.8 (−0.1, 22.2)
0–2	12.3 (3.0, 22.1)	18.8 (4.6, 33.8)
0–3	17.1 (5.8, 29.3)	26.3 (8.9, 45.0)
0–4	20.0 (6.7, 34.4)	30.6 (10.3, 52.7)
0–5	20.2 (5.4, 36.3)	31.0 (8.3, 55.7)
0–6	18.9 (2.7, 36.9)	29.0 (4.1, 56.6)
0–7	18.5 (0.4, 38.8)	28.4 (0.6, 59.4)
0–8	20.8 (0.5, 43.9)	31.9 (0.7, 67.3)
0–9	26.8 (3.2, 54.2)	41.2 (4.9, 83.1)

[a] Calculated using study-specific background incidence rate (1.5%).
[b] Calculated using background prevalence rate from Ghana Maternal Health Survey 2017) (2.3%).

lower-moderate heat stress ranges as compared to the median UTCI (also moderate heat stress), acclimatisation could have explained the observed lack of association or "protective" effects at these thresholds. We also observed a lower or "protective" effect at the 99th percentile

Table 4
The ratio of relative risk (RRR) and 95% confidence intervals (95% CI) of stillbirth for comparing the risk between two subgroups at 90th percentile relative to the median UTCI in Ghana, 2012–2020.

Lag month	Season	Population density	GDP	$PM_{2.5}$
	Winter vs summer	Low vs High	Low vs High	Low vs High
0	1.04 (0.95, 1.14)	1.04 (0.97, 1.11)	1.02 (0.95, 1.09)	0.96 (0.89, 1.03)
0–1	1.04 (0.90, 1.19)	1.07 (0.96, 1.19)	1.07 (0.96, 1.19)	0.98 (0.88, 1.10)
0–2	1.02 (0.86, 1.21)	1.10 (0.97, 1.26)	1.13 (0.99, 1.29)	1.04 (0.90, 1.19)
0–6	1.00 (0.70, 1.43)	1.16 (0.92, 1.45)	1.41 (1.11, 1.79)	1.21 (0.95, 1.55)
0–7	1.04 (0.70, 1.55)	1.17 (0.91, 1.52)	1.47 (1.13, 1.92)	1.19 (0.92, 1.55)
0–8	1.11 (0.72, 1.69)	1.22 (0.92, 1.62)	1.55 (1.15, 2.09)	1.16 (0.86, 1.56)
0–9	1.19 (0.76, 1.88)	1.29 (0.93, 1.79)	1.63 (1.16, 2.28)	1.11 (0.79, 1.56)

(strong heat stress) as compared to the median UTCI (moderate heat stress). While this could be due to small births within the 99th UTCI percentile range, this observation also suggest that pregnant women are more likely to adopt behavioural or coping interventions such as minimising outdoor activities, drinking water, using water or ice to cool down during the unbearable strong heat stress episodes as compared to moderate heat stress (Spencer et al., 2022). The dryness of the environment and associated dust blown by the strong wind from the Sahel desert during harmattan, especially stronger in the northern part may explain the observed greater risk in the dry winter season as compared to the rainy summer season.

4.2. Modifying effects of population density, socioeconomic status, and air pollution

We observed that districts with low population density, low GDP, and comparatively low air pollution which could collectively be defined as rural districts were at higher risk as compared to those in the high level (most likely urban districts). Compared to urban areas, rural areas are sociodemographically more vulnerable to many other underlying major risk factors such as infection, malnutrition, anaemia, poor sanitation, and lack of access to quality antenatal care (UN, 2020). Moreover, rural residents, including pregnant women predominantly engage in small-scale subsistence farming. This would expose them to heat stress during the farming activities, nutritional depletion from temperature elated effects on crop production, and indirect effects from other climate change-related extreme events (Davenport et al., 2020; Giudice et al., 2021; Spencer et al., 2022). Thus, the association of climate change with higher risks of stillbirth may be direct through heat stress or indirect (Giudice et al., 2021), but heat stress comparatively has more direct biological impacts (Davenport et al., 2020). Furthermore, pregnant women in rural settings often travel long distances and may have to walk through unfavourable climatic conditions to access a distant healthcare service. For example, a study conducted in the second most urbanised and developed region of Ghana (Ashanti region) revealed that members of some rural districts in the region had to travel long distances as far as 39 km to access the nearest health facility (Ashiagbor et al., 2020). Urban resident women are also more likely to adopt better heat stress mitigation strategies such as use of cooling facilities (air conditioner and fan) and better housing conditions than their rural counterparts. The greater effect estimates for those from rural settings are roughly the same as known harmful hazards such as the effects of smoking on stillbirth (Gould et al., 2020).

4.3. Plausible pathophysiologic pathways

Plausible pathophysiologic pathways have been established by several experimental and clinical observational studies. Pregnancy results in higher-fat deposits, high basal metabolic rate, and reduced systemic vascular resistance which increases thermal susceptibility (Edwards et al., 2003; Wells and Cole, 2002). As a result, heat stress can cause hyperthermia and in turn, causes the death of proliferating cells or apoptosis and disruption of normal processes of embryogenesis and organogenesis. These can result in heat-induced structural and functional defects in the central neuroendocrine and inflammatory systems, and placental development and physiology (Edwards et al., 2003; Ziskin and Morrissey, 2011). The fetoplacental exchange of materials such as oxygen, water, nutrients, and removal of fetal toxic waste materials is decreased. Consequently, fetal health, growth, and development are affected where fetal death or stillbirth is the endpoint (Ziskin and Morrissey, 2011). Experimental studies identified excess reactive oxygen species and high concentration of serum heat shock proteins in the heat-induced impacts on biological processes that elevate the risks of pregnancy complications and birth outcomes (Ayinzat et al., 2021; Berestoviy et al., 2021; Edwards et al., 2003). Also, increased dehydration due to increased sweating and urination, and heat dissipation that reduces uterine blood flow decreases fetoplacental transport of essential materials (Edwards et al., 2003; Ziskin and Morrissey, 2011). Given that the maternal thermoregulatory capacity determines the *in utero* thermal environment and that of the developing fetus (Ziskin and Morrissey, 2011), a direct effect of the heat-shock response in the developing fetus is also a plausible pathway (Edwards et al., 2003). At lower temperatures, protective responses in reduced concentrations of heat shock proteins have also been reported (Edwards et al., 2003). This could explain why we observed “protective effects” in the ranges of no thermal stress up to lower-moderate heat stress, relative to higher-moderate heat stress.

4.4. Public health and climate governance strategies and policies

The increasing pace of anthropogenic-induced climate change and its disproportionate impacts on vulnerable subpopulations, particularly pregnant women in sociodemographically deprived settings require that climate change should be integrated with the known non-climatic factors in managing birth outcomes (Giudice et al., 2021; IPCC, 2021). Together with actionable evidence from the previous findings (Sexton et al., 2021), public health and environmental or climate governance policies and education for attitudinal change are required to save the environment and save lives. These include increased awareness and response to climate change crisis, reduce outdoor activities during thermal stress episodes, protecting and managing the ecological environment (e.g., greening the environment), increase access to essential thermal mitigation and adaptation resources, increasing investments in biotechnological solutions, and transitioning to clean and renewable energy sources such as wind, wave, solar, and geothermal (Pereira et al., 2021; Zhao et al., 2022). These measures and building climate change-resilient health systems will contribute substantially to reducing the climate change crisis and associated impacts on health outcomes and health costs (Ebi et al., 2021). More geodemographic-specific studies that use a thermophysiological index such as UTCI are required to monitor the impacts of the ongoing climate change crisis on birth outcomes to help design appropriate mitigation and adaptation strategies suitable for the climatic and sociodemographic conditions of a given setting (Romaszko et al., 2022; Sexton et al., 2021; Vanos et al., 2020).

4.5. Strengths and limitations

This study has several strengths. Our study is among the few studies that evaluated the long-term effects of heat stress on stillbirth (Sexton et al., 2021). Our study controls for temporal and spatial confounding by design. Rather than investigate ambient temperature, a practice that has been debated recently (Staiger et al., 2019; Vanos et al., 2020), we used the relatively suitable recommended contemporary human thermophysiological metric, the UTCI (Blazejczyk et al., 2012; Bröde et al., 2013; Staiger et al., 2019; Vanos et al., 2020) as reported elsewhere (Khodadadi et al., 2022; Nyadanu et al., 2022b, 2022c; Romaszko et al., 2022). As the results were interpreted within the context of standard thermophysiological stress, the comparability and physiological relevance of the findings are enhanced (Jendritzky et al., 2012; Romaszko et al., 2022). To the best of our knowledge, this is the first study in the SSA region to examine the long-term effect of heat stress on stillbirth and with clinically diagnosed stillbirth data as well as using a thermophysiological metric such as UTCI. Given similar geodemographic, socioeconomic, and climatic conditions in SSA, our findings could be generalised particularly in neighbouring West African countries.

We also note several limitations of our study. We did not account for indoor thermal conditions, daily activity patterns, and maternal migration during pregnancy which could lead to exposure misclassifications. However, the impact of maternal migration is expected to be negligible because of the within-district-region conditioning approach used in this study. It is also less likely for a pregnant woman to travel into another district in another region during pregnancy as compared to migration into another district in the same region that we controlled for by design. Any related residual effect would be non-differential, biasing the estimates towards the null. We only have annual instead of monthly data on the population density, GDP, and ambient air pollution. Although minimised by design, the ability to include more clinical factors, especially infection would also be helpful. Finally, our findings were based on an aggregated longitudinal dataset which is less well-powered than individual-level analysis. Nonetheless, the novel methodology may be applied in other SSA countries that currently do not have maternal and child electronic health registries for large-scale individual-level longitudinal cohort investigations (Froen et al., 2016). Moreover, our approach is similar to individual-level cohort studies that assigned exposures at group levels, which is the common practice (Sexton et al., 2021). Previous studies have also demonstrated the methodological strengths of this approach in short-term effects analyses (Cheng et al., 2021; Jegasothy et al., 2022; Khodadadi et al., 2022).

5. Conclusions

Our findings suggest that long-term exposure to moderate heat stress during pregnancy elevated the risk of stillbirth in Ghana as reported in many studies from developed countries (Sexton et al., 2021). Pregnant women in deprived socioeconomic areas or rural districts were more susceptible than those in urban districts. Heat stress exposure during the preconception period also showed potential risk. Taken together, we recommend increased awareness and precautionary or preventive measures among pregnant women, women of reproductive age, healthcare providers, and policymakers to lessen maternal exposure to heat stress, particularly in rural areas. This is critical given that severe climate change events are projected to increase in intensity, frequency, and duration in the coming years globally (IPCC, 2021). Implementing heat warning systems with a human thermophysiological index may be beneficial (Krüger, 2021; Vanos et al., 2020). Well-designed individual-level cohort studies with spatiotemporal UTCI exposure and more studies from developing and SSA countries are required to confirm our results to facilitate appropriate evidence-based thermal adaptation and mitigation strategies and climate governance policies.

Author contributions

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, Project administration, Supervision. BK-B: Conceptualisation, Investigation, Writing—Critical Review and Editing, Supervision. AAO: Writing—Critical Review and Editing. GP: Conceptualisation, Methodology, Investigation, Writing—Critical Review and Editing, Project administration, Supervision. All authors have read and approved the final version of the manuscript.

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Ethical approval

The study was approved by Curtin University Human Research Ethics Committee (Number HRE2020-0523) and Ghana Health Service Ethics Review Committee (Number GHS-ERC016/12/20). Participants' consent is not applicable as routinely collected district-level data was used without any direct involvement of participants or collection of personally identifiable information.

Declaration of competing interest

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

Data availability

Except for the birth dataset, all datasets used in this study were open access and cited accordingly. Formal requests for the birth data can be made from the Ghana Health Service.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2023.115385.

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