Environmental Research 212 (2022) 113596

Contents lists available at ScienceDirect

Environmental Research

journal homepage: www.elsevier.com/locate/envres

Ambient temperature during pregnancy and risk of maternal hypertensive disorders: A time-to-event study in Johannesburg, South Africa

Chérie Part [a,*], Jean le Roux [b], Matthew Chersich [b], Shobna Sawry [b], Véronique Filippi [c], Nathalie Roos [d], Lee Fairlie [b], Britt Nakstad [e,f], Jeroen de Bont [g], Petter Ljungman [g,h], Massimo Stafoggia [i], Sari Kovats [a], Stanley Luchters [j,k,l], Shakoor Hajat [a]

[a] Department of Public Health, Environments and Society, London School of Hygiene & Tropical Medicine, London, United Kingdom
[b] Wits Reproductive Health and HIV Institute, Faculty of Health Sciences, University of the Witwatersrand, Johannesburg, South Africa
[c] Department of Infectious Disease Epidemiology, London School of Hygiene & Tropical Medicine, London, United Kingdom
[d] Department of Medicine, Karolinska Institutet, Stockholm, Sweden
[e] Division of Paediatrics and Adolescent Medicine, Institute of Clinical Medicine, University of Oslo, Oslo, Norway
[f] Department of Pediatrics and Adolescent Health, University of Botswana, Gaborone, Botswana
[g] Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden
[h] Department of Cardiology, Danderyd Hospital, Stockholm, Sweden
[i] Department of Epidemiology, Lazio Regional Health Service, Rome, Italy
[j] Institute of Human Development, Aga Khan University, Nairobi, Kenya
[k] Department of Public Health and Primary Care, Ghent University, Ghent, Belgium
[l] Department of Epidemiology and Preventive Medicine, Monash University, Melbourne, Australia

ARTICLE INFO

Keywords:
Hypertension
Pre-eclampsia
Eclampsia
Ambient temperature
Heat
Climate change

ABSTRACT

Hypertensive disorders in pregnancy are a leading cause of maternal and perinatal mortality and morbidity. We evaluate the effects of ambient temperature on risk of maternal hypertensive disorders throughout pregnancy. We used birth register data for all singleton births (22–43 weeks' gestation) recorded at a tertiary-level hospital in Johannesburg, South Africa, between July 2017–June 2018. Time-to-event analysis was combined with distributed lag non-linear models to examine the effects of mean weekly temperature, from conception to birth, on risk of (i) high blood pressure, hypertension, or gestational hypertension, and (ii) pre-eclampsia, eclampsia, or HELLP (hemolysis, elevated liver enzymes, low platelets). Low and high temperatures were defined as the 5th and 95th percentiles of daily mean temperature, respectively. Of 7986 women included, 844 (10.6%) had a hypertensive disorder of which 432 (51.2%) had high blood pressure/hypertension/gestational hypertension and 412 (48.8%) had pre-eclampsia/eclampsia/HELLP. High temperature in early pregnancy was associated with an increased risk of pre-eclampsia/eclampsia/HELLP. High temperature (23 °C vs 18 °C) in the third and fourth weeks of pregnancy posed the greatest risk, with hazard ratios of 1.76 (95% CI 1.12–2.78) and 1.79 (95% CI 1.19–2.71), respectively. Whereas, high temperatures in mid-late pregnancy tended to protect against pre-eclampsia/eclampsia/HELLP. Low temperature (11°) during the third trimester (from 29 weeks' gestation) was associated with an increased risk of high blood pressure/hypertension/gestational hypertension, however the strength and statistical significance of low temperature effects were reduced with model adjustments. Our findings support the hypothesis that high temperatures in early pregnancy increase risk of severe hypertensive disorders, likely through an effect on placental development. This highlights the need for greater awareness around the impacts of moderately high temperatures in early pregnancy through targeted advice, and for increased monitoring of pregnant women who conceive during periods of hot weather.

1. Introduction

High ambient temperatures are known to increase the risk of preterm birth and other adverse pregnancy outcomes (Kuehn and McCormick, 2017; Chersich et al., 2020; Roos et al., 2021). Heat exposure has a range of physiological effects including a reduction in placental blood flow due to vasodilation (Wang et al., 2020), and an inflammatory response that

* Corresponding author. Department of Public Health, Environments and Society, LSHTM, 15-17 Tavistock Place, London, WC1H 9SH, United Kingdom.
E-mail address: cherie.part@lshtm.ac.uk (C. Part).

https://doi.org/10.1016/j.envres.2022.113596
Received 7 March 2022; Received in revised form 10 May 2022; Accepted 30 May 2022
Available online 2 June 2022

may trigger early labor (Samuels et al., 2022). There is some evidence that ambient temperature affects hypertensive disorders (HTDs) in pregnancy (Beltran et al., 2014; Cil and Cameron, 2017; Xiong et al., 2020), however such research is lacking in sub-Saharan Africa despite rapid warming in this region (IPCC et al., 2021).

Abbreviations

aHR	Adjusted hazard ratio
CI	Confidence interval
hBP	High blood pressure/hypertension/gestational hypertension
HELLP	Hemolysis, elevated liver enzymes, and low platelet liver disease
HR	Hazard ratio
HTD	Hypertensive disorder
IQR	Interquartile range
PEH	Pre-eclampsia, eclampsia/severe pre-eclampsia/ imminent eclampsia, or HELLP syndrome

HTDs in pregnancy are a leading cause of maternal mortality worldwide (World Health Organization, 2019). Approximately 10% of pregnancies in Africa are affected (Noubiap et al., 2019), putting women at increased risk of placental abruption and postpartum hemorrhage (Ye et al., 2014) as well as stroke, coronary heart disease, and chronic kidney disease in later life (Garovic et al., 2020). HTD-associated placental abnormalities also increase the risk of adverse perinatal outcomes, including intrauterine growth restriction and death (Awuah et al., 2020).

HTDs in pregnancy range in severity and time of onset. Chronic hypertension (systolic/diastolic blood pressure ≥140/90 mmHg) predates pregnancy or presents within the first 20 weeks, whereas gestational hypertension presents after 20 weeks' gestation (Brown et al., 2018; American College of Obstetricians and Gynecologists, 2021). Either may develop into pre-eclampsia; a more serious and complex disorder with significant proteinuria, hematological or biochemical abnormalities, and/or intrauterine growth restriction (Brown et al., 2018; American College of Obstetricians and Gynecologists, 2021). Pre-eclampsia typically occurs in the third trimester and can progress rapidly (Brown et al., 2018; American College of Obstetricians and Gynecologists, 2021) into the more severe forms of eclampsia (characterized by seizures) and HELLP syndrome (characterized by hemolysis, elevated liver enzymes, and low platelet liver disease) (Ferreira et al., 2021); both of which can be fatal.

Studies in East Asia and Australia show seasonal patterns in gestational hypertension and overall HTD prevalence, with the highest rates observed among women who deliver in winter (Umesawa and Kobashi, 2017). A systematic review showed that pre-eclampsia risk tends to increase with conception during the warmest months and delivery during the coolest months (Beltran et al., 2014). It has been proposed that heat affects placental development and spiral artery remodeling, while cold increases HTD risk through the well-established mechanism of vasoconstriction (Beltran et al., 2014). However, seasonal patterns are difficult to interpret and do not provide direct evidence of temperature effects (Beltran et al., 2014). Indeed, the validity of a causal relationship between temperature and pre-eclampsia has been questioned given demonstrated confounding bias by season of conception (tendency towards higher conception rates in summer) and length of gestation (increased risk of preterm birth and induced labor in women with pre-eclampsia) (Auger et al., 2017).

This study evaluates the effects of ambient temperature during each week of pregnancy, from conception to birth, on the risk of hypertensive disorders among women in Johannesburg, South Africa. High ambient temperatures in early gestation were hypothesized to increase the risk of hypertensive disorders in pregnant women, therefore we also explored the potential impacts of extreme heat episodes (heatwaves) in early pregnancy.

2. Material and methods

We undertook an observational, time-to-event study using data from secondary sources in Johannesburg. Johannesburg is the provincial capital of Gauteng and the largest city in South Africa, with approximately five million inhabitants (Statistics South Africa, 2018). Almost 98% of women in the Gauteng province give birth in a health facility (Statistics South Africa, 2020). The region has a temperate climate with warm summers and dry winters.

2.1. Data

Maternal health, demographic, and obstetric history data were collected from birth registries to include all births between July 01, 2017 and June 30, 2018 at one tertiary referral hospital in inner city Johannesburg. Data were originally collected as part of a population-based observational medical record review study (parent study). Approximately 8500, predominantly urban, women deliver in this hospital annually. It serves inner city Johannesburg and surrounding suburban areas, receiving referrals from primary care and secondary level facilities for high-risk deliveries. Singleton births between 22 and 43 weeks' gestation were eligible for inclusion in the study.

Daily meteorological data (mean, minimum and maximum temperature [°C], relative humidity [%], and windspeed [km/h]) were obtained from www.tutiempo.net (TuTiempo, 2021) for a single weather station in Johannesburg Botanical Gardens, located approximately 6 km north of the hospital. Data spanned September 01, 2016 to June 30, 2018 to assess the impacts of temperature from conception to birth.

2.2. Outcomes

Two mutually exclusive composite outcomes were assessed: (1) High blood pressure, hypertension, or gestational hypertension (hBP); and (2) Pre-eclampsia, eclampsia/severe pre-eclampsia/imminent eclampsia, or HELLP syndrome (PEH).

All disorders were recorded in birth registers as antepartum complications or reasons for referral into the tertiary hospital. Diagnoses were made by attending clinicians during pregnancy or at the time of delivery, using standardized definitions within the Obstetric units. hBP diagnoses were not differentiated in the birth registers (i.e. were recorded as one complication/reason for referral). PEH diagnoses were differentiated in the birth registers and were grouped herein to increase statistical power and minimize potential misclassification of disorders. Our PEH grouping is consistent with the clinical classification of HTDs of pregnancy in which eclampsia and HELLP syndrome are defined as severe manifestations of pre-eclampsia, and not as separate disorders (Brown et al., 2018). HTD is defined as the diagnosis of any hypertensive disorder in pregnancy listed in outcomes (1) and (2) above. We did not assess HTD as a composite outcome because risk factor effect sizes as well as maternal and perinatal outcomes differ between gestational hypertension and pre-eclampsia, indicating that these disorders may differ in pathophysiology and mechanism (Shen et al., 2017).

Date of conception was calculated using date of delivery and gestational age at delivery. Gestational age was based on date of last menstrual period, and/or ultrasound in early or late pregnancy.

2.3. Exposures

The primary exposure was mean weekly temperature (constructed from daily mean temperature). High and low mean weekly temperatures were defined as the 95th and 5th percentile, respectively, of daily mean temperature between July 2017 and June 2018.

Our secondary exposure was extreme heat episodes in early pregnancy (any time between 0 and 8 weeks' gestation). Two definitions for extreme heat episodes were used: (1) Three consecutive days above the 95th percentile of daily mean temperature (heatwave95); and (2) Three consecutive days above the 99th percentile of daily mean temperature (heatwave99). Eleven days of temperature data were missing over the study period and were excluded from calculations.

2.4. Statistical analysis

Birth registry and exposure data were linked by estimated date of conception at individual level. We tested for characteristic differences between women with and without HTD using chi-squared (categorical variables), Fisher's exact (≤5 expected counts per cell), or Mann-Whitney U tests (continuous variables).

Cox proportional hazards regression analyses were used to examine associations between weekly mean temperature and risk of hBP and PEH, with separate models for each outcome. The time-scale was gestational age. A distributed lag non-linear modeling framework was employed to explore potential non-linear and delayed effects of temperature (Gasparrini, 2011, 2014). To model the time-varying exposure, we split the dataset by failure times (i.e. the gestational ages at which women with hBP or PEH delivered), which occurred from gestation week 22 through to 43. We then constructed individual exposure histories (weekly mean temperature from estimated date of conception) for each woman at all gestational ages at which she contributed to each risk set (i.e. gestation week 22 through to gestation week at delivery). The resulting exposure matrix was fitted using Cox regression. Natural cubic splines with 3 equally-spaced knots were used to model both exposure and lag dimensions in order to flexibly capture any non-linear and delayed effects of temperature, respectively. We included an intercept in the lag dimension to flexibly capture temperature effects in early pregnancy. A 43-week lead period was chosen to examine the effects of temperature throughout pregnancy. Week 0 reflected the first week following conception (estimated day of conception to six days post-conception).

Models adjusted for season of conception (spring, summer, autumn, winter) and season of birth (spring, summer, autumn, winter) due to the wide range of gestation lengths, maternal age (≤19; 20–34; ≥35 years), parity (nulliparous vs multiparous), gravidity, ethnicity (black African, Indian South African, multiple heritage, white; PEH model only), and maternal HIV status (negative, positive), based on confounding and individual risk factors identified in previous literature (Nakimuli et al., 2014; Auger et al., 2017; Hinkosa et al., 2020). A linear term for calendar time (in weeks) was included to control for any secular trends in risk of hypertensive disorders not accounted for by the delayed effects of temperature (Gasparrini, 2014). We specified interaction terms with time for covariates where the proportionality assumption of Cox regression was not met.

Heatwave effects were examined using Kaplan-Meier cumulative event curves and log rank tests, and the adjusted Cox regression models described above with heatwave95 and heatwave99 included as secondary exposures. All estimates are presented as hazard ratios (HR) and 95% confidence intervals (CI). Predictions were centered at the 50th percentile of daily mean temperature.

As sensitivity analyses, models were respecified with an alternative method of seasonal control: Natural cubic splines of calendar time with 7 degrees of freedom replaced season of conception, season of birth, and a linear term for calendar time.

Analyses were performed in R 4.1.1 (R Core Team, 2021), using RStudio and facilitated by the following packages: survival (Therneau, 2021), dlnm (Gasparrini, 2011), splines (R Core Team, 2021), survminer (Kassambara et al., 2021), ggplot2 (Wickham, 2016).

2.5. Ethical approval

The research protocol for the parent study was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand on October 29, 2018 (reference: 180707). The secondary analysis was approved by the Human Research Ethics Committee (Medical) of the University of the Witwatersrand on October 5, 2020 (reference: 180707) and by the Observational Research Ethics Committee of the London School of Hygiene & Tropical Medicine on January 25, 2021 (reference: 19201). A waiver of informed consent was granted as historical data were used.

3. Results

A total of 8503 births were recorded between July 2017 and June 2018, of which 8090 births were confirmed eligible for this study (49 births occurred outside 22–43 weeks' gestation; 130 had no information on gestational age at delivery; 233 were non-singleton; two births to the same woman). One hundred and four births were excluded due to missing date of delivery, leaving 7986 singleton births.

Eight hundred and forty-four women (10.6%) had HTD, of which 432 (51.2%) had hBP and 412 (48.8%) had PEH. There was strong evidence that maternal age, diabetes mellitus or high hemoglobin glucose test during pregnancy, HIV status, and gestational age at delivery differed between women with and without HTD (Table 1). Diabetes was more frequent, and HIV less frequent, in women with HTD. Women with HTD also tended to be older and to give birth earlier. Median gestation at delivery for women with hBP was 38 weeks (IQR 37–39 weeks) and for women with PEH 35 weeks (IQR 31–38 weeks).

Induction of labor was recorded for 15.5% of women with hBP and for 5.6% of women with PEH. However, the rate of emergency C-section was much higher among women with PEH (73.8% vs 30.1% in women with hBP). Complications in women with no HTD included fetal distress/compromise (15.7%), post-term birth (7.7%), prolonged labor/failure to progress (6.7%), meconium-stained liquor (4.9%), premature rupture of the membranes (3.7%), and abnormal presentation (3.1%), which may explain the high incidence of emergency C-section in this group (Table 1).

The intra-annual range in daily mean temperature was 7.2–27.8 °C; summer range (December–February) = 14.9–27.8 °C and winter range (June–August) = 7.2–17.8 °C (see Figure S1). The 5th and 95th percentiles of daily mean temperature were 11 °C (defined as low temperature) and 23 °C (defined as high temperature), respectively (median = 18 °C).

Exposure to mean weekly temperature of 23 °C (vs 18 °C) in early pregnancy (2–5 weeks' gestational age) was associated with an increased risk of PEH (Fig. 1a and b). High temperatures (23 °C vs 18 °C) during the third and fourth weeks of pregnancy posed the greatest risk, with associated HRs of 1.76 (95% CI 1.12–2.78) and 1.79 (95% CI 1.19–2.71; Fig. 2a), respectively, following adjustment (unadjusted HRs in Table S3). Estimates were robust to alternative methods of seasonal control (Figure S2a, S2b; Figure S3a, S3b).

Low mean weekly temperature between 7 and 34 weeks' gestation was associated with an increased risk of PEH. Exposure to 11 °C (vs 18 °C) at a gestational age of 31 weeks, for example, increased the risk of PEH by 52% (aHR 1.52, 95% CI 1.13–2.04; Fig. 2b). There was also a tendency towards a reduced risk of PEH with high temperatures at this time (Fig. 2b). With alternative seasonal control (sensitivity analysis), adverse effects of low temperature during pregnancy were attenuated and no longer statistically significant, whilst the protective effect of high temperature in mid-to-late pregnancy was accentuated (Figure S3c,d).

There was no association detected between mean weekly temperatures of 23 °C at any time during gestation and risk of hBP, following adjustment (Fig. 1d). However, there was a tendency towards an increased risk of hBP with high temperatures during the first few weeks of pregnancy (Table S3).

Table 1
Characteristics of the study population at delivery.

Variable	No HTD		Any HTD		*P*-value
	N	%	N	%	
Total	7142	89.4	844	10.6	–
Hypertensive disorder					
High Blood Pressure/ Hypertension/GH (hBP)	–	–	432	51.2	–
Pre-eclampsia	–	–	209	24.8	–
Eclampsia/Severe pre-eclampsia	–	–	193	22.9	–
HELLP Syndrome	–	–	42	5.0	–
Season of conception					0.11[a]
Summer (December-February)	1807	25.3	231	27.4	
Winter (June-August)	1726	24.2	192	22.7	
Spring (September-November)	1876	26.3	197	23.3	
Autumn (March-May)	1733	24.3	224	26.5	
Season of birth					0.12[a]
Summer (December-February)	1679	23.5	204	24.2	
Winter (June-August)	1875	26.3	206	24.4	
Spring (September-November)	1818	25.5	243	28.8	
Autumn (March-May)	1770	24.8	191	22.6	
Maternal age at delivery [years] (median, IQR)	28	24–33	30	25–35	<0.001[b]
Not recorded	16	0.2	5	0.6	
Ethnicity					0.71[c]
Black African	6981	97.7	828	98.1	
White	61	0.9	7	0.8	
Multiple heritage	51	0.7	3	0.4	
Indian South African	26	0.4	2	0.2	
Not recorded	23	0.3	4	0.5	
Parity					0.59[a]
0	2050	28.7	250	29.6	
1+	5070	71.0	592	70.1	
Not recorded	22	0.3	2	0.2	
Gravidity (median, range)	2	2–3	2	1–3	0.21[b]
Not recorded	39	0.5	7	0.8	
Gestational age at delivery [weeks] (median, IQR)	38	37–40	37	34–39	<0.001[b]
Birth weight [grams] (median, IQR)	3100	2700–3410	2820	2000–3220	<0.001[b]
Sex of infant					0.12[c]
Male	3513	49.2	391	46.3	
Female	3440	48.2	421	49.9	
Ambiguous	2	0.03	1	0.1	
Not recorded	187	2.6	31	3.7	
Mode of delivery					<0.001[c]
Normal vaginal delivery	3307	46.3	369	43.7	
Emergency C-section	3259	45.6	434	51.4	
Elective C-section	319	4.5	9	1.1	
Vacuum/Kiwi ventouse	82	1.1	8	0.9	
Forceps	13	0.2	4	0.5	
Other	5	0.1	1	0.1	
Not recorded	157	2.2	19	2.3	
Diabetes mellitus/ GDM/High HGT	77	1.1	19	2.3	0.003[a]
Maternal HIV status					0.001[a]
Negative	5133	71.9	649	76.9	
Positive	1790	25.1	167	19.8	
Newly positive	92	1.3	6	0.7	
Not recorded	127	1.8	22	2.6	

Number (N) and % of total, or summary statistics specified.
Abbreviations: HTD, hypertensive disorder; GH, gestational hypertension; GDM, gestational diabetes mellitus; HGT, hemoglobin glucose test; IQR, interquartile range.
[a] Chi-squared test.
[b] Mann-Whitney *U* test.
[c] Fisher's exact test.

Low temperatures during the third trimester (week 29 onwards) were associated with an increased risk of hBP. Exposure to 11 °C (vs 18 °C) on gestation week 37 increased the risk of hBP by 86% (aHR 1.86, 95% CI 1.36–2.53) (Fig. 2d). The pattern remained, but was attenuated and no longer statistically significant, with alternative seasonal control (Figure S4c, S4d).

Within the first nine weeks of pregnancy, 1983 women (24.8%) experienced a heatwave above the 95th percentile (heatwave95) and 673 women (8.4%) experienced one above the 99th percentile (heatwave99). Comparatively fewer women developed PEH if exposed to a heatwave in early pregnancy (4.2% of women exposed to heatwave95 vs 5.5% of women not exposed; 2.8% of women exposed to heatwave99 vs 5.4% not exposed).

Women with PEH were also more likely to deliver at a later gestational age if exposed to a heatwave in early pregnancy, i.e. they were more likely to reach full-term (37 weeks) if exposed to a heatwave (heatwave95: $P = 0.002$; heatwave99: $P < 0.001$) (Fig. 3). Median gestation at delivery for women with PEH was 37 weeks (IQR = 33.5–38.5 weeks) if exposed to heatwave95, and 35 weeks (IQR = 31–38 weeks) if unexposed. However, after adjusting for mean weekly temperature, confounders, and maternal characteristics, heatwave exposure had no effect on the overall risk of PEH (heatwave95: aHR 1.18, 95% CI 0.65–2.16; heatwave99: aHR 1.33, 95% CI 0.62–2.83).

Kaplan-Meier curves for hBP did not differ significantly (Figure S5). Heatwave exposure had no significant effect on the risk of hBP after adjustment.

4. Discussion

This study shows that exposure to high temperatures in early pregnancy increases the risk of PEH, which is consistent with an effect of heat on implantation and early placental development. We also find suggestive evidence of an increased risk of hBP with high temperatures during the first few weeks of pregnancy.

Our findings agree with previous reports of a higher pre-eclampsia risk among women who conceive during the warmest months of the year (Beltran et al., 2014). A study in Israel also found that an increase in temperature during the first trimester was associated with a higher risk of pre-eclampsia, particularly early-onset pre-eclampsia (<34 weeks' gestation), among women spending most of their pregnancy during warmer months (Shashar et al., 2020). A large-scale study in China found a tendency towards an increased risk of pre-eclampsia or eclampsia with high temperatures around the time of implantation, but reported that high temperature during weeks 13–20 incurred a much greater risk. The authors proposed that heat may impair placental development and trophoblast invasion (Xiong et al., 2020), although reported effect estimates were not adjusted for season.

Heat exposure during early pregnancy has been shown to increase clinically unobserved pregnancy losses, occurring pre- or post-implantation (Hajdu and Hajdu, 2021). This creates a “culling” or “harvesting” effect, whereby embryos with below-average health do not survive (Hajdu and Hajdu, 2021). However, early heat stress is likely to create a “scarring effect” on surviving embryos (Hajdu and Hajdu, 2021), which may increase the risk of HTDs through a variety of mechanisms including vascular disruption and placental insufficiency (Bennett, 2010).

Exposure to cold in late pregnancy may increase the risk of HTDs through activation of the sympathetic nervous system and/or alteration of endothelial biology, resulting in vascular resistance (Fares, 2013). Low temperature has previously been associated with an increase in systolic and/or diastolic blood pressure among normotensive and hypertensive, non-pregnant adults (Fares, 2013). Our finding that high ambient temperature in mid-to-late pregnancy may protect against PEH

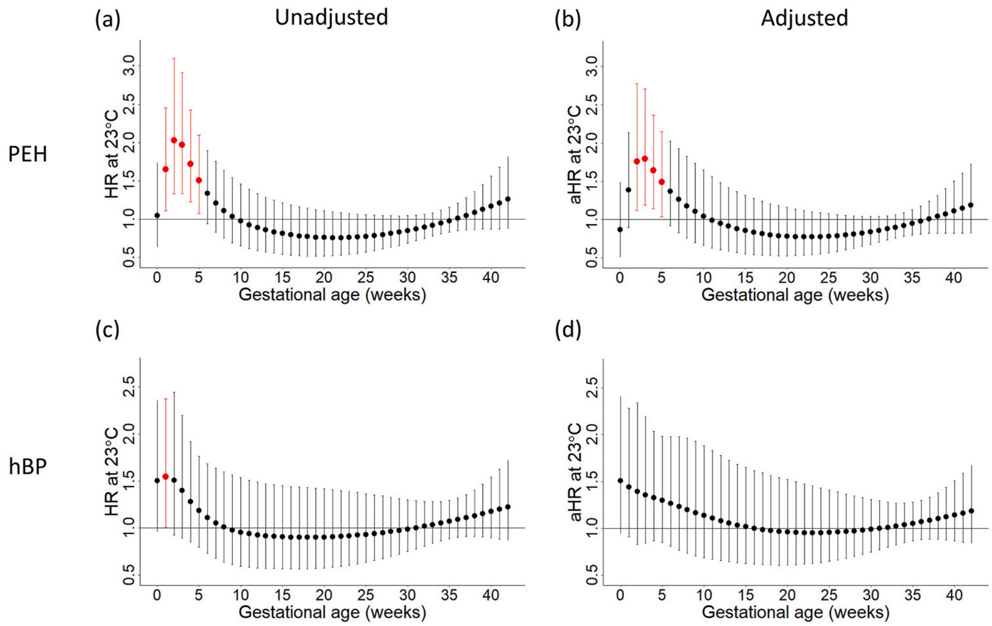

Fig. 1. (a) Unadjusted hazard ratio (HR) and **(b)** adjusted hazard ratio (aHR) of PEH (pre-eclampsia, eclampsia/severe pre-eclampsia/imminent eclampsia, or HELLP syndrome) at 23 °C throughout gestation (95th percentile of daily mean temperature). **(c)** HR and **(d)** aHR of hBP (high blood pressure/hypertension/gestational hypertension) at 23 °C throughout gestation. All predictions were centered at 18 °C (50th percentile of daily mean temperature). Red indicates an increased hazard, significant at the 5% level. Adjusted estimates accounted for season of conception, season of birth, maternal age, ethnicity (PEH model only), parity, gravidity, and HIV status. (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

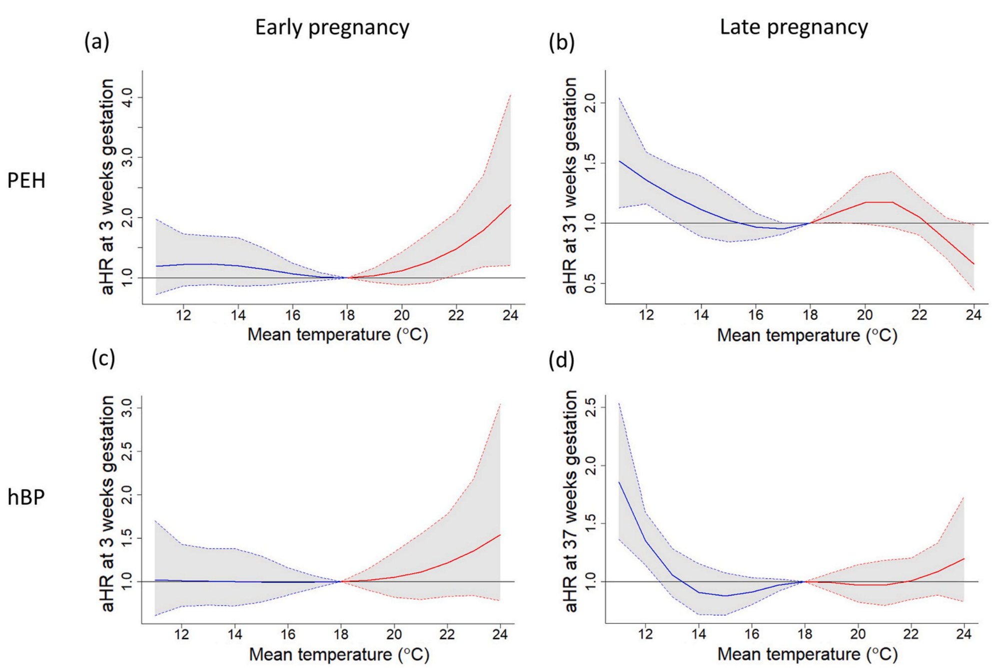

Fig. 2. Adjusted hazard ratio (aHR) of PEH (pre-eclampsia, eclampsia/severe pre-eclampsia/imminent eclampsia, or HELLP syndrome) associated with mean weekly temperature at **(a)** 3 weeks' and **(b)** 31 weeks' gestation; and of hBP (high blood pressure/hypertension/gestational hypertension) at **(c)** 3 weeks' and **(d)** 37 weeks' gestation. Predictions were centered at 18 °C. Red lines indicate temperatures above 18 °C and blue lines indicate temperatures below 18 °C (50th percentile of daily mean temperature). (For interpretation of the references to colour in this figure legend, the reader is referred to the Web version of this article.)

is consistent with previous reports of a strong inverse relationship between temperature and systolic blood pressure in elderly populations (Alpérovitch et al., 2009).

Many studies have shown that women who give birth in the coolest months of the year tend to be at greater risk of pre-eclampsia, eclampsia (Beltran et al., 2014), gestational hypertension, and overall HTD prevalence (Umesawa and Kobashi, 2017). However, there is inconsistency in findings when assessing the impacts of season (Umesawa and Kobashi, 2017), temperature, or thermal indices in late pregnancy (Shashar et al., 2020; Dastoorpoor et al., 2021; Khodadadi et al., 2022). In some cases, onset of the disorder may precede the exposure (e.g. month of birth), leading to negative or spurious findings. In other cases, temperature in late pregnancy may not reflect a causal factor but, rather, may exacerbate or ameliorate pre-existing HTDs. For example, in our study, exposure to high temperatures towards the end of pregnancy may have improved vasodilation in women with PEH, reducing the risk of early labor (spontaneous or induced).

Our finding of no heatwave effects in early pregnancy (after adjusting for weekly mean temperature and important confounders) are consistent with those of Cil and Cameron (2017). Women might take extra precautions during extreme heat episodes, whereas they may be less aware of health risks associated with moderate heat. However, heatwave exposure during the second and third trimesters has previously been associated with an increased incidence of gestational hypertension and eclampsia (Cil and Cameron, 2017). Heatwave exposure during pregnancy has also been associated with an immediate increase in emergency department visits due to HTD complications (Qu et al., 2021). We did not assess the impacts of heatwave exposure during the

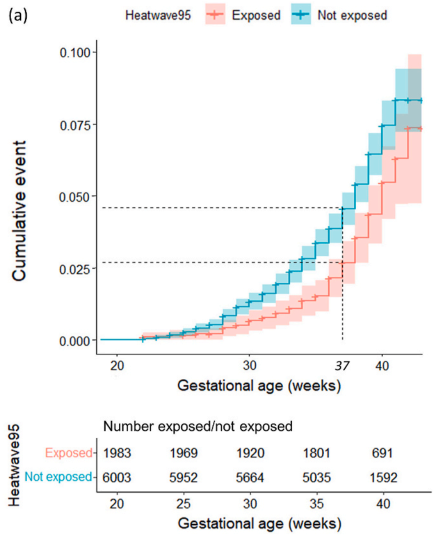

Fig. 3. Kaplan-Meier cumulative event curves of preeclampsia, eclampsia, or HELLP syndrome (PEH), stratified by exposure to a heatwave above the **(a)** 95th percentile of daily mean temperature and **(b)** 99th percentile of daily mean temperature in early pregnancy (0–8 weeks' gestation).

second or third trimesters, although we found no strong evidence to suggest adverse effects of high temperature in mid to late pregnancy. The discrepancy between our findings and those of Cil and Cameron (2017) may be attributed to methodological differences, such as our use of individual data rather than monthly panel data, which enabled us to control for gestational age at delivery (previously shown to bias the relationship between pre-eclampsia and temperature at the end of pregnancy; Auger et al., 2017). The seeming discrepancy between our findings and those of Qu et al. (2021) may be due to confounding by duration of pregnancy in Qu et al.'s (2021) analyses, and/or due to differences in study outcomes (delivery with hBP or PEH vs emergency department visits due to HTD complications). Indeed, Qu et al. (2021) did not find any heatwave effect on hospital admissions for HTD complications. Further, exposure to extreme heat episodes was found to increase the risk of HTD-related emergency department visits in September only, whereas exposure in summer months reduced the risk (Qu et al., 2017). Nevertheless, there is evidence to suggest that heat stress during the third trimester reduces placental weight, volume, and transport efficiency (Wang et al., 2020), and therefore may play a role in the development of late-onset pre-eclampsia in some settings.

South Africa has a mild, temperate climate, which is reflected in the value of high temperature as defined herein (23 °C). However, it should be noted that women exposed to a weekly mean temperature of 23 °C were often exposed to daily maximum temperatures above 30 °C. Mean temperatures above 25 °C have been found to increase the risk of gestational hypertension and pre-eclampsia/eclampsia in China (Xiong et al., 2020), where temperatures are generally cooler than in South Africa. Similarly, 12-weekly mean temperatures above 25 °C were associated with an increased prevalence of pre-eclampsia in Israel (Shashar et al., 2020), where temperatures are slightly warmer than in South Africa. In Canada, where temperatures are generally much cooler, mean temperatures above 3 °C in early pregnancy were associated with an increased risk of pre-eclampsia (Auger et al., 2017); suggesting that heat thresholds are relative, rather than absolute. However, all early temperature effects observed in Canada disappeared following adjustment for season of conception, including any effect of mean temperatures up to 24 °C. This suggests that temperature may interact with other risk factors (e.g. ethnicity, socio-economic status; Ross et al., 2019) to affect the incidence of PEH. More high quality studies are needed in different climatic regions to identify absolute and relative temperature thresholds above or below which risk of PEH increases. Such findings could inform both local interventions to reduce the impacts of high temperature in early pregnancy, and guidance for women of child-bearing age who relocate to warmer climates.

Our study has several strengths. It is the first to assess the effects of temperature on HTD risk throughout gestation, at a weekly resolution. This enabled us to identify windows of susceptibility to temperature effects at a relatively fine temporal scale. We accounted for important confounders (season of conception and length of gestation) typically not considered, and potentially biasing previous findings (Auger et al., 2017). This study is also amongst the first to quantify the effects of high temperature on health, and particularly maternal health, in Africa, which is increasingly recognized as a priority area for research (Kuehn and McCormick, 2017; Roos et al., 2021).

There are also several limitations to our study. Dates of onset for hBP and PEH were unknown, therefore we cannot distinguish between potentially causative or exacerbating/ameliorating effects of temperature on PEH in mid-late pregnancy, nor could we distinguish between chronic and gestational hypertension (assessed as one outcome), which may have reduced our ability to detect a statistically significant relationship between gestational hypertension and temperature in early pregnancy. When based on last menstrual period, gestational age at delivery may be over-estimated, resulting in a one-to-two week shift of estimated temperature exposure. We used temperature recorded at one weather station in Johannesburg, located close to the hospital of admission. We could not assign exposures to women's residential address, but daily variability in temperature exposures were found to be consistent over the hospital catchment area. The very small number of women residing outside the hospital catchment area during pregnancy is unlikely to have affected the direction or magnitude of reported estimates. Although the period of data collection was limited to 12 months, 2017–2018 was a climatically typical year for Johannesburg. Lastly, our study sample was not population-based and was likely to be at higher risk of pregnancy complications than the general population given delivery at a tertiary (referral) hospital. However, our findings are likely to be generalizable to other tertiary hospital settings in temperate climates with similar rates of HTDs in pregnancy.

We recommend that clinicians inform women about the risks associated with exposure to high temperatures around the time of conception and very early pregnancy. Women who conceive shortly before or during periods of high temperature should be monitored carefully. Our findings support the need for monitoring for hypertension during the third trimester. Further research is required to explore a potential ameliorating effect of exposure to high temperatures in mid-late pregnancy on severe hypertensive disorders.

5. Conclusion

This study shows that high ambient temperatures in early pregnancy are associated with an increased risk of pre-eclampsia, eclampsia, or HELLP syndrome. High mean temperatures at weeks two and three of gestation pose the greatest risk, suggesting that heat interferes with implantation and early placental development. Low ambient temperatures during the third trimester may increase the risk of high blood pressure/gestational hypertension. Additional research is required to understand how temperatures in mid-late pregnancy might impact on the development of severe hypertensive disorders. Our findings highlight the need for greater awareness around the impacts of moderately high temperatures in early pregnancy, and call for tight monitoring of pregnant women who conceived during periods of hot weather. Such actions are particularly important in the context of global warming.

CRediT author statement

CP: Methodology, Formal analysis, Data curation, Visualization, Writing – original draft, Writing – review & editing. JlR: Investigation, Resources, Data curation, Writing – review & editing. MC: Conceptualization, Writing – review & editing, Supervision. SS: Investigation, Resources, Writing – review & editing. VP: Conceptualization, Writing–Review and Editing. NR: Conceptualization, Writing – review & editing. LF: Investigation, Resources, Writing – review & editing. BN: Conceptualization, Writing – Review and Editing. JlB: Writing – Review and Editing. PL: Writing – Review and Editing. MS: Writing –Review and Editing. SK: Conceptualization, Writing – review & editing, Supervision, Project administration, Funding acquisition. SL: Writing – Review and Editing. SH: Methodology, Writing – review & editing, Supervision.

Funding

This work was supported by the Natural Environment Research Council (NERC) [grant numbers NE/T013613/1, NE/T01363X/1]; Research Council of Norway (RCN) [grant number 312601]; and The Swedish Research Council for Health, Working Life and Welfare in collaboration with the Swedish Research Council (Forte) [grant number 2019-01570]; coordinated through a Belmont Forum partnership. Data collection was conducted under grant C1091006, funded by Pfizer. Funding bodies were not involved in the study design; data collection, analysis, or interpretation; preparation of the manuscript, or in the decision to submit this article for publication.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: M.C., J.l.R., S.S., and L.F. hold investments in the fossil fuel industry through their pension funds. The University of the Witwatersrand holds investments in the fossil fuel industry through their endowments and other financial reserves.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113596.

References

Alpérovitch, A., Lacombe, J.M., Hanon, O., Dartigues, J.F., Ritchie, K., Ducimetière, P., Tzourio, C., 2009. Relationship between blood pressure and outdoor temperature in a large sample of elderly individuals: the Three-City study. Arch. Intern. Med. 169, 75–80. https://doi.org/10.1001/archinternmed.2008.512.

American College of Obstetricians and Gynecologists, 2021. Preeclampsia and high blood pressure during pregnancy. https://www.acog.org/womens-health/faqs/preeclampsia-and-high-blood-pressure-during-pregnancy#:~:text=What%20is%20gestational%20hypertension%3F,normal%20b. (Accessed 11 February 2022).

Auger, N., Siemiatycki, J., Bilodeau-Bertrand, M., Healy-Profitós, J., Kosatsky, T., 2017. Ambient temperature and risk of preeclampsia: b iased association? Paediatr. Perinat. Epidemiol. 31, 267–271. https://doi.org/10.1111/ppe.12362.

Awuah, S.P., Okai, I., Ntim, E.A., Bedu-Addo, K., 2020. Prevalence, placenta development, and perinatal outcomes of women with hypertensive disorders of pregnancy at Komfo Anokye Teaching Hospital. PLoS One 15, e0233817. https://doi.org/10.1371/journal.pone.0233817.

Beltran, A.J., Wu, J., Laurent, O., 2014. Associations of meteorology with adverse pregnancy outcomes: a systematic review of preeclampsia, preterm birth and birth weight. Int. J. Environ. Res. Publ. Health 11, 91–172. https://doi.org/10.3390/ijerph110100091.

Bennett, G.D., 2010. Hyperthermia: malformations to chaperones. Birth Defects Res. B Dev. Reprod. Toxicol. 89, 279–288. https://doi.org/10.1002/bdrb.20254.

Brown, M.A., Magee, L.A., Kenny, L.C., Karumanchi, S.A., McCarthy, F.P., Saito, S., Hall, D.R., Warren, C.E., Adoyi, G., Ishaku, S., 2018. Hypertensive disorders of pregnancy. Hypertension 72, 24–43. https://doi.org/10.1161/HYPERTENSIONAHA.117.10803.

Chersich, M.F., Pham, M.D., Areal, A., Haghighi, M.M., Manyuchi, A., Swift, C.P., Wernecke, B., Robinson, M., Hetem, R., Boeckmann, M., Hajat, S., 2020. Associations between high temperatures in pregnancy and risk of preterm birth, low birth weight, and stillbirths: systematic review and meta-analysis. BMJ 371, m3811. https://doi.org/10.1136/bmj.m3811.

Cil, G., Cameron, T.A., 2017. Potential climate change health risks from increases in heat waves: abnormal birth outcomes and adverse maternal health conditions. Risk Anal. 37, 2066–2079. https://doi.org/10.1111/risa.12767.

R Core Team, 2021. R: A Language and Environment for Statistical Computing. R Foundation for Statistical Computing, Vienna, Austria. https://www.R-project.org/.

Dastoorpoor, M., Khanjani, N., Khodadadi, N., 2021. Association between physiological equivalent temperature (PET) with adverse pregnancy outcomes in ahvaz, southwest of Iran. BMC Pregnancy Childbirth 21, 415. https://doi.org/10.1186/s12884-021-03876-5.

Fares, A., 2013. Winter hypertension: potential mechanisms. Int. J. Health Sci. 7, 210–219. https://doi.org/10.12816/0006044.

Ferreira, L.C., Gomes, C.E.M., Duggal, P., De Paula Holanda, I., de Lima, A.S., do Nascimento, P.R.P., Jeronimo, S.M.B., 2021. Genetic association of ERAP1 and ERAP2 with eclampsia and preeclampsia in northeastern Brazilian women. Sci. Rep. 11, 6764. https://doi.org/10.1038/s41598-021-86240-z.

Garovic, V.D., White, W.M., Vaughan, L., Saiki, M., Parashuram, S., Garcia-Valencia, O., Weissgerber, T.L., Milic, N., Weaver, A., Mielke, M.M., 2020. Incidence and long-term outcomes of hypertensive disorders of pregnancy. J. Am. Coll. Cardiol. 75, 2323–2334. https://doi.org/10.1016/j.jacc.2020.03.028.

Gasparrini, A., 2011. Distributed lag linear and non-linear models in R: the package dlnm. J. Stat. Software 43, 1–20. https://doi.org/10.18637/jss.v043.i08.

Gasparrini, A., 2014. Modeling exposure-lag-response associations with distributed lag non-linear models. Stat. Med. 33, 881–899. https://doi.org/10.1002/sim.5963.

Hajdu, T., Hajdu, G., 2021. Post-conception heat exposure increases clinically unobserved pregnancy losses. Sci. Rep. 11, 1987. https://doi.org/10.1038/s41598-021-81496-x.

Hinkosa, L., Tamene, A., Gebeyehu, N., 2020. Risk factors associated with hypertensive disorders in pregnancy in Nekemte referral hospital, from July 2015 to June 2017, Ethiopia: case-control study. BMC Pregnancy Childbirth 20, 16. https://doi.org/10.1186/s12884-019-2693-9.

IPCC, 2021. In: Masson-Delmotte, V., Zhai, P., Pirani, A., Connors, S.L., Péan, C., Berger, S., Caud, N., Chen, Y., Goldfarb, L., Gomis, M.I., Huang, M., Leitzell, K., Lonnoy, E., Matthews, J.B.R., Maycock, T.K., Waterfield, T., Yelekçi, O., Yu, R., Zhou, B. (Eds.), Climate Change 2021: the Physical Science Basis. Contribution of Working Group I to the Sixth Assessment Report of the Intergovernmental Panel on Climate Change. Cambridge University Press (in press). https://www.ipcc.ch/report/ar6/wg1/#FullReport. (Accessed 12 December 2021).

Kassambara, A., Kosinski, M., Biecek, P., 2021. survminer: drawing Survival Curves using 'ggplot2'. R package version 0.4.9. https://CRAN.R-project.org/package=survminer.

Khodadadi, N., Dastoorpoor, M., Khanjani, N., Ghasemi, A., 2022. Universal thermal climate index (UTCI) and adverse pregnancy outcomes in ahvaz, Iran. Reprod. Health 19, 33. https://doi.org/10.1186/s12978-022-01344-7.

Kuehn, L., McCormick, S., 2017. Heat exposure and maternal health in the face of climate change. Int. J. Environ. Res. Publ. Health 14, 853. https://doi.org/10.3390/ijerph14080853.

Nakimuli, A., Chazara, O., Byamugisha, J., Elliott, A.M., Kaleebu, P., Mirembe, F., Moffett, A., 2014. Pregnancy, parturition and preeclampsia in women of African ancestry. Am. J. Obstet. Gynecol. 210, 510–520. https://doi.org/10.1016/j.ajog.2013.10.879 e1.

Noubiap, J.J., Bigna, J.J., Nyaga, U.F., Jingi, A.M., Kaze, A.D., Nansseu, J.R., Fokom Domgue, J., 2019. The burden of hypertensive disorders of pregnancy in Africa: a systematic review and meta-analysis. J. Clin. Hypertens. 21, 479–488. https://doi.org/10.1111/jch.13514.

Qu, Y., Zhang, W., Ryan, I., Deng, X., Dong, G., Liu, X., Lin, S., 2021. Ambient extreme heat exposure in summer and transitional months and emergency department visits and hospital admissions due to pregnancy complications. Sci. Total Environ. 777, 146134 https://doi.org/10.1016/j.scitotenv.2021.146134.

Roos, N., Kovats, S., Hajat, S., Filippi, V., Chersich, M., Luchters, S., Scorgie, F., Nakstad, B., Stephansson, O., CHAMNHA Consortium, 2021. Maternal and newborn health risks of climate change: a call for awareness and global action. Acta Obstet. Gynecol. Scand. 100, 566–570. https://doi.org/10.1111/aogs.14124.

Ross, K.M., Dunkel Schetter, C., McLemore, M.R., Chambers, B.D., Paynter, R.A., Baer, R., Feuer, S.K., Flowers, E., Karasek, D., Pantell, M., Prather, A.A., Ryckman, K., Jelliffe-Pawlowski, L., 2019. Socioeconomic status, preeclampsia risk and gestational length in black and white women. J Racial Ethn Health Disparities 6, 1182–1191. https://doi.org/10.1007/s40615-019-00619-3.

Samuels, L., Nakstad, B., Roos, N., Bonell, A., Chersich, M., Havenith, G., Luchters, S., Day, L.-T., Hirst, J.E., Singh, T., Elliott-Sale, K., Hetem, R., Part, C., Sawry, S., Le Roux, J., Kovats, S., 2022. Physiological mechanisms of the impact of heat during pregnancy and the clinical implications: review of the evidence from an expert group meeting. Int. J. Biometeorol. https://doi.org/10.1007/s00484-022-02301-6.

Shashar, S., Kloog, I., Erez, O., Shtein, A., Yitshak-Sade, M., Sarov, B., Novack, L., 2020. Temperature and preeclampsia: epidemiological evidence that perturbation in maternal heat homeostasis affects pregnancy outcome. PLoS One 15, e0232877. https://doi.org/10.1371/journal.pone.0232877.

Shen, M., Smith, G.N., Rodger, M., White, R.R., Walker, M.C., Wen, S.W., 2017. Comparison of risk factors and outcomes of gestational hypertension and pre-eclampsia. PLoS One 12, e0175914. https://doi.org/10.1371/journal.pone.0175914.

Statistics South Africa, 2018. Provincial profile: Gauteng. Community survey 2016 statistics South Africa. Pretoria, South Africa. http://cs2016.statssa.gov.za/wp-content/uploads/2018/07/Gauteng.pdf. (Accessed 10 February 2022).

Statistics South Africa, 2020. Maternal health indicators: further analysis of the 1998 and 2016 South Africa demographic and health surveys. Pretoria, South Africa. http://www.statssa.gov.za/publications/Report-03-06-03/Report-03-06-032020.pdf. (Accessed 10 February 2022).

Therneau, T., 2021. A package for survival analysis in R. R package version 3.2-11. https://CRAN.R-project.org/package=survival.

TuTiempo, 2021. Weather JOHANNESBURG BOT. G. Climate data, pp. 2013–2021. https://www.tutiempo.net/clima/ws-683610.html. (Accessed 12 April 2021).

Umesawa, M., Kobashi, G., 2017. Epidemiology of hypertensive disorders in pregnancy: prevalence, risk factors, predictors and prognosis. Hypertens. Res. 40, 213–220. https://doi.org/10.1038/hr.2016.126.

Wang, J., Liu, X., Dong, M., Sun, X., Xiao, J., Zeng, W., Hu, J., Li, X., Guo, L., Rong, Z., He, G., Sun, J., Ning, D., Chen, D., Zhang, Y., Zhang, B., Ma, W., Liu, T., 2020. Associations of maternal ambient temperature exposures during pregnancy with the placental weight, volume and PFR: a birth cohort study in Guangzhou, China. Environ. Int. 139, 105682 https://doi.org/10.1016/j.envint.2020.105682.

Wickham, H., 2016. ggplot2: Elegant Graphics for Data Analysis. Springer-Verlag, New York.

World Health Organization, 2019. Maternal mortality. https://www.who.int/news-room/fact-sheets/detail/maternal-mortality. (Accessed 17 January 2022).

Xiong, T., Chen, P., Mu, Y., Li, X., Di, B., Li, J., Qu, Y., Tang, J., Liang, J., Mu, D., 2020. Association between ambient temperature and hypertensive disorders in pregnancy in China. Nat. Commun. 11, 2925. https://doi.org/10.1038/s41467-020-16775-8.

Ye, C., Ruan, Y., Zou, L., Li, G., Li, C., Chen, Y., Jia, C., Megson, I.L., Wei, J., Zhang, W., 2014. The 2011 survey on hypertensive disorders of pregnancy (HDP) in China: prevalence, risk factors, complications, pregnancy and perinatal outcomes. PLoS One 9, e100180. https://doi.org/10.1371/journal.pone.0100180.