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Ambient air temperature exposure and foetal size and growth in three European birth cohorts

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ABSTRACT

Introduction: Ambient air temperature may affect birth outcomes adversely, but little is known about their impact on foetal growth throughout pregnancy. We evaluated the association between temperature exposure during pregnancy and foetal size and growth in three European birth cohorts.
Methods: We studied 23,408 pregnant women from the English Born in Bradford cohort, Dutch Generation R Study, and Spanish INMA Project. Using the UrbClim^{TM} model, weekly ambient air temperature exposure at 100x100m resolution at the mothers' residences during pregnancy was calculated. Estimated foetal weight, head circumference, and femur length at mid and late pregnancy and weight, head circumference, and length at birth were converted into standard deviation scores (SDS). Foetal growth from mid to late pregnancy was calculated (grams or centimetres/week). Cohort/region-specific distributed lag non-linear models were combined using a random-effects meta-analysis and results presented in reference to the median percentile of temperature (14 °C).
Results: Weekly temperatures ranged from −5.6 (Bradford) to 30.3 °C (INMA-Sabadell). Cold and heat exposure during weeks 1–28 were associated with a smaller and larger head circumference in late pregnancy, respectively (e.g., for 9.5 °C: −1.6 SDS [95 %CI −2.0; −0.4] and for 20.0 °C: 1.8 SDS [0.7; 2.9]). A susceptibility period from weeks 1–7 was identified for cold exposure and a smaller head circumference at late pregnancy. Cold exposure was associated with a slower head circumference growth from mid to late pregnancy (for 5.5 °C: −0.1 cm/week

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[-0.2; −0.04]), with a susceptibility period from weeks 4–12. No associations that survived multiple testing correction were found for other foetal or any birth outcomes.
Conclusions: Cumulative exposure to cold and heat during pregnancy was associated with changes in foetal head circumference throughout gestation, with susceptibility periods for cold during the first pregnancy trimester. No associations were found at birth, suggesting potential recovery. Future research should replicate this study across different climatic regions including varying temperature profiles.

1. Introduction

Global climate change has increased the frequency of extreme temperatures and severe weather events, posing substantial threats to human health and the environment (IPCC, 2022). As the world population grows and urbanization continues, global warming is likely to reach a 1.5 °C increase before 2040 (IPCC, 2022). The World Health Organization and European Environmental Agency warned of irreversible impacts on nature and human health, particularly in Europe where temperature increases are predicted to pass global trends (2022; WHO, 2021).

Studies showed that exposure to extreme temperatures, both heat and cold, result in a range of health effects, including increased morbidity and mortality (Rocque et al., 2021). Pregnant women and their foetuses are especially vulnerable due to the developmental processes during this lifetime period (Syed et al., 2022; Veenema et al., 2023). The biological mechanism by which temperature influences foetal development remains unclear (Samuels et al., 2022). Studies suggest that sudden changes in temperature may disrupt proper thermoregulation in pregnant women through various mechanisms, including inflammatory responses, oxidative stress, and altered uterine-placental blood flow (Ferguson et al., 2018; Samuels et al., 2022). Rises in ambient air temperature can also trigger the release of heat shock proteins (Ha et al., 2018). Further, exposure to colder temperatures could aggravate beforementioned mechanisms, especially if this co-occurs with an increase in infections with a seasonal pattern (Moriyama et al., 2020). Additionally, seasonal variations have been linked to pregnancy complications like preeclampsia (Liao et al., 2023; Pitakkarnkul et al., 2011). All mechanisms might damage the placenta and contribute to disrupted intrauterine growth (Ferguson et al., 2018; Ha et al., 2018; Samuels et al., 2022).

Studies evaluating temperature exposure during pregnancy generally find that exposure to heat or cold is associated with an increased risk of preterm birth or stillbirth, and reduced birth weight (Bakhtsiyarava et al., 2022; Chen et al., 2023; de Bont et al., 2022; Giorgis-Allemand et al., 2017; Hough et al., 2022; McElroy et al., 2022; Syed et al., 2022; Yitshak-Sade et al., 2021; Yu et al., 2023). This has been evaluated across various continents and countries with varying temperature profiles (e.g., Latin America, China, Europe, USA). Most studies evaluate the effect of long-term weekly or monthly temperature exposure during entire gestation (Bakhtsiyarava et al., 2022; Chen et al., 2023; de Bont et al., 2022; Yitshak-Sade et al., 2021). Associations have also been identified with short-term temperature exposure (i.e., daily temperature exposure prior to the adverse birth outcome) (Hough et al., 2022; McElroy et al., 2022; Yu et al., 2023). However, some studies contradict these findings, showing no associations or even decreased risks (Chen et al., 2023; de Bont et al., 2022; Syed et al., 2022). Researchers have also attempted to identify susceptibility periods for temperature exposure and adverse birth outcomes by employing distributed lag non-linear models (DLNM) (Gasparrini, 2014). Identified periods, however, vary in length from weeks to months and in timing across trimesters (Bakhtsiyarava et al., 2022; Chen et al., 2023; McElroy et al., 2022; Yitshak-Sade et al., 2021). For cold exposure, one study identified increased susceptibility during the first two months of gestation and another one week before delivery (Chen et al., 2023; Yu et al., 2023).

To our knowledge, only one study evaluated the association between temperature exposure and foetal size metrics throughout pregnancy, concluding that higher temperature exposure during pregnancy was associated with smaller head parameters in early- to mid-pregnancy (Leung et al., 2022). During gestation, the foetus undergoes various developmental stages, including the periconceptional and placental formation periods in the initial trimesters, increased adipogenesis in later pregnancy, and brain development throughout gestation (Barbour & Hernandez, 2018; de Graaf-Peters & Hadders-Algra, 2006; Pardi & Cetin, 2006; Steegers-Theunissen et al., 2013). Importantly, various foetal metrics underlie these developmental stages and evaluating them individually is crucial to gain a deeper understanding of changes in foetal development versus focussing solely on endpoint measures like birth weight. Deviations in foetal growth, both restriction and overgrowth, have been associated with increased health risks (Damhuis et al., 2021). While short-term exposure to temperature has been associated with adverse birth outcomes, evaluating foetal development throughout gestation requires a long-term exposure approach to capture any possible deviations. Investigating how and when long-term temperature exposure influences developmental periods during pregnancy is crucial, as varying long-term consequences might arise (Pardi & Cetin, 2006). Our main aim is to evaluate the association between ambient air temperature exposure across pregnancy and foetal size and growth in three European birth cohorts. Our secondary aim is to identify specific periods of susceptibility to air temperature exposure throughout pregnancy.

2. Methods

2.1. Population and study design

This study is embedded in three population-based birth cohort studies, namely the English Born in Bradford Study, the Dutch Generation R Study, and the Spanish INfancia y Medio Ambiente (INMA) Project. Born in Bradford recruited 12,453 pregnant women living in the city of Bradford, the United Kingdom, between 2007 and 2011, who were planning to deliver at the city's main maternity unit (Wright et al., 2013). Generation R recruited 8,879 pregnant women living in Rotterdam, the Netherlands, who were expected to deliver between April 2002 and January 2006 (Kooijman et al., 2016). INMA recruited pregnant women living in several regions of Spain between 1997 and 2008 (Guxens et al., 2012). The current study includes women from four regions, namely Asturias (N = 494), Gipuzkoa (N = 638), Sabadell (N = 657), and Valencia (N = 827), who were recruited between 2003 and 2008. We included women with live singleton births, complete temperature data during weeks 1 – 32 of pregnancy, and at least one outcome measure available, resulting in a total sample size of 23,408 participants (Figure S1). The 32-week threshold was selected to ensure we lost less than 5% of the population while only excluding extremely and very preterm births. Prior to recruitment, ethical approval was obtained for Born in Bradford (Bradford Leeds NHS Research Ethics Committee), Generation R (Medical Ethical Committee of Erasmus University Medical Centre Rotterdam, in accordance with Dutch law), and INMA (Ethical Committee of the Municipal Institute of Medical Investigation and the Ethical Committee of the hospitals involved in the study). Informed consent was obtained from participants.

2.2. Temperature exposure

Assessment of ambient air temperature exposure was done using the urban climate model UrbClim™ (De Ridder et al., 2015). The model uses a 3D atmospheric boundary layer module coupled with urban physics and includes information on the urban structure. The model has been validated in various European countries, and more detailed methodology is described in Methods S1 and elsewhere (De Ridder et al., 2015; Garciá-Diéz et al., 2016; Lauwaet et al., 2015, 2016). Hourly 2-meter air temperature (℃) was estimated at a high spatial resolution of 100 x 100 m (Figure S2) and converted into daily data. The daily data were assigned to the geocoded address where the mother lived on that day, thereby accounting for any changes in address. Daily data started on the date of the last menstrual period. The last menstrual period in the Born in Bradford cohort was determined by subtracting 14 days from the conception date, the latter determined by subtracting the estimated gestational age at the ultrasound examination from the date of birth; in Generation R it was obtained from the referral letter and questionnaires and confirmed at enrolment, and in INMA it was reported at recruitment and confirmed during the first ultrasound examination. If the last menstrual period was missing (2.4% of all participants with temperature data in Born in Bradford, 0.9% in Generation R, and 0.0% in INMA), it was estimated by subtracting 280 days from the date of birth. If the first-known address was recorded after the date of the last menstrual period (12.9% of all participants in Born in Bradford, 15.3% in Generation R, and 1.6% in INMA), we assumed this address to be representative for the address since the date of the last menstrual period and used it for all following days until a next address was recorded. Mean temperatures for each week of pregnancy (i.e., seven consecutive days from the date of the last menstrual period until the 7th day of the 32nd week of pregnancy) were calculated by averaging the daily data.

We validated the daily UrbClim™ temperature with the data of measuring stations from E-OBS (daily gridded observational data for temperature in Europe (Cornes et al., 2018)). The performance was very good and showed a multiple R^2 of 0.89, 0.97, and 0.95, and a root mean squared error of 1.71, 1.20, and 1.57 °C for Born in Bradford, Generation R, and INMA, respectively.

2.3. Foetal assessment

2.3.1. Foetal size at mid and late pregnancy

During pregnancy, ultrasound examinations were carried out by trained sonographers, and foetal size measurements were collected following specific guidelines within each cohort (Iñiguez et al., 2016; Kirwan, 2010; Verburg et al., 2008). The examinations at mid pregnancy took place during the second trimester of pregnancy (at an average of 20.4 weeks of gestation for Born in Bradford, and 20.6 for Generation R and INMA) and at late pregnancy during the third trimester (at an average of 32.8 weeks of gestation for Born in Bradford, 30.5 for Generation R, and 33.3 for INMA) (Table S1). During the ultrasound examinations, head circumference and femur length were measured in centimetres (cm). The estimated foetal weight in grams (g) was calculated using the Hadlock formula IV, with abdominal circumference, femur length, head circumference, and biparietal diameter as input variables (Hadlock et al., 1985; Hammami et al., 2018):

$$
\begin{aligned}
Log10(\textit{estimated foetal weight}) = {} & 1.3596 - 0.00386 \\
& \times \textit{abdominal circumference} \times \textit{femur length} \\
& + 0.0064 \times \textit{head circumference} + 0.0061 \\
& \times \textit{biparietal diameter} \\
& \times \textit{abdomincal circumfernce} + 0.0424 \\
& \times \textit{abdomincal circumference} + 0.174 \\
& \times \textit{femur length}
\end{aligned}
$$

Raw measurements of estimated foetal weight, head circumference, and femur length were harmonized across cohorts by converting them into gestational age- and sex-adjusted standard deviation scores (SDS) based on European reference growth curves from the World Health Organization (Kiserud et al., 2017).

2.3.2. Foetal growth from mid to late pregnancy

Foetal growth was defined as the absolute change in foetal size from mid to late pregnancy. It was calculated for estimated foetal weight (g/week), head circumference (cm/week), and femur length (cm/week) by determining the difference between the foetal size measure at late and mid pregnancy divided by the difference in gestational age between late and mid pregnancy.

2.4. Birth outcomes assessment

Measurements at birth were collected from medical records within each cohort (Iñiguez et al., 2016; Kirwan, 2010; Verburg et al., 2008). Birth weight (g), head circumference at birth (cm), and birth length (cm) were assessed. The raw measurements of birth weight, head circumference at birth, and birth length were converted into gestational age- and sex-adjusted SDS using growth reference charts specific to each cohort (Gurrin et al., 2001; Niklasson et al., 1991; Freeman et al., 1995). For Born in Bradford, SDS of head circumference at birth were not available and birth length data was not collected.

2.5. Potential confounding variables

Potential confounding variables for all cohorts were determined a priori using a directed acyclic graph based on previous scientific literature, biological plausibility, and available data (Figure S3). We harmonized the variables across cohorts. We included information on maternal age (years), national/ethnic origin (White British, South Asian, or Other in Born in Bradford; the Netherlands, Morocco, Suriname/Dutch Antilles, Turkey, or Other in Generation R; and Spain or Other in INMA), family status (couple or single parent), parity (nulliparous, one child, two or more children), maternal smoking use (never in pregnancy, until pregnancy known, continued), maternal alcohol use (never in pregnancy, until pregnancy known, occasionally, frequent), and maternal and paternal education level (low, medium, high). Maternal height (cm) and pre-pregnancy weight (kg) were measured or self-reported in the first trimester of pregnancy and subsequently used to calculate body mass index (BMI, kg/m^2). Exposure to surrounding greenness at the residential address during pregnancy in a buffer of 300 metres was determined using the Normalized Difference Vegetation Index (considering changes of address). The value was determined using satellite data estimating the degree of absorbance of red light of vegetation, and the index ranges from −1 to 1, with a higher value indicating more greenness (Rhew et al., 2011). We adjusted the models for seasonality by including month of conception. We additionally adjusted for foetal sex (female or male) in foetal growth analyses. We did not adjust for air pollution exposure because temperature is involved in the formation and therefore quantity of air pollutants (Buckley et al., 2014; Reid et al., 2012), making air pollution a mediator on the causal pathway between temperature and health outcomes (Jakpor et al., 2020) (Figure S3).

2.6. Statistical analyses

Missing values of potential confounding variables were imputed following the procedure for expectation–maximization imputation using the 'Amelia' R package v1.8.0 (Honaker et al., 2012). Imputation was performed independently in each cohort/region including subjects that have available data on temperature exposure during weeks 1 to 32 of pregnancy and at least one outcome available (Table S2). For all potential confounding variables, the percentage of missing values was below 30%, except paternal educational level in Born in Bradford and Generation R (38.4% and 39.6%, respectively). Imputed and observed datasets showed comparable distributions for each cohort (Table S3).

Within each cohort, mothers that were included in the analyses had some different characteristics compared to those excluded (Table S4). We performed inverse probability weighting in the full sample of each cohort/region separately, to correct for selection bias and prevent underrepresentation of characteristics in the study sample (Weisskopf et al., 2015). We used a generalized linear model that includes determinants of participation (list of variables used can be found in Table S5) to predict the marginal probability of participation in the current study. The final weight per subject was calculated as the inverse of the probability and used as weights in all DLNM. The distribution of the weights in each cohort/region can be found in Figure S4.

To evaluate the delayed association between ambient air temperature exposure during pregnancy and each outcome, we used DLNM (Gasparrini, 2014; Gasparrini et al., 2010). These models estimate the exposure–response relationship while simultaneously accounting for the delayed associations between exposure and response (lag-response relationship), considering the correlation within the time-series data. The interval of time between the delayed effect of the exposure and the outcome is defined as the lag scale and can be divided into equally spaced time periods. Some model specifications were set based on visual inspection of the data, previous literature, and biological plausibility. First, we harmonized the exposure period for all participants, since the exposure matrix does not allow for missing lags. We established weekly exposure windows that started from the first week of gestation and ended prior to each outcome's assessment. We selected the longest possible threshold while ensuring maximum sample size after evaluating possible window thresholds between the minimum (14.1 weeks for mid and 28.1 for late pregnancy) and the mean (20.5 weeks for mid and 31.8 for late pregnancy) of gestational age in the analysis sample of 23,408. This meant that we finally included 18 one-week lags for outcomes at mid pregnancy or growth from mid to late pregnancy and 28 one-week lags for outcomes at late pregnancy. For birth outcomes we included the threshold of 32 one-week lags as described previously. Second, we defined the functions of the DLNM cross-basis (dimensional space of two functions describing the exposure–response and lag-response relationships). We used generalised additive models to explore the linearity of the dose–response relationship between each week of exposure and each outcome. After visual inspection, we observed that most relationships were non-linear. We therefore modelled the exposure–response relationship using natural cubic splines with knots at the 25^{th} and 75^{th} percentile of temperature exposure distribution for the relevant lag periods. For the lag-response relationship, we selected natural cubic splines and added one knot centred over the full lag period of each outcome.

Our main analysis followed a two-stage approach: we performed cohort/region-specific DLNMs for each outcome and then a meta-analysis. In the first stage, we evaluated the cumulative association between ambient air temperature exposure during pregnancy and i) foetal *size* (at mid and at late pregnancy), ii) foetal *growth* from mid to late pregnancy, and iii) birth outcomes. The cumulative association represents the combined effect of exposure to temperature throughout the entire lag period on the outcome of interest. To avoid the influence of very extreme percentiles, for each cohort/region-specific DLNM, we determined the estimated coefficients for the 1^{st} to 99^{th} temperature percentiles based on the exposure matrix for the lag-period and cohort/region of interest. Models were adjusted for all beforementioned potential confounding variables. We set the centring value (reference temperature) to the 50^{th} percentile of the cohort/region-specific temperature distribution respective to each lag period.

In the second stage, we combined the estimated coefficients from the cohort/region-specific DLNM using a random effects meta-analysis including a random effect by cohort/region. To reduce heterogeneity when present, we tested the inclusion of temperature characteristics of the three climatic regions representing our study population as fixed effects. These three climatic regions were the following: i) subtropical maritime (INMA-Asturias and INMA-Gipuzkoa), ii) subtropical continental (INMA-Sabadell and INMA-Valencia), and iii) temperate maritime (Born in Bradford and Generation R) (European Environmental Agency, 2012). The temperature characteristics of each climatic region (i.e., range of temperature and average temperature) were tested in models including all possible combinations (either one or the other or both of them). We chose the model that showed a lower I^2 statistic and significant Wald test ($p < 0.05$) for the selected fixed effect variables. As a result of these analyses, the range of temperature was included in models evaluating head circumference at late pregnancy; the average temperature was included in models evaluating head circumference at mid pregnancy and femur length at late pregnancy; both characteristics were included in models evaluating estimated foetal weight at mid pregnancy and head circumference growth and femur length growth from mid to late pregnancy; and no temperature characteristics were included for all other outcomes. Random-effects meta-analysis were fitted through restricted maximum likelihood. The final global estimates were plotted as dose–response curves including the confidence intervals that show the cumulative association between ambient air temperature exposure during pregnancy and each outcome centred at the 50^{th} percentile of temperature distribution averaged across all cohorts (14 °C). Following the approach by Galwey, we corrected for multiple testing on the outcome by determining the eigenvalues to identify the effective number of tests using the 'poolr' package and 'meff' function in R (Galwey, 2009). The effective number of tests was six for the foetal analyses (three exposure periods and three foetal outcomes) and two for the birth outcomes analyses (one exposure period and the three birth outcomes) making the new statistical significance level $0.05/6 = 0.0083$ for foetal analyses, and $0.05/2 = 0.025$ for the birth outcomes analyses. Associations that remained statistically significant after correction for multiple testing were highlighted in the final plots.

As a secondary analysis, we attempted to identify susceptibility periods during pregnancy if any meta-analysed dose–response curve obtained from the second stage showed statistically significant associations after multiple testing correction. We used the cohort/region-specific DLNM to estimate the coefficients for each pregnancy week when exposed to specific predictors for cold (2.5^{th} percentile of temperature) or heat (97.5^{th} percentile of temperature) (Table S6), depending on the statistically significant associations found in the main analysis. The centring value was set to the 50^{th} percentile of the cohort/region-specific temperature distributions. The same meta-analysis approach as the second stage of the main analysis was then used. Final global estimates were plotted as lag-response curves including the confidence intervals, that show the association between ambient air temperature exposure at the selected predictor for cold (2.5^{th} versus 50^{th} percentile) or heat (97.5^{th} versus 50^{th} percentile) for each week of pregnancy and the outcome. The final centring value was set to the 50^{th} percentile of the temperature distribution averaged across all cohorts respective to each full exposure period (averaged to 14 °C, Table S6).

To evaluate the robustness of our results, we performed sensitivity analyses and tested different DLNM specifications: i) we set the knots in the exposure–response relationship at the 10^{th} and 90^{th} percentile of temperature distribution; ii) we modelled the lag-response relationship linearly and with two equally distributed knots in the lag period; iii) we excluded children born moderate to late preterm by only including mothers that have temperature exposure during weeks 1 to 38 of pregnancy and used a lag period of 38 instead of 32 weeks for birth outcomes; iv) we evaluated the associations for birth outcomes using a lag period of 18 or 28 weeks to compare with the results of foetal size and foetal growth outcomes; v) we stratified the main analysis by foetal sex; vi) we included only mothers with a national origin from the respective cohort; vii) we stratified by cohort/region for the outcomes in which a cumulative association was found; viii) we evaluated all associations excluding the Born in Bradford cohort; and finally, ix) we evaluated associations for the foetal outcomes including only mothers with available data at mid and late pregnancy for each foetal metric.

All analyses were done using R version 4.0.3 [R Core Team 2020], the DLNM and meta-analyses were conducted using the 'dlnm' and 'mixmeta' packages, respectively.

3. Results

3.1. Population characteristics

Table 1 shows all population characteristics. The average age of mothers varied between 27.4 and 31.5 years across the cohorts. Parents from Generation R were more highly educated (42.3% of mothers and 50.9% of fathers), while parents from INMA mostly had a medium education level (average of 41.4% of mothers and 44.2% of fathers across regions), and those from Born in Bradford a low education level (56.8% of mothers and 53.0% of fathers). Between 11.5% and 22.8% of mothers continued to smoke during pregnancy across cohorts. The temporal pattern for weekly ambient air temperature in the 30x30 km temperature domain(s) for each cohort/region throughout the years of pregnancy is shown in Fig. 1. During pregnancy weeks 1 to 32, Born in Bradford had mothers who experienced the coldest average weekly temperatures (minimum −5.6 °C) and INMA-Sabadell the hottest (maximum 30.3 ℃). From mid to late pregnancy, estimated foetal weight growth ranged from 125.9 (Standard Deviation, SD 18.3) g/week in Generation R to 151.7 (SD 18.4) in INMA-Sabadell; head circumference growth ranged from 0.9 (SD 0.1) cm/week in INMA-Gipuzkoa and

Table 1
Population characteristics of the three European birth cohorts.

	Born in Bradford	Generation R	INMA			
			Asturias	Gipuzkoa	Sabadell	Valencia
	(N = 12,701)	*(N = 8,319)*	*(N = 469)*	*(N = 599)*	*(N = 611)*	*(N = 709)*
Child Characteristics						
Sex (female *vs.* male)	48.5	49.6	48.0	49.6	49.6	47.2
Season of conception						
Summer	22.8	23.7	21.3	30.2	28.6	22.7
Fall	25.9	27.4	28.6	23.0	23.4	20.7
Winter	25.1	26.7	26.2	16.7	21.0	31.6
Spring	26.2	22.2	23.9	30.1	27.0	25.0
Gestational age at birth (weeks)	39.6 (1.7)	39.9 (1.6)	39.5 (1.4)	39.8 (1.4)	39.7 (1.4)	39.7 (1.5)
Birth weight (grams)	3207 (574)	3243 (540)	3275 (459)	3301 (448)	3246 (425)	3255 (488)
Head circumference at birth (centimetres)	na[1]	33.8 (1.7)	34.2 (1.4)	34.8 (1.4)	34.2 (1.2)	34.1 (1.5)
Birth length (centimetres)	na	50.2 (2.4)	49.7 (2.0)	49.0 (1.9)	49.4 (1.9)	50.2 (2.1)
Maternal Characteristics						
Age (years)	27.4 (5.6)	29.7 (5.3)	31.5 (4.4)	31.4 (3.6)	30.2 (4.4)	29.8 (4.5)
Pre-pregnancy body mass index (kg/m^2)	26.0 (5.7)	23.6 (4.3)	23.8 (4.3)	22.9 (3.6)	23.7 (4.5)	23.8 (4.7)
Education level						
High	27.6	42.3	36.5	51.1	29.0	23.4
Medium	15.6	30.8	44.8	35.7	43.0	42.2
Low	56.8	26.9	18.7	13.2	28.0	34.4
National/ethnic origin						
Country of cohort	41.0	49.6	96.4	95.8	89.0	88.2
South Asian	54.0	na	na	na	na	na
Morocco	na	6.9	na	na	na	na
Suriname / Dutch Antilles	na	12.3	na	na	na	na
Turkey	na	9.4	na	na	na	na
Other	5.0	21.8	3.6	4.2	11.0	11.8
Alcohol use during pregnancy						
Never	80.2	47.6	89.1	82.2	77.9	74.4
Until pregnancy known	6.7	12.9	5.3	6.0	5.7	7.8
Occasionally	9.5	32.0	5.6	11.8	16.4	17.8
Frequent	3.6	7.5	na	na	na	na
Smoking during pregnancy						
Never	83.7	72.9	71.4	76.3	69.7	59.0
Until pregnancy known	2.9	8.6	11.0	12.2	16.0	18.2
Continued	13.4	18.5	17.6	11.5	14.3	22.8
Parity						
0 children	39.3	55.5	61.0	53.8	56.5	55.0
1 child	29.0	30.0	33.9	40.0	37.1	36.4
2+ children	31.7	14.5	5.1	6.2	6.4	8.6
Family status (couple *vs.* single parent)	83.9	85.6	98.1	99.3	98.8	97.6
Paternal Characteristics						
Education level						
High	33.4	50.9	22.8	26.3	21.1	14.9
Medium	13.6	26.5	46.2	49.1	43.5	38.2
Low	53.0	22.6	31.0	24.6	35.4	46.9
Residential Characteristics						
Surrounding greenness	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.4 (0.1)	0.2 (0.1)	0.2 (0.1)

Values are percentage for categorical and mean (standard deviation) for continuous variables. Na: not available. [1] Head circumference at birth was available in absolute values (centimetres) but not as standard deviation scores in the Born in Bradford cohort and therefore not used in the current manuscript or shown in the table.

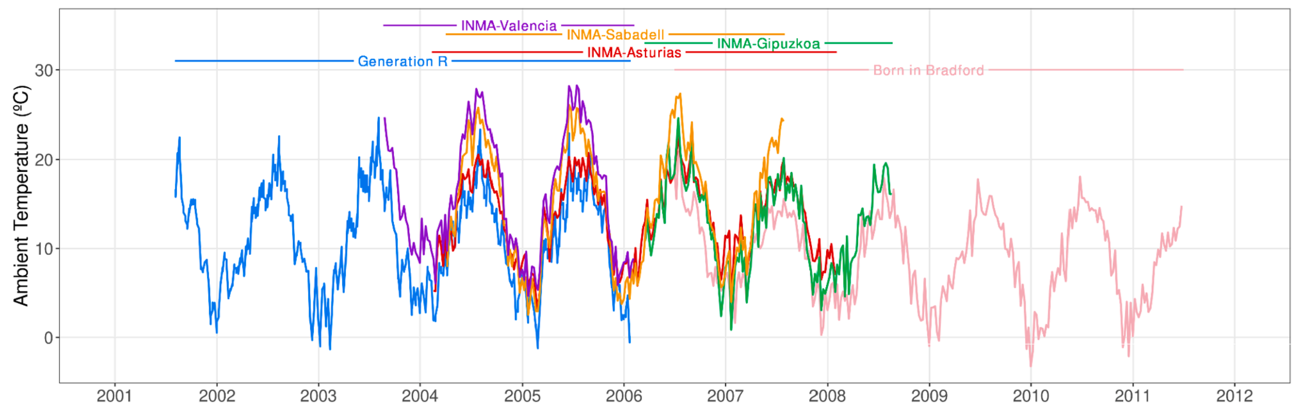

Fig. 1. Average weekly ambient air temperature in ℃ during the years of pregnancy in the three European birth cohorts.

INMA-Sabadell to 1.1 (SD 0.1) in Generation R; and femur length growth was 0.2 (SD 0.02) cm/week for all cohorts (Table S7).

3.2. Foetal size at mid and late pregnancy

Results from the meta-analysis for the foetal size measures show that after correction for multiple testing, cumulative exposure to colder or hotter temperatures in the central range of temperature from conception to week 28 of pregnancy was associated with a smaller and larger head circumference in late pregnancy, respectively (e.g., exposure to 9.5 °C (vs. 14.0 °C) was associated with −1.61 SDS of head circumference [95 % Confidence Interval (CI) −2.81; −0.42] and exposure to 20 °C (vs. 14.0 °C) was associated with 1.78 larger SDS of head circumference [95 % CI 0.66; 2.85]) (Fig. 2B and Table S8). A susceptible period for exposure to cold (2.5th percentile or 4.2 °C) was found between weeks 1 and 7 for a smaller head circumference at late pregnancy (cumulative effect estimate of −0.1 SDS), but not for exposure to heat (Fig. 3A and Table S9). Results further show associations for exposure to hotter

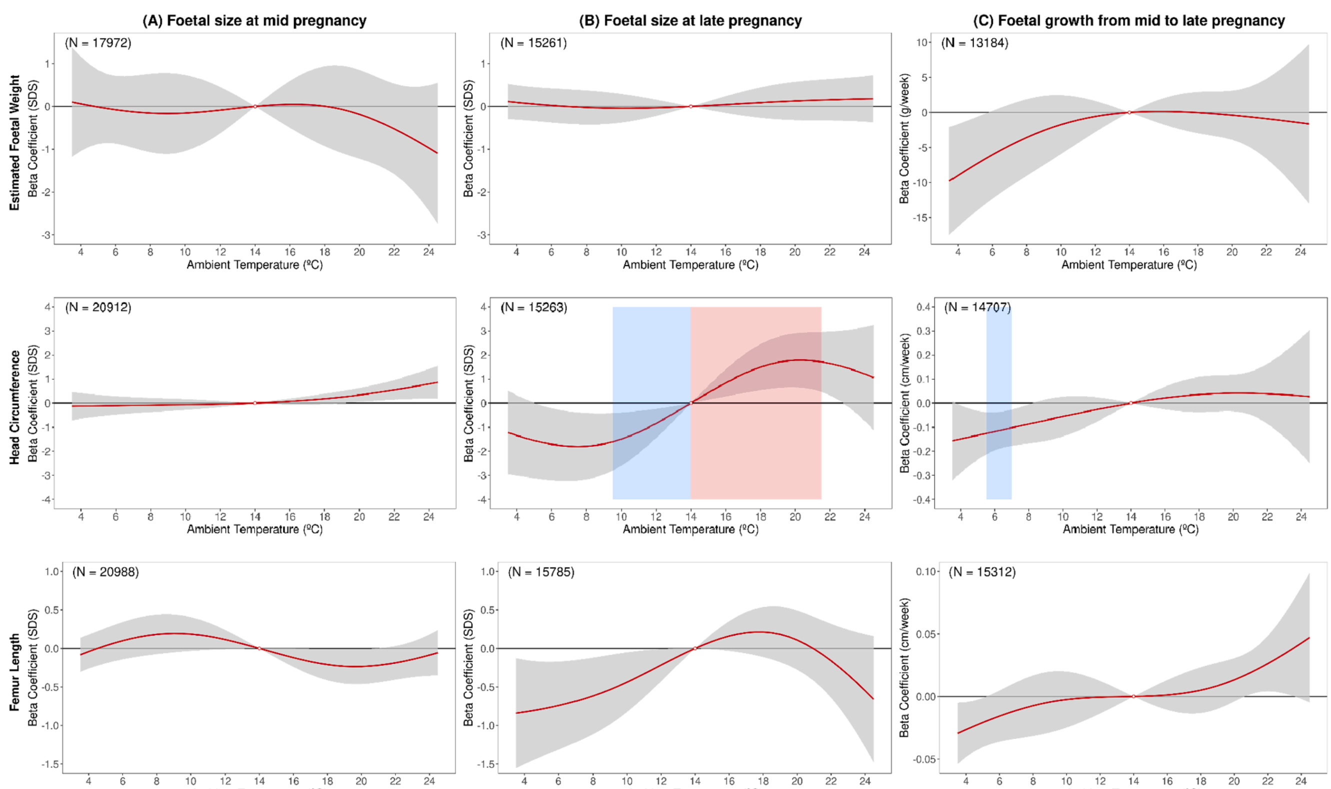

Fig. 2. Adjusted associations between cumulative ambient air temperature exposure (°C) during pregnancy and foetal size at mid (A) and late (B) pregnancy, and foetal growth from mid to late pregnancy (C) in the three European birth cohorts. Ambient air temperature exposure during weeks 1 to 18 (A and C) or 1 to 28 (B) of pregnancy. The continuous red line represents the population-average curve with the 95% confidence intervals shaded in grey obtained from random-effects meta-analysis. Estimates are centred at the 50th percentile of temperature (14 °C). Blue or red shaded areas (exposure to colder and hotter temperatures, respectively, as compared to 14 °C) indicate statistically significant associations after correction for multiple testing (p-value $<$ 0.0083). Within each cohort/region, distributed lag non-linear models were adjusted for maternal age, education level, national origin, body mass index, smoking and alcohol use during pregnancy, parity, paternal education, family status, surrounding greenness, and month of conception. Models evaluating foetal growth outcomes were additionally adjusted for foetal sex. Standard deviation scores are gestational age- and sex-adjusted. Abbreviations: SDS, standard deviation score. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

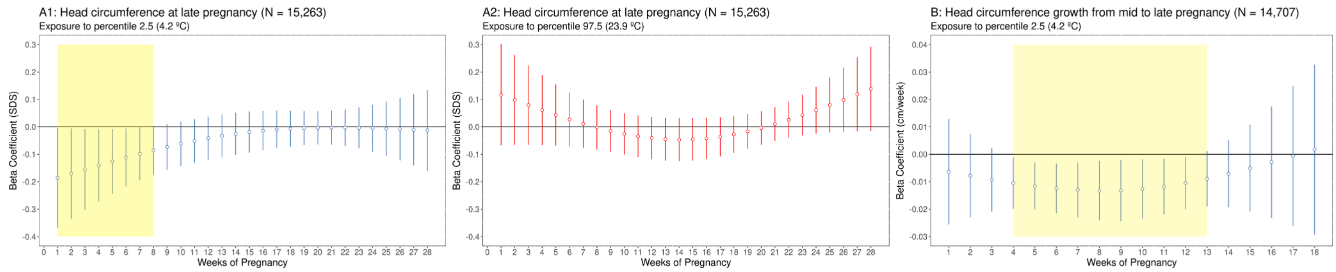

Fig. 3. Adjusted associations between ambient air temperature exposure to cold (blue) or heat (red) during each week of pregnancy and (A) head circumference at late pregnancy or (B) head circumference growth from mid to late pregnancy. Dots represent the global estimate of the association between the exposure to the respective percentile at each lag and the foetal outcome with the 95% confidence intervals as vertical lines obtained from random-effect meta-analysis. Blue or red dots and vertical lines indicate exposure to the 2.5th and 97.5th percentile of temperature exposure within each cohort, respectively, centred to the 50th percentile (14 °C). Yellow shaded areas indicate associations that were statistically significant at the 0.05 level. Within each cohort/region, distributed lag non-linear models were adjusted for maternal age, education level, national origin, body mass index, smoking and alcohol use during pregnancy, parity, paternal education level, family status, surrounding greenness, and month of conception. Models evaluating foetal growth outcomes were additionally adjusted for foetal sex. Standard deviation scores are gestational age- and sex-adjusted. Abbreviations: SDS, standard deviation score. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

temperatures and a larger head circumference but smaller femur length at mid pregnancy (Fig. 2A) and for exposure to colder temperatures and a smaller femur length at late pregnancy (Fig. 2B), although these associations did not survive correction for multiple testing. No associations for estimated foetal weight at mid or late pregnancy were found (Fig. 2).

3.3. Foetal growth from mid to late pregnancy

Results from the meta-analysis for the foetal growth outcomes show that after correction for multiple testing cumulative exposure to colder temperatures between 5.5 and 7.0 °C (vs. 14.0 °C) from conception to week 18 of pregnancy was associated with a slower head circumference growth from mid to late pregnancy (e.g., exposure to 5.5 °C was associated with −0.1 cm/week of head circumference [95 % CI −0.2; −0.04] (Fig. 2C and Table S10). A susceptibility period for exposure to cold (2.5th percentile or 4.2 °C) was found between weeks 4 and 12 for a slower head circumference growth from mid to late pregnancy (cumulative effect estimate of −0.01 cm/week) (Fig. 3B and Table S11). Results further show associations for exposure to colder temperatures and a slower estimated foetal weight and femur length growth from mid to late pregnancy and to hotter temperatures and a faster femur length growth from mid to late pregnancy, although these associations did not survive correction for multiple testing (Fig. 2C).

3.4. Birth outcomes

We found no statistically significant evidence of associations between cumulative temperature exposure from conception to week 32 of pregnancy and birth weight (Fig. 4 and Table S12) or head circumference at birth or birth length (Figure S5 and Table S12).

3.5. Sensitivity analyses

When adjusting the DLNM specifications by changing the knot placements in the exposure–response relationship or evaluating the lag-response relationship linearly or with two knots, results from the meta-analysis for all outcomes showed similar global curves (Figures S6, S7 and S8). Further, limiting the sample size to mothers with temperature data during weeks 1 to 38 of pregnancy showed comparable results (Figure S9). Adjusting the lag period to 18 or 28 weeks for all birth outcomes also showed similar curves to the main analysis (Figure S10). When stratifying the main analysis for foetal sex, results for head circumference at late pregnancy were observed for both girls and boys, but the effects of cold on head circumference growth were only seen in boys and not girls (Figure S11). Restricting the population to only

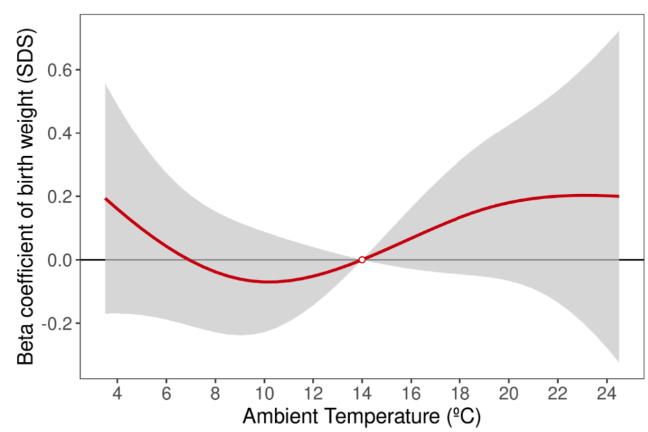

Fig. 4. Adjusted association between cumulative ambient air temperature exposure levels (°C) during pregnancy and birth weight in the three European birth cohorts (N = 22,950). Ambient air temperature exposure during weeks 1 to 32 of pregnancy. The continuous red line represents the population-average curve with the 95% confidence intervals shaded in grey obtained from random-effects meta-analysis. Estimates are centred at the 50th percentile of temperature (14 °C). Within each cohort/region, distributed lag non-linear models were adjusted for maternal age, education level, national origin, body mass index, smoking and alcohol use during pregnancy, parity, paternal education, family status, surrounding greenness, and month of conception. Standard deviation scores are gestational age- and sex-adjusted. Abbreviations: SDS, standard deviation score. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

mothers with a national origin of their respective cohorts showed comparable plots as the main analysis (Figure S12). Cohort/region-specific plots for head circumference at late pregnancy and growth from mid to late pregnancy suggested that the overall association was mainly driven by the INMA-Asturias cohort (Figures S13 and S14). Finally, both excluding the Born in Bradford cohort from analyses or restricting the population to only mothers with available foetal data at both mid and late pregnancy revealed similar curves (Figures S15 and S16).

4. Discussion

In this study using data from three birth cohorts in Europe, we found that cumulative exposure to colder and hotter temperatures was associated with changes in head circumference size and growth during gestation. Susceptibility periods for exposure to cold were identified during pregnancy weeks 1 to 7 for a smaller head circumference at late pregnancy and weeks 4 to 12 for a slower head circumference growth. Although associations were identified for other foetal metrics, these did not survive multiple testing correction. No evidence of associations was found between temperature exposure and birth outcomes.

Exposure to hot temperatures can lead to heat stress in pregnant woman, initiating processes that might damage placental growth and consequently contribute to disrupted foetal growth (Ferguson et al., 2018; Ha et al., 2018; Samuels et al., 2022). Animal and human studies have elucidated that maternal heat stress can prompt vasodilation, redistributing blood flow away from the uterine and placental regions towards the skin, disrupt nutrient exchange, and deprive the foetus of oxygen, all at the expense of critical placental and foetal organ development (Cowell et al., 2023; Herrick & Bordoni, 2023; Wang & Zhao, 2010). We observed a larger head circumference at late pregnancy with exposure to warmer temperatures, but found no susceptible periods. Head circumference serves as an indicator for head growth, a process intertwined with many brain developmental processes, particularly during early- and mid-pregnancy (Gale et al., 2004, 2006; Thompson & Nelson, 2001). To our knowledge, only one study evaluated temperature exposure and head circumference size throughout pregnancy, and found results contradictory to ours; higher temperatures from conception to week 20 of pregnancy were associated with a smaller head circumference at mid or late pregnancy (Leung et al., 2022). Further, in contrast to most literature, we found no evidence of associations between hotter temperatures and birth weight, even when considering different exposure periods. Studies have found associations between heat and a lower birth weight, with variable susceptibility periods ranging from weeks during the first trimester to the final months of pregnancy, or across the entire gestational period (Bakhtsiyarava et al., 2022; Basagaña et al., 2021; Leung et al., 2022; Yitshak-Sade et al., 2021). The inconsistency in susceptibility periods could be due to the varying exposure windows (months versus weeks) or the location-specific differences in climate (Latin America, Israel, and Massachusetts, USA), highlighting also why we might not be finding any associations.

Cold temperature exposure can result in increased blood viscosity and vasoconstriction, elevating blood pressure in pregnant women (Kimura et al., 1998; Sun et al., 2023; Usselman et al., 2015). Changes in uterine-placental blood flow, similar to heat exposure, can disrupt development of vital foetal organs, including the brain (Herrick & Bordoni, 2023; Wang & Zhao, 2010). This might explain why we see a smaller head circumference at late pregnancy and a slower head circumference growth from mid to late pregnancy for exposure to colder temperatures. Susceptibility periods to cold temperature exposure were identified during the first trimester of pregnancy. From the first until the second trimester, foetal brain development is characterized by neurogenesis and gliogenesis, processes integral for proper formation and functioning of the central nervous system (Leibovitz et al., 2022). Our results suggest that exposure to cold could potentially disrupt crucial brain developmental processes. Further, the identified seven- and nine-week susceptible periods for exposure to cold during the first trimester, align with susceptible periods found by Leung *et al.* for exposure to heat (Leung et al., 2022). Our results for exposure to colder and hotter temperatures and the associations found by Leung and colleagues, might suggest that head circumference size and growth throughout gestation could be influenced by both hot and cold temperatures (Leung et al., 2022). Finally, associations of exposure to cold and hot temperatures and head circumference at late pregnancy were identifiable in both male and female foetuses, while associations for exposure to cold with a slower head circumference growth were only seen in male foetuses. To the best of our knowledge, only one study has explored sex-related differences in vulnerability to temperature exposure and foetal metrics during gestation, and found increased vulnerability for female foetuses (Leung et al., 2022). However, the exact mechanisms are still unknown and further research is needed to understand whether our results are confirmed or due to chance finding.

Overall, even though we found associations of exposure to heat and cold with measurements of foetal growth across pregnancy, no associations were found with the corresponding birth outcomes, suggesting that the effects seen throughout gestation might recover at birth. Also, our results might be due to chance finding, even though we applied correction for multiple testing. It is worth noting that the magnitude of the identified associations was small and that the results for head circumference at late pregnancy only indicated associations in the central range of temperature while we were expecting stronger results for the temperature extremes. Furthermore, the duration of the identified susceptible periods during the first trimester of pregnancy are relatively short within the broader context of pregnancy and might not translate into clinically significant effects. Nevertheless, the changes we observed in foetal size and growth could represent transient effects experienced by relatively short periods of exposure to relatively moderate cold or hot temperatures that are not constant across the entire pregnancy. Even though the magnitude and duration might limit the practical significance of the results, these effects might be further aggravated by climate change if exposure periods to cold or hot temperatures become more extreme and longer.

Our study has several important strengths. Firstly, we were able to include a large sample size from different population-based birth cohort studies based in countries with varying climates, increasing our external validity, and making the results from our multi-site study more robust. Aside from capturing the climate variability, our population was ethnically diverse with detailed data on socio-economic and lifestyle characteristics. We were able to adjust for some maternal behaviours during pregnancy that might contribute to foetal growth restriction. Further, we employed inverse probability weighting to limit selection bias and ensure representative results of the initial study population. Second, we had temperature data with a high temporal and spatial resolution, which minimizes exposure misclassification and more precisely accounts for the temporal and spatial variation. Considering the between-subject variability in exposure properly helps mitigate bias in our effect estimates. Third, we used an appropriate model for the delayed relationship between our exposure and response, ensuring the maximum amount of data was used for analyses. DLNMs minimize confounding by seasonality by mutually adjusting for the temperature exposure in other pregnancy weeks and avoiding multiple comparisons for the exposure. Also, modelling the lag-exposure–response relationship non-linearly ensures that trends associated with both cold and hot temperatures are adequately captured. Lastly, the DLNM approach allows for evaluation of possible susceptible periods throughout gestation, aiding a deeper understanding of which foetal developmental phases might be more affected.

However, our study also encompasses some limitations related to the exposure and outcome assessments, and to the study design that merit discussion. With regards to the temperature assessment, we must consider the possibility of measurement error of the exposure and subsequent exposure misclassification. We have collected information on outdoor residential values, but were not able to account for factors that may modify the individual levels of exposure (e.g., air conditioning or heating use, behavioural and activity patterns). Additionally, we were unable to account for temperature acclimatization, a process that occurs when individuals are repeatedly exposed to extreme temperatures over a multi-day period, potentially diminishing the effects we observe as it influences physiological responses and makes an individual more capable of handling extreme exposure (Soultanakis-Aligianni, 2003). For example, populations that experience hotter temperatures, INMA-Sabadell and -Valencia, are more likely to be acclimatized to these temperatures and have a higher preparedness with regards to heat. Lastly, although ambient air temperature is a widely used measure of temperature that can capture the direct effects on health outcomes, future studies should aim to incorporate other health-related measures of temperature, such as apparent temperature or the urban heat island index to evaluate the complexity of combined effects with other atmospheric factors. We chose not to incorporate the former in the current study due to its high correlation with ambient air temperature (0.99) in our sample. With regards to the outcome assessment, we need to consider the possibility of live-birth bias. We might conclude that the effect of temperature exposure on the foetal and birth metrics is less harmful because we are excluding information from those foetuses that are more susceptible (i.e., excluding extremely and very preterm children and miscarriages). We were also unable to calculate foetal growth from mid or late pregnancy to birth because the foetal size metrics were not directly comparable to the metrics at birth. Finally, while the reference growth curves utilized to compute SDS for foetal size outcomes are based on expansive, representative datasets for foetal growth patterns from the World Health Organization, discernible disparities between cohort/regions – such as genetic variations or healthcare access – underscore the potential limitations in accurately representing each cohort/region to an equal degree. With regards to our statistical analysis, even though DLNMs are powerful tools to evaluate time-series data, they have some limitations. First, many model decisions are made a priori and do not follow specific guidelines. The model can be sensitive to parameter changes, and results should therefore be interpreted with caution; however, our sensitivity analyses testing different parameters showed comparable results to the main analysis. Also, an artefact of the cubic constraint of the DLNM is the over-smoothing of associations, assuming that the exposure–response relationship varies smoothly over the lagged exposures (Mork & Wilson, 2022). Lastly, the DLNM requires the exposure history of a participant to contain no missing values, meaning that we could be missing important weeks of exposure closer to the outcome assessment or at the end of gestation. However, selected thresholds at mid and late pregnancy were close to the means of the gestational ages of the sample and our sensitivity analyses in participants with exposure during weeks 1 to 38 showed comparable results, suggesting our results to be robust.

5. Conclusion

In conclusion, we found evidence that cumulative exposure to cold or hot temperatures during pregnancy was associated with changes in head circumference size and growth throughout gestation, with corresponding susceptibility periods during the first pregnancy trimester. Considering the predicted exacerbation of climate change, the identified transient effects on foetal development might become more prominent in magnitude and duration. However, results need to be interpreted with caution since we found no associations at birth, suggesting potential recovery of the identified changes. Future research should explore the association between temperature exposure and foetal size and growth further and replicate this study across different climatic regions and including varying temperature profiles. Also, understanding when during pregnancy temperature may exert its influence is crucial to further clarify physiological mechanisms and provides a basis for developing strategies to mitigate the adverse health impacts experienced by pregnant women and their children amid the escalating climate crisis.

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CRediT authorship contribution statement

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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

Data will be made available on request.

Appendix A. Supplementary material

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envint.2024.108619.

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