A Section 508–conformant HTML version of this article
is available at https://doi.org/10.1289/EHP8117.

Low and High Ambient Temperatures during Pregnancy and Birth Weight among 624,940 Singleton Term Births in Israel (2010–2014): An Investigation of Potential Windows of Susceptibility

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Background: Exposure to heat during pregnancy has been associated with reduced fetal growth. Less is known about associations with cold and the potential for critical time windows of exposure.

Objectives: We aimed to evaluate, in a national retrospective cohort, critical windows of susceptibility during pregnancy to extreme temperatures (low and high) and fetal growth, among 624,940 singleton term births in Israel during the period 2010–2014.

Methods: Temperature exposures were estimated using a spatially refined gridded climate data set with a 1-h and 1-km^2 resolution. Percentiles of temperature were categorized by climatic zone for the entire pregnancy and by trimesters and weeks. Generalized additive models with the distributed lag nonlinear model framework were used to estimate unadjusted and adjusted associations between percentiles and categories of temperature and fetal growth markers: term [births after 36 weeks of gestational age (GA)] mean birth weight and term low birth weight (tLBW, term infants with birth weight below 2,500 g).

Results: After adjustment, extreme temperatures (percentiles) during the entire pregnancy were associated with a lower mean birth weight {≤10th vs. 41st–50th percentile: –56 g [95% confidence interval (CI): –63 g, –50 g)]; >90th vs. 41st–50th percentile: –65 g; 95% CI: –72 g, –58 g}. Similar inverse U-shaped patterns were observed for all trimesters, with stronger associations for heat than for cold and for exposures during the third trimester. For heat, results suggest critical windows between 3–9 and 19–34 GA-weeks, with the strongest association estimated at 3 GA-weeks (temperature >90th vs. 41st–50th percentiles: –3.8 g; 95% CI: –7.1 g, –0.4 g). For cold, there was a consistent trend of null associations early in pregnancy and stronger inverse associations over time, with the strongest association at 36 GA-week (≤10th vs. 41st–50th percentiles: –2.9 g; 95% CI: –6.5 g, 0.7g). For tLBW, U-shape patterns were estimated for the entire pregnancy and third trimester exposures, as well as nonsignificant associations with heat for 29–36 GA-weeks. Generally, the patterns of associations with temperatures during the entire pregnancy were consistent when stratified by urbanicity and geocoding hierarchy, when estimated for daily minimum and maximum temperatures, when exposures were classified based on temperature distributions in 49 natural regions, and when estimated for all live births.

Discussion: Findings from our study of term live births in Israel (2010–2014) suggest that exposure to extreme temperatures, especially heat, during specific time windows may result in reduced fetal growth. https://doi.org/10.1289/EHP8117

Background

Increases in mean temperature and the frequency and intensity of extreme weather events due to climate change are expected to increase climate-related morbidity and mortality (Basagaña 2018; IPCC 2014). In Israel, summers have become significantly warmer during the last 30 y (Yosef et al. 2019), and concomitantly, climate change has increased the frequency and severity of heat waves, and the occurrence of snow events (Yosef et al. 2016, 2021). Given projected increases in average and extreme ambient temperatures, it is important to investigate the potential effects of climate change on birth outcomes in Israel (Hochman et al. 2020).

In utero and during the early postnatal period, environmental exposures can permanently alter physiology and metabolism, predisposing individuals to the development of serious chronic pathologies later in life (e.g., cardiovascular, metabolic, respiratory, and neurodegenerative diseases) (Heindel et al. 2015). Low birth weight (LBW; birth weight <2,500 g) may indicate abnormalities in intrauterine growth and is a risk factor for mortality and morbidity during early childhood and over the entire life course (Barker 2004; Blencowe et al. 2013; Heindel et al. 2015; The global burden of preterm birth 2009). In Israel, although LBW prevalence rates are similar to those of Europe (Agay-Shay et al. 2018), the mean number of births per woman is the highest among the Organization for Economic Co-operation and Development (OECD) countries (Rubin et al. 2017), resulting in a high public health burden from LBW (The Gertner Institute 2007).

Most epidemiological studies of associations between mean or extreme ambient temperatures and pregnancy outcomes have reported significant inverse associations between high temperatures and gestational duration, or positive associations with preterm delivery, as summarized in previous reviews, meta-analyses, and pooled analysis (Bekkar et al. 2020; Beltran et al. 2013; Carolan-Olah and Frankowska 2014; Chersich et al. 2020; Giorgis-Allemand et al. 2017; Poursafa et al. 2015; Spolter et al. 2020; Strand et al. 2011b; Zhang et al. 2017). In the most recent

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Supplemental Material is available online (https://doi.org/10.1289/EHP8117).

The authors declare they have no actual or potential competing financial interests or any other conflicts of interest.

Received 19 August 2020; Revised 24 August 2021; Accepted 25 August 2021; Published 13 October 2021.

meta-analysis, Chersich et al. (2020) summarized existing evidence on the association between fetal growth and high ambient temperature. They reported that in 18 out of 28 studies higher temperature was associated with lower birth weight, and that in 10 of 16 studies higher temperature was positively associated with LBW, though there was considerable statistical heterogeneity among studies. Zhang et al. (2017) concluded that future studies should focus on more sophisticated study designs than ecological studies, more accurate estimation of temperature exposure during pregnancy, and more efficient methods to evaluate exposure windows, as well as associations between cold temperatures and birth outcomes.

Effects of *in utero* environmental exposures on fetal development (and subsequently, future health) may require exposure during specific phases of development, resulting in distinct time windows of vulnerability during gestation (Barr et al. 2000). Identifying windows of vulnerability to an environmental exposure may shed light on potential mechanisms of effect. Several studies have evaluated trimester-specific associations between temperature and birth weight [see review by Chersich et al. (2020) and (Lawrence et al. 2021; Yitshak-Sade et al. 2020)]. However, only some of these studies (Ha et al. 2017; Kloog et al. 2018; Sun et al. 2019; Yitshak-Sade et al. 2020) mutually adjusted for exposures during all three trimesters. This approach is recommended and can reduce confounding by correlated exposures among trimesters due to seasonality (Wilson et al. 2017). In addition, pregnancy trimesters are relatively broad time periods that may not align with the timing of physiological processes during pregnancy. To our knowledge, only one previous study (of 4,771 singleton births in France) estimated associations between gestational week–specific temperatures and term birth weight using distributed lag models (DLM) to overcome the challenge of studying multiple periods simultaneously (Jakpor et al. 2020).

The goal of the present study was to estimate associations between birth weight, an important marker of fetal growth, and extreme temperatures during pregnancy using high-resolution spatiotemporal estimates of exposures to evaluate associations during specific time windows of pregnancy [trimesters and gestational age (GA) weeks], based on data for 624,940 singleton term live births throughout Israel during the period 2010–2014.

Methods

Population

This study was based on a national birth cohort registry. Birth certificate data for all live births was obtained from the National Birth and Birth Defect Registry, which is operated by the Department of Mother and Child Health in the Public Health Service of the Israel Ministry of Health. Reporting of all live births to the Ministry of Interior and to the Ministry of Health is obligatory under Israeli law. Reports include infant birth outcomes, parental sociodemographic characteristics, and birth address. We extracted information on 714,599 live-born infants with estimated last menstrual period (LMP) dates from 1 January 2010 (when exposure data first become available) through 18 March 2014. Because our data set did not include births after 2014, we excluded births with an estimated LMP after 18 March 2014 ($n = 7{,}543$) to avoid fixed cohort bias (Neophytou et al. 2021; Strand et al. 2011a). After births without information on birth weight ($n = 105$) or birth address ($n = 13{,}180$) were excluded, there were 693,771 births. For our final main analysis, we restricted the population to 624,940 singleton term live births, after excluding multiple births and pregnancies with an unknown number of offspring ($n = 34{,}116$) and preterm deliveries (≤ 36 GA-weeks, $n = 52{,}187$).

Outcome

The National Birth and Birth Defect Registry reports GA in completed weeks and not the LMP date. The GA is based on the woman's history, in conjunction with a confirmatory ultrasound or, in the case of discrepancies between the stated date of the LMP and the ultrasound estimation, by an ultrasound performed before 20 GA-weeks. We calculated the estimated LMP date by the difference between the date of birth and the GA-weeks. Birth weight (BW) $<2{,}500$ g was classified as LBW. For our main analysis the outcomes were term birth weight (tBW): birth weight in infants >36 GA-weeks, and term LBW (tLBW): term births with birth weight $<2{,}500$ g.

Exposure Assessment

We geocoded birth addresses using interactive sessions and different geocoding services (HERE, Google) and the Israeli property mapping database (GZIRNET). We geocoded 80% of all birth addresses ($n = 500{,}651$) at the home or street level and geocoded the remaining 20% at the settlement level. These 20% were births to women living in small, nonurban settlements (e.g., local councils, villages, community settlements, kibbutzim) without street addresses, and births with missing data for the street address.

Data on hourly temperatures 2 m above ground level that were estimated at a 1-km^2 resolution were obtained from the Israel Meteorological Service (IMS). The IMS data are based on the INCA (Integrated Nowcasting through Comprehensive Analysis) system developed by the Austrian Meteorological Service (Haiden et al. 2011, 2010; Wang et al. 2017). The system considers physical effects like cooling or warming of the surface at night or day, topography, and mass conservation of wind and is capable of combining data from the Integrated Forecasting System (IFS) numerical weather prediction model, automated weather station data, rain radar data, and remote sensing information from satellites (though satellite data and rain radar data were not used for the present study).

Cross-validation ("leave-one-out") provides an assessment of system performance at locations without observations. Cross-validation for the current study was conducted using measured temperature data from five monitoring stations in 2012 and 2014. The root mean square error (RMSE), mean absolute error (MAE), and coefficient of determination (R^2) for the hourly measurements ranged between 0.72°C and 1.63°C, 0.58°C and 1.36°C, and 0.95 and 1.0, respectively (for scatterplots and summary statistics for hourly measurements from each station, see Figure S1 and Table S1).

We used the maternal residence address at birth, as well as the estimated LMP date, to assign estimates of daily temperature data (mean, minimum, and maximum temperatures) to each day of pregnancy. The spatial estimate of daily temperature corresponded to a specific 1-km^2 grid cell (for addresses geocoded at the home or street level) or the spatial mean of the settlement for women living in areas without street addresses. Daily temperature data were used to estimate average temperatures during each GA week, each trimester (first: GA >2–13 GA-weeks; second: 14–26 GA-weeks; third: 27 GA-weeks to birth), and the entire pregnancy (from GA-weeks >2 to birth).

Populations tend to be adapted to their local climates (via behaviors, built environment, etc.); hence, the same absolute temperature may have greater health effects on a population if that temperature represents a local extreme than if it is relatively common in the area (Hondula et al. 2015). Although Israel is a small country, it has a highly variable climate, determined by altitude, latitude, and proximity to the Mediterranean. We classified Israel into three climatic zones based on the Köppen classification (Beck et al. 2018): Mediterranean (Köppen classification Csa: temperate climate, dry and hot summer), Steppe/semi-arid (combining Köppen classifications BSh and BSk for areas characterized by hot and cold temperatures, respectively), and Desert/arid (combining Köppen classifications BWh and BWk, also characterized by hot and cold temperatures, respectively) (Figure S2A).

For each climatic zone, we converted average daily temperatures during each time period (GA week, trimester, entire pregnancy) to percentiles based on the distribution among all women in the cohort who resided in the climatic zone (see Tables S2 and S3 for pregnancy- and trimester-average distributions of daily mean, maximum, and minimum temperatures for study subjects in each climatic zone).

Our main analysis refers to exposure estimates that were calculated based on daily mean temperatures.

Statistical Analyses

Analysis by entire pregnancy and trimester. The potential nonlinear unadjusted associations between average mean daily temperature during pregnancy and tBW were estimated using generalized additive models (GAM) with temperature fitted with a thin plate regression spline, taking 9 as the dimension of the basis of the smooth term.

We used separate unadjusted GAMs for each climatic zone and included indicator variables for absolute temperatures (climatic zone-specific models) to estimate associations with absolute values of average daily mean temperatures (Figure S3A–C). To derive estimates for Israel as a whole, we converted average daily mean temperatures for each trimester and the entire pregnancy into climatic zone-specific percentiles based on the temperature distribution during each time period in each zone. Unadjusted GAM included only the indicator variables for zone-specific temperature percentiles (for country-wide models) (Figure S3D). Based on the patterns of associations, we categorized percentiles into deciles, using the decile spanning the 41st–50th percentiles as the reference, as suggested previously (Sun et al. 2019). Extreme temperatures were defined as cold temperatures equal to or below the 10th percentile and hot temperatures above the 90th percentile. Generalized linear models with normal distribution and identity link function were used to estimate associations [estimated differences in mean tBW with 95% confidence intervals (CIs)] between deciles of temperature over the entire pregnancy, and during each trimester, compared with the reference category. Similarly, we fitted generalized linear models with binomial family and logit link function to estimate odds ratios (ORs) and 95% CIs for tLBW. To avoid potential bias due to the use of separate models for each trimester, we modeled temperatures during all three trimesters in a single model (Neophytou et al. 2021; Wilson et al. 2017).

Covariates included in adjusted models were selected based on prior knowledge and directed acyclic graphs (DAGs) (Greenland et al. 1999; Textor et al. 2016) (Figure S4). The final multivariate models included the following covariates from birth records: newborn ethno-religious group (Sharabi 2018) as declared by the parents (categorized as Jewish, Muslim, Christian, or Druze), parity (reported as a continuous variable and categorized as 0, 1, 2–4, 5–8, >8 previous births), maternal age (categorized as ≤ 20, 21–29, 30–35, 36–40, ≥ 41 y), maternal origin (categorized as Israel, former USSR, America or Europe, Africa or Asia), maternal education [categorized according to the country-specific coding scheme provided by ISCED-2011 (International Standard Classification of Education) as high (ISCED 4–8: postsecondary nontertiary to doctoral or equivalent level), or medium and low (ISCED 01–3: preprimary to lower secondary education and upper secondary education)], maternal working status (working, yes or no). We also adjusted for month and year of LMP (modeled using indicator terms for each month and year). In addition, we adjusted for area-level socioeconomic status (SES; in tertiles) based on the geocoded birth address. The area-level SES variable published by the Israeli Central Bureau of Statistics (CBS) is calculated differently for small settlements and small statistical areas within cites. Therefore, we obtained data from the CBS on nine area-level socioeconomic variables that are comparable between the two geocoding levels and used principal-component analysis (PCA) to identify a single composite variable (factor) that captured 67% of the variance of the original variables (Figure S5; Table S4). Our models did not account for multiple births from the same mother.

Covariate data for maternal occupation were missing for 32.4% of births, with smaller numbers of missing observations for other variables (e.g., 0.1% of births for maternal age). We used complete-case analyses for our primary estimates, but we also estimated associations between the outcomes and exposures during the entire pregnancy, and by trimester, using multiple imputation to account for missing covariate data and evaluate potential bias from the complete-case approach. We imputed five data sets using multiple imputation models that were more general than the analyses models and included the outcomes, the variables related to the missingness, and auxiliary variables that were associated with the outcome and the exposure (Azur et al. 2011; White et al. 2011). Detailed information regarding the imputation process and a list of the variables used is provided in Supplemental Material, "Description of the Imputation Procedure."

Analysis by GA-weeks. Distributed lag nonlinear models (DLNM) were used to investigate potential windows of vulnerability. Because the minimum gestational age of term births was 37 GA-weeks, we fitted all weekly exposure estimates, from GA-weeks greater than 2 to 36 GA-weeks (34 lags) using one model.

To estimate the effect of temperature on the outcomes in the country as a whole, we first converted absolute values of average daily mean temperatures to percentiles based on the climatic zone-specific temperature distribution for eligible births to mothers living in each zone. We then used the dlnm R package (Gasparrini 2011) to estimate associations between the outcomes and temperature percentiles during each GA-week. The lag-response function was modeled as a natural spline with equidistant knots and the degree of freedom (between 2 and 6) that minimized the model AIC. The exposure–response function was modeled first as a continuous variable using a cubic regression spline with five equidistant internal knots. To provide more stable estimates, the exposure–response function was subsequently modeled as a categorical variable using indicator terms for each decile of the temperature distribution, with the 41st–50th percentile category as a common reference. We adjusted for the same covariates used in models of entire pregnancy- and trimester-average temperatures and performed complete-case analyses. R code used to derive temperature percentiles and run DLNM models for categorical percentiles is provided in Supplemental Material ("DLNM Syntax for R").

A priori statistical significance was defined as $p < 0.05$. R (version 3.6.1; R Development Core Team) and SPSS 25 (version 25.0; IBM SPSS Statistics for Windows) statistical software were used for all the analyses described above.

Further Analyses

Evaluation of the associations based on the geocoding level and by urbanicity level. Potential modification by urbanicity (urban, rural, or semirural settlement, based on 20 categories of settlement type) (Rebhun and Brown 2015) and geocoding level

Table 1. Characteristics of singleton term live births in Israel during the period 2010–2014 for the entire cohort ($n = 624{,}940$), and for births exposed to extreme average daily mean temperatures during pregnancy (at or below the 10th percentile or above the 90th percentile of the distribution in the climate zone of the residence at birth). Data are reported as counts (%) or means ± SD.

Variables	All population	Exposed to cold (≤10th)	Exposed to heat (>90th)
Total singleton term births	624,940	62,495	62,492
Information from birth certificates			
Term low birth weight (tLBW)	16,860 (2.7%)	1,452 (2.3%)	2,196 (3.6%)
Mean birth weight (g)	3,302 (±430)	3,286 (±433)	3,255 (±435)
Gestational age (wk)	39.4 (±1.2)	39.3 (±1.3)	39.1 (±1.2)
Newborn ethno-religious group			
Jewish	471,457 (78.0%)	42,069 (68.7%)	55,265 (91.9%)
Muslim	116,155 (19.2%)	15,047 (24.6%)	4,527 (7.5%)
Christian	7,645 (1.3%)	1,089 (1.8%)	225 (0.4%)
Druze	9,087 (1.5%)	3,060 (5.0%)	118 (0.2%)
Unknown	20,596	1,227	2,357
Newborn sex			
Male	319,611 (51.2%)	32,182 (51.5%)	32,023 (51.2%)
Female	305,230 (48.8%)	30,294 (48.5%)	30,461 (48.8%)
Unknown	99	16	8
Parity			
0	184,718 (29.7%)	17,255 (28.0%)	19,477 (31.2%)
1	167,069 (26.9%)	14,708 (23.9%)	17,905 (28.7%)
2–4	217,445 (35.0%)	22,255 (36.2%)	20,917 (33.5%)
5–8	44,916 (7.2%)	6,216 (10.1%)	3,567 (5.7%)
>8	7,035 (1.1%)	1,095 (1.8%)	508 (0.8%)
Unknown	3,757	963	118
Year of LMP			
2010	143,240 (22.9%)	10,848 (17.4%)	27,211 (43.5%)
2011	147,580 (23.6%)	26,924 (43.1%)	1,272 (2.0%)
2012	148,595 (23.8%)	10,089 (16.1%)	15,933 (25.5%)
2013	152,565 (24.4%)	13,906 (22.3%)	11,478 (18.4%)
2014	32,960 (5.3%)	725 (1.2%)	6,598 (10.6%)
Month of LMP			
January	65,635 (10.5%)	1,192 (1.9%)	7,191 (11.5%)
February	58,446 (9.4%)	1,079 (1.7%)	18,250 (29.2%)
March	57,994 (9.3%)	1,173 (1.9%)	18,287 (29.3%)
April	48,350 (7.7%)	980 (1.6%)	8,749 (14.0%)
May	49,702 (8.0%)	1,874 (3.0%)	2,115 (3.4%)
June	47,010 (7.5%)	4,259 (6.8%)	1,194 (1.9%)
July	47,443 (7.6%)	7,777 (12.4%)	1,075 (1.7%)
August	46,115 (7.4%)	11,341 (18.1%)	1,033 (1.7%)
September	46,829 (7.5%)	12,669 (20.3%)	1,067 (1.7%)
October	51,181 (8.2%)	11,786 (18.9%)	1,104 (1.8%)
November	51,966 (8.3%)	6,912 (11.1%)	1,094 (1.8%)
December	54,269 (8.7%)	1,450 (2.3%)	1,333 (2.1%)
Maternal marital status			
Married	584,756 (93.7%)	60,014 (96.2%)	57,354 (91.8%)
Unmarried	39,583 (6.3%)	2,394 (3.8%)	5,100 (8.2%)
Unknown	601	84	38 (0.1%)
Maternal origin			
Israel	516,678 (83.5%)	51,496 (84.5%)	50,667 (81.3%)
Former USSR	56,404 (9.1%)	3,619 (5.9%)	7,240 (11.6%)
America or Europe	29,769 (4.8%)	4,464 (7.3%)	2,617 (4.2%)
Africa or Asia	16,170 (2.6%)	1,385 (2.3%)	1,805 (2.9%)
Unknown	5,919	1,528	163
Maternal age (y)	30.1 (±5.6)	29.0 (±5.8)	30.7 (±5.4)
≤20	18,207 (2.9%)	3,056 (4.9%)	1,214 (1.9%)
21–29	277,084 (44.3%)	32,021 (51.2%)	24,875 (39.8%)
30–35	216,320 (34.6%)	18,104 (29.0%)	23,714 (37.9%)
36–40	93,146 (14.9%)	7,500 (12.0%)	10,551 (16.9%)
≥41	20,108 (3.2%)	1,800 (2.9%)	2,135 (3.4%)
Unknown	75	11	3
Maternal education – ISCED-2011 (y)	14.2 (±2.5)	13.8 (±2.4)	14.4 (±2.5)
Low (≤9)	1,894 (0.4%)	365 (1.0%)	89 (0.2%)
Medium (10–12)	188,873 (43.6%)	17,668 (47.5%)	18,816 (40.5%)
High (≥12)	242,490 (56.0%)	19,136 (51.5%)	27,503 (59.3%)
Unknown	191,683	25,323	16,084
Maternal working status			
Not working	120,138 (28.7%)	16,148 (41.9%)	7,920 (18.6%)
Working	298,235 (71.3%)	22,435 (58.1%)	34,605 (81.4%)
Unknown	206,567	23,909	19,967

Table 1. (*Continued.*)

Variables	All population	Exposed to cold (≤10th)	Exposed to heat (>90th)
Information based on address			
Climatic zones (based on Köppen classification)			
Steppe, semi-arid, hot (BSh) and cold (BSk)	56,066 (9.0%)	5,606 (9.0%)	5,606 (9.0%)
Arid, desert, hot (BWh) and cold (BWk)	6,166 (1.0%)	616 (1.0%)	616 (1.0%)
Temperate, dry and hot summer (Csa)	562,708 (90.0%)	56,270 (90.0%)	56,270 (90.0%)
Area-level socioeconomic factor	0.0 (±1.0)	−0.4 (±1.0)	0.3 (±1.0)
Low (tertile1)	207,560 (33.3%)	30,305 (48.6%)	12,180 (19.5%)
Medium (tertile 2)	207,506 (33.3%)	18,763 (30.1%)	23,693 (37.9%)
High (tertile 3)	207,615 (33.3%)	13,247 (21.3%)	26,591 (42.6%)
Unknown	2,259	177	28
Urbanicity level			
Rural or semirural	130,591 (20.9%)	12,354 (19.8%)	7,178 (11.5%)
Urban	494,349 (79.1%)	50,138 (80.2%)	55,314 (88.5%)
Geocoding level			
Settlement level	124,289 (19.9%)	6,663 (10.7%)	4,828 (7.7%)
Home or street level	500,651 (80.1%)	55,829 (89.3%)	57,664 (92.3%)

Note: ISCED, International Standard Classification of Education; LMP, last menstrual period; SD, standard deviation; tLBW, term low birth weight (births >36 gestational age weeks with birth weight <2,500 g).

(home- or street-level vs. settlement level) was assessed by stratifying on these variables and comparing estimated effects.

Natural regions. In addition to the three climatic zones, Israel is classified by the CBS into 51 natural regions that are as uniform as possible with regard to physical structure, climate zone, and land use and in terms of the demographic, economic, and cultural characteristics of the population. Therefore, we repeated analyses of average daily mean temperatures during pregnancy using centiles of exposure for 49 natural regions (two natural regions were merged due to small numbers) based on the temperature distribution for births in each region.

Evaluation of the associations based on the daily maximum and minimum temperature. We further explored whether patterns of associations with average daily maximum and minimum temperatures during pregnancy were similar to patterns of associations with daily mean temperature during pregnancy. As for the primary analysis, we used climatic zone-specific temperature distributions to define exposure centiles.

Evaluation of the associations for all live births. Although GA may be a causal intermediate between ambient temperature and birth weight, we restricted our main analysis to term births to facilitate assessment of potential windows of vulnerability (Delbaere et al. 2007; VanderWeele et al. 2012). However, we repeated analyses of pregnancy average daily mean temperatures and the outcomes among all live births (including preterm births and multiple births) using temperature centiles calculated for each climatic zone based on distributions among all live births.

Ethical approval. All methods were performed in accordance with the relevant guidelines and regulations. Informed consent was not necessary (no contact with study subjects; the use of protocols to protect confidentiality and anonymity). The study was approved by the Ethics Committee of the Israeli Ministry of Health. Approvals from the head of Public Health Services as well as from the legal advisor in the Israeli Ministry of Health and the Ministry of Interior were also obtained.

Results

Descriptive Analysis

Our study population comprised singleton term live births in Israel with calculated LMP from 1 January 2010 to 18 March 2014. This population included 624,940 infants born during the period 17 September 2010–31 December 2014. Of these, 2.7% were classified as tLBW (Table 1). The proportion of tLBW was lower among those categorized as exposed to extreme cold (2.3%) but was higher among those exposed to extreme heat (3.6%), based on the average daily mean temperature during pregnancy (≤10th or >90th percentile for the climatic zone of the maternal residence at birth, respectively). Mean birth weight for infants exposed *in utero* to heat was slightly lower [mean ± standard deviations (SD) 3,255 g (±435)] than that of the overall population [3,302 g (±430)] and to those exposed to cold *in utero* [3,286 g (±433)]. Similarly, average GA were lower for births exposed to heat, compared with the overall population [39.1 (±1.2) vs. 39.4 (±1.2), respectively], whereas there was barely any difference for births exposed to cold [39.3 (±1.3)]. As expected, there were differences in the distribution of LMP months between those exposed to cold or heat. The year 2010 was the hottest year, and 2011 was the coldest (Yosef et al. 2019). Consequently, 44% of the births exposed to heat were with LMP year at 2010 (compared with 23% of the total population and 17% of births exposed to cold), and 43% of all births exposed to cold were with LMP year at 2011 (compared with 24% of the total population and only 2% of the births exposed to heat). Among those exposed to heat, in comparison with the total population, the proportion of unmarried mothers was higher (8.2% vs. 6.3%, respectively), mothers were more likely to have worked (81% vs. 71%, respectively), and they were more likely to live in an area in the highest area-level SES tertile (43% vs. 33%) and more likely to live in urban areas (89% vs. 79%, respectively). Among newborns exposed to cold, in comparison with the total population, the proportion of unmarried mothers was lower (3.8%), mothers were less likely to have worked during pregnancy (58%) and were more likely to live in an area in the lowest area-level SES tertile (49% vs. 33%, respectively). Parents of newborns exposed to heat were more likely to classify their child's ethno-religious group as Jewish (92%) and less likely to classify their child as Muslim (7.5%) than parents of children in the overall population (78% and 19%, respectively) and parents of children exposed to cold (69% and 25%, respectively.)

Analysis by Entire Pregnancy and Trimesters

Unadjusted GAMs of tBW and daily mean temperatures averaged over the entire pregnancy in each of the three climatic zones (Figure S3A–C), and of associations between tBW and zone-specific temperature percentiles for all three zones combined (Figure S3D), indicated inverse U-shaped associations, such that the coldest and warmest temperatures were associated with lower term birth weights than were temperatures near the middle of each distribution.

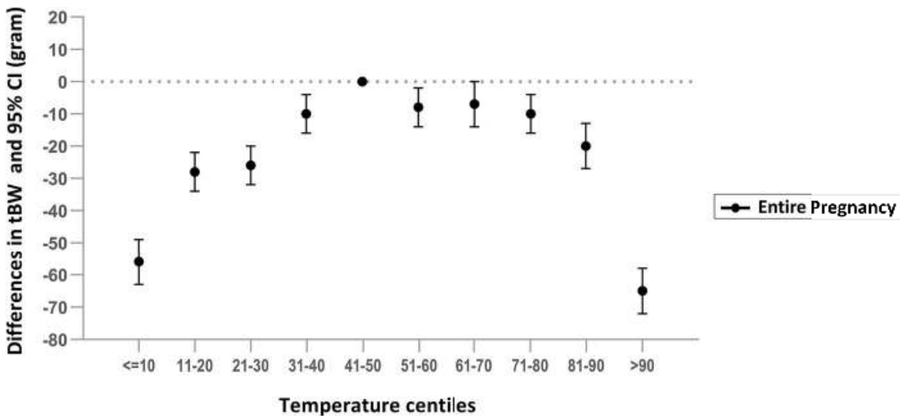

Figure 1. Estimated differences in mean tBW (g) and 95% CI according to climate zone-specific centiles of average daily mean temperature during pregnancy relative to the reference category (41st–50th centile) among singleton term live births in Israel during the period 2010–2014. Estimates were derived using a generalized linear model (normal distribution and identity link function) adjusted for newborn ethno-religious group, parity, maternal age, maternal marital status, maternal origin, maternal occupation, maternal education, year and month of LMP, and area-level SES. Complete case analysis, $n = 370{,}691$. See Table S5 for corresponding numeric data and estimates based on unadjusted models and models based on imputed covariate data ($n = 624{,}940$) and Table S2 for absolute temperatures corresponding to centile cut points for each climatic zone. Note: CI, confidence intervals; LMP, last menstrual period; SES, socioeconomic status; tBW, term mean birth weight (mean birth weight among births >36 GA-weeks).

The inverse U-shaped pattern was also evident based on adjusted associations between tBW and average temperature deciles for the pregnancy as a whole ($n = 370{,}691$ for the complete-case analysis), with an estimated mean decrease in tBW of 56 g (95% CI: –63 g, –50 g) for temperatures equal to or below the 10th percentile compared with average temperatures in the 41st–50th percentile range, and an estimated mean decrease of 65 g (95% CI: –72 g, –58 g) for temperatures above the 90th percentile compared with the reference range (Figure 1; Table S5). Unadjusted estimates and estimates based on the imputed data set were very similar to the estimates based on the complete case analyses (Table S5).

Trimester-specific associations between temperature deciles and tBW also showed inverse U-shaped patterns, with the strongest associations estimated for extreme temperatures during the third trimester (adjusted estimates relative to the 41st–50th percentile range of –46 g; 95% CI: –55 g, –38 g for temperatures ≤10th percentile, and –51 g; 95% CI: –59 g, –43 g for temperatures >90th percentile) (Figure 2; Table S6). Inverse associations between tBW and the coldest and warmest temperatures were also significant for the first and second trimesters but were weaker than corresponding estimates for the third trimester and close to the null for intermediate temperature deciles, particularly for the first trimester. Trimester-specific estimates based on unadjusted models and models using imputed data were generally consistent with the adjusted model estimates (Table S6).

Associations between tLBW and entire-pregnancy average temperature deciles were also strongest for the coldest and hottest temperatures relative to the 41st–50th percentile reference range, with adjusted ORs of 1.35 (95% CI: 1.22, 1.49) for temperatures ≤10th percentile and 1.58 (95% CI: 1.43, 1.74) for temperatures >90th percentile (Figure 3; Table S5). Unadjusted estimates and estimates based on the imputed data were similar to the primary model estimates (Table S5).

Trimester-specific associations between temperature deciles and tLBW showed a U-shaped pattern for third trimester exposures, with adjusted ORs relative to the 41st–50th percentile reference range of 1.26 (95% CI: 1.12, 1.43) for temperatures ≤10th percentile and 1.65 (95% CI: 1.47, 1.86) for temperatures >90th percentile (Figure 4; Table S6). For first trimester exposures,

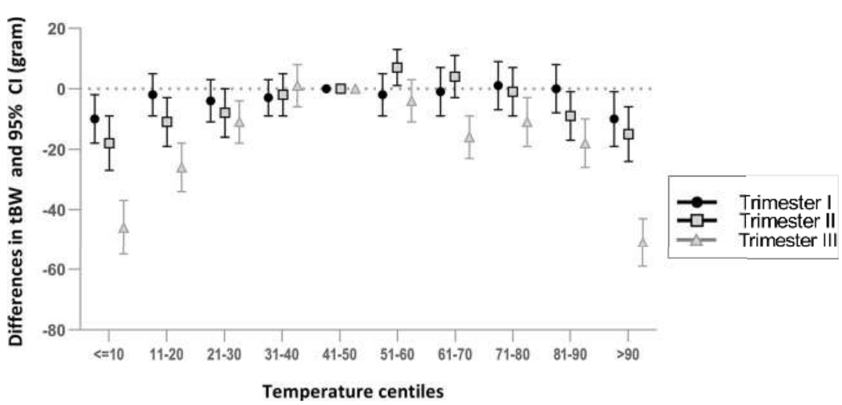

Figure 2. Estimated differences in mean tBW (g) and 95% CIs according to climatic zone-specific centiles of average daily mean temperature during each trimester relative to the reference category (41st–50th centile) among singleton live births in Israel during the period 2010–2014. Estimates were derived using a generalized linear model (normal distribution and identity link function) that was mutually adjusted for exposures during all trimesters and for newborn ethno-religious group, parity, maternal age, maternal marital status, maternal origin, maternal occupation, maternal education, year and month of LMP, area-level SES. Complete case analysis, $n = 370{,}691$. See Table S6 for corresponding numeric data and estimates based on unadjusted models and models based on imputed covariate data ($n = 624{,}940$). See Table S2 for absolute temperatures corresponding to centile cut points for each climatic zone. Note: CI, confidence interval; LMP, last menstrual period; SES, socioeconomic status; tBW, term mean birth weight (mean birth weight among births >36 GA-weeks).

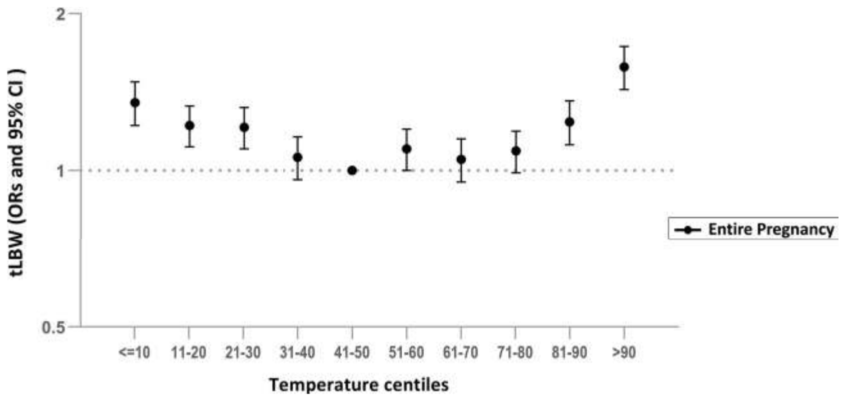

Figure 3. Adjusted ORs and 95% CIs for tLBW according to climate zone-specific centiles of average daily mean temperature during pregnancy relative to the reference category (41st–50th centile) among singleton term live births in Israel during the period 2010–2014. Estimates were derived using a generalized linear model (binomial family and logit link function) adjusted for newborn ethno-religious group, parity, maternal age, maternal marital status, maternal origin, maternal occupation, maternal education, year and month of LMP, and area-level SES. Complete case analysis, $n = 370,691$. See Table S5 for corresponding numeric and estimates based on unadjusted models and based on imputed covariate data ($n = 624,940$). See Table S2 for absolute temperatures corresponding to centile cut points for each climatic zone. Note: CI, confidence interval; LMP, last menstrual period; OR, odds ratio; SES, socioeconomic status; tLBW, term low birth weight (births >36 gestational age weeks with birth weight <2,500 g).

temperatures above the 90th percentile were significantly associated with tLBW (adjusted OR 1.14; 95% CI: 1.00, 1.13), but associations with lower temperatures varied around the null, without a clear pattern. Model estimates for tLBW and temperatures during the second trimester indicated weak nonsignificant positive associations with extreme temperatures [ORs of 1.06; (95% CI: 0.94, 1.19) and 1.06 (95% CI: 0.94, 1.20) for temperatures ≤10th and >90th percentiles, respectively] and a significant inverse association for temperatures in the 50th–60th percentile range (OR 0.89; 95% CI: 0.81, 0.98). Unadjusted trimester-specific ORs and estimates based on imputed data were generally consistent with the adjusted model estimates (Table S6).

Analysis by GA-Weeks

3D plots of the exposure–lag-response associations between the outcomes and GA-week-specific temperature centiles are provided for completeness though they are difficult to interpret (Figure S6).

DLNM estimates of associations between tBW and cold temperatures (≤10th percentile) during each GA-week (relative to temperatures in the 41st–50th percentile range) suggest a consistent trend from null associations early in pregnancy to stronger inverse associations over time, with the strongest association with cold temperatures found during GA-week 36 (adjusted estimate –2.9 g; 95% CI: −6.5 g, 0.7 g) (Figure 5; Table S7). Unadjusted associations between cold and tBW were also inverse (indicating lower mean tBW) later in pregnancy, though estimates did not show a consistent decline from the null until approximately GA-week 25 (Table S7). Associations between tBW and GA-week-specific exposures to temperatures above the 90th percentile were inverse during the GA-weeks 3–9 and 19–35, with the strongest associations estimated for hot temperatures during GA-week 3 (–3.8 g; 95% CI: –7.1 g, –0.4 g) and during GA-weeks 26–27 (for GA-week 26, –2.6 g; 95% CI: –4.6 g, –0.5 g) (Figure 5; Table S7). Unadjusted estimates were consistently inverse until approximately GA-week 35, with the strongest associations observed during GA-weeks 23–26 (for GA-week 26, –2.7 g; 95% CI: –4.1 g, –1.2 g) (Table S7).

Associations between tLBW and GA-week-specific temperatures equal to or below the 10th percentile (relative to the 41st–50th percentile) were close to the null throughout pregnancy, both before and after adjustment (Figure 6; Table S8). Adjusted

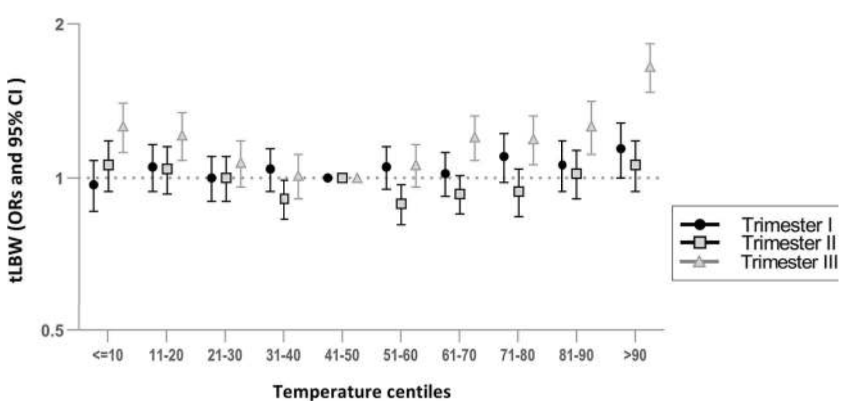

Figure 4. Adjusted ORs and 95% CI for tLBW according to climate zone-specific centiles of average daily mean temperature during each trimester relative to the reference category (41st–50th centile) among singleton term live births in Israel during the period 2010–2014. Estimates were derived using a generalized linear model (binomial family and logit link function) that was mutually adjusted for exposures during all trimesters and for newborn ethno-religious group, parity, maternal age, maternal marital status, maternal origin, maternal occupation, maternal education, year and month of LMP, and area-level SES. Complete case analysis, $n = 370,691$. See Table S6 for corresponding numeric and estimates based on unadjusted models and based on imputed covariate data ($n = 624,940$). See Table S2 for absolute temperatures corresponding to centile cut points for each climatic zone. Note: CI, confidence interval; LMP, last menstrual period; OR, odds ratio; SES, socioeconomic status; tLBW-term low birth weight (births >36 gestational age weeks with birth weight <2,500 g).

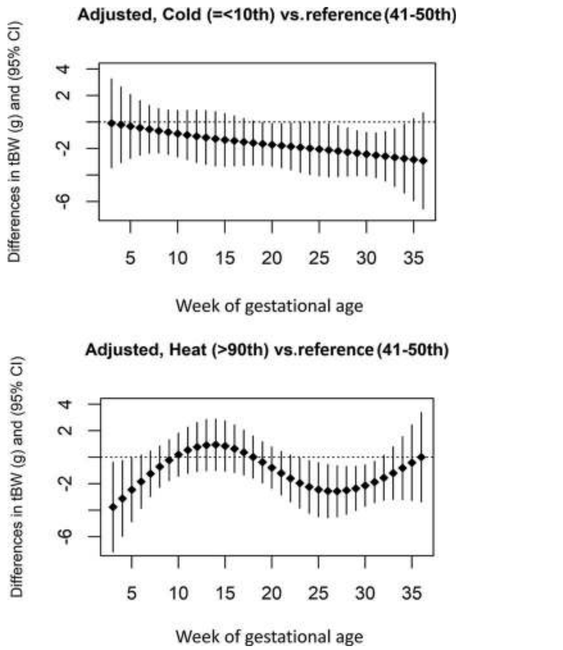

Figure 5. Estimated differences in mean tBW(g) and 95% CI associated with extreme cold and hot daily mean temperatures (≤10th or >90th the percentile for each climate zone, respectively, relative to the 41st–50th centile) during each gestational age week among singleton live births in Israel during the period 2010–2014. Estimates were derived using DLNM (lag-response function modeled as a natural spline with equidistant knots and 2–6 degrees of freedom, exposure–response function modeled using indicator terms for each decile of the temperature distribution). Models were adjusted for newborn ethno-religious group, parity, maternal age, maternal marital status, maternal origin, maternal occupation, maternal education, year and month of LMP, and area-level SES. Complete case analysis, $n = 370{,}691$. See Table S7 for corresponding numeric data and unadjusted estimates ($n = 624{,}940$). Note: CI, confidence interval; DLNM, distributed lag nonlinear models; LMP, last menstrual period; SES, socioeconomic status; tBW-term mean birth weight (mean birth weight among births >36 gestational age weeks).

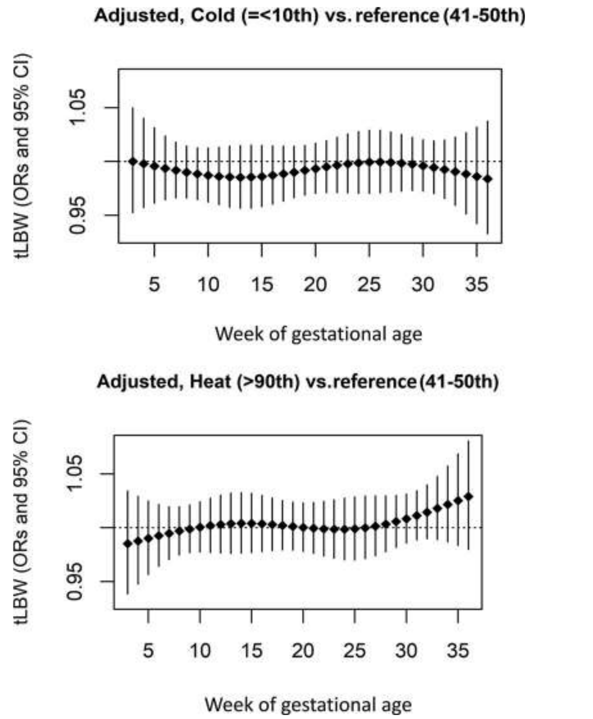

Figure 6. Adjusted ORs and 95% CI for tLBW in association with extreme cold and hot daily mean temperatures (≤10th or >90th the percentile for each climate zone, respectively, relative to the 41st–50th centile) during each week of gestational age among singleton live births in Israel during 2010–2014. Estimates were derived using DLNM (lag–response function modeled as a natural spline with equidistant knots and 2–6 degrees of freedom, exposure–response function modeled using indicator terms for each decile of the temperature distribution). Models were adjusted for newborn ethno-religious group, parity, maternal age, maternal marital status, maternal origin, maternal occupation, maternal education, year and month of LMP, and area-level SES. Complete case analysis, $n = 370{,}691$. See Table S8 for corresponding numeric data and unadjusted estimates ($n = 624{,}940$). Note: CI, confidence interval; DLNM, distributed lag nonlinear models; LMP, last menstrual period; OR, odds ratio; SES, socioeconomic status; tLBW, term low birth weight (births >36 gestational age weeks with birth weight <2,500 g).

associations between tLBW and GA-week-specific temperatures above the 90th percentile were close to the null throughout pregnancy except for a weak nonsignificant association in late pregnancy (for week 36, OR 1.03; 95% CI: 0.98, 1.08). Unadjusted estimates indicated weak but significant positive associations between tLBW and temperatures >90th percentile during 8–20 and 31–36 GA-weeks (for GA-week 35, OR 1.04; 95% CI: 1.01, 1.07) (Table S8).

Further Analyses

Modification by urbanicity and geocoding levels. Similar to our main analysis, the pattern of associations between the centiles of entire pregnancy temperature and tBW and tLBW were inverse U-shape and U-shape relationships, respectively, for those living in urban and rural areas (Table S9) and for those with residences geocoded at the settlement level and home or street level (Table S10).

Natural regions. When estimated separately for the 49 natural regions in Israel (Figure S2B), the median, 10th, and 90th percentiles of average daily mean temperatures during pregnancy, for all births included in the analysis, ranged from 15.3°C–25.3°C, 13.2°C–22.5°C, and 18.0°C–28.5°C, respectively (Table S11). The natural regions better reflect the spatial distributions of temperature compared to the climatic zones. Consistent with the primary analysis that classified exposures using temperature distributions for the three climatic zones (Tables S5 and S6), associations between tBW and temperatures during the entire pregnancy were inverse U-shaped when temperature percentiles were based on distributions in each of the 49 natural zones (Table S12). However, associations with temperatures equal to or below the 20th percentile and above the 70th percentile (relative to temperatures in the 41st–50th percentile range for each natural region) were stronger than the corresponding estimates from the primary analysis, whereas associations with intermediate temperatures were closer to the null (Table S12). Associations between tBW and temperatures during the second and third trimesters followed a similar pattern, with stronger associations with lower and higher temperatures when based on natural zone-specific distributions than the corresponding estimates from the primary analysis. Consistent with the primary analysis, associations between tBW and temperatures during the first trimester were close to the null, though associations with colder temperatures were positive instead of inverse.

Associations between tLBW and natural region-specific temperature percentiles followed a similar pattern, with stronger associations for lower and higher temperatures during the entire pregnancy and the second and third trimesters (Table S12) in comparison with the corresponding estimates based on temperature distributions in the three climatic zones (Tables S5 and S6).

Evaluation of the associations based on the daily maximum and minimum temperature. Similar to the main exposure analysis, associations of entire pregnancy average temperature, calculated for the daily maximum and minimum temperatures, demonstrated similar patterns of associations with tBW and tLBW (Table S13).

Evaluation of the associations for all live births. When the study population was expanded to include all live births, 52,187 (7.5%) were preterm (<37 GA-weeks) and 31,777 (4.6%) were multiple births (Table S14). Generally, maternal characteristics were similar to the primary study population. As expected, average birth weight was lower relative to the primary population of singleton term births (3,213 g ± 525 g compared with 3,302 g ± 430 g), the proportion of LBW was higher (7.9% compared with 2.7%), and the average GA-weeks at birth were lower (39.0 ± 2.0 GA-weeks compared with 39.4 ± 1.2 GA-weeks).

Associations with daily mean temperature percentiles averaged over the entire pregnancy were similar to the main analysis, showing inverse U-shaped associations with birth weight and U-shaped associations with LBW (Table S15). However, associations with colder and hotter temperatures (vs. temperatures in the 41st–50th percentile range) were stronger for both outcomes. For example, adjusted estimates for mean birth weight in association with temperatures equal to or below the 10th percentile and above the 90th percentile were –142 g (95% CI: −150 g, −135 g) and –190 g (95% CI: −198 g, −183 g), respectively. Similarly, adjusted ORs for LBW were 2.10 (95% CI: 1.99, 2.22) for temperatures ≤10th percentile, and 2.73 (95% CI: 2.59, 2.88) for temperatures >90th percentile.

Discussion

In the current study, we estimated associations of term birth weight and tLBW with ambient temperatures over the course of the entire pregnancy, for each trimester, and for every GA-week, using spatiotemporal temperature exposure estimates for 624,940 singleton term live births in Israel during the period 2010–2014. Our main finding was that exposure to the highest average daily mean temperatures during the entire pregnancy and each trimester was associated with a higher odds of tLBW and lower mean tBW, in comparison with the reference category. For tLBW, associations with heat were stronger than associations with cold for all windows of exposure (entire pregnancy, trimesters, and individual GA-weeks). For tBW and heat (>90th percentile vs. 41st–50th percentile), associations were strongest for exposures during the third trimester, whereas GA-week-specific estimates suggested that heat during GA-weeks 3–9 and 19–34 was associated with lower birth weight, with the strongest association estimated for exposure to heat at 3 GA-weeks. tBW was inversely associated with cold (≤10th percentile vs. 41st–50th percentile) throughout most of pregnancy, with stronger associations for exposures later in gestation. tLBW did not appear to be associated with cold during any GA-week, but tLBW was associated with heat during GA-weeks 29–36, with the strongest association estimated for exposure to heat at GA-week 36. Patterns of associations between both outcomes and average temperatures during pregnancy were consistent with the main analysis when stratified by urbanicity and geocoding level, when estimated for average exposures based on daily minimum and maximum temperature percentiles (instead of daily mean temperature distributions), when exposures were classified based on temperature distributions in 49 natural regions (instead of 3 climatic zones), and when based on all live births, including preterm births and multiple births (instead of singleton term births only).

Comparing our findings with those from previous studies of temperature and birth weight is complicated by the different approaches used in each study and other methodological issues, such as controlling for GA. GA may be a causal intermediate linking extreme ambient temperatures and birth weight; if so, effect estimates that are adjusted for GA, restricted to term deliveries, or based on birth weight standardized to GA, will not represent the total effect of temperature on birth weight (Delbaere et al. 2007; VanderWeele et al. 2012) and this could explain some of the heterogeneity in results among previous studies. We excluded preterm deliveries because our primary aim was to evaluate time windows of vulnerability during 34 consecutive weeks of gestation and each trimester. When we expanded the study population to include all live births, the majority of additional births were preterm (76% of the added births, 7.5% of the population as a whole). As hypothesized, inverse associations between extreme average temperatures during pregnancy and birth weight were stronger, consistent with indirect effects of temperature on birth weight secondary to effects on the risk of preterm birth, in addition to direct effects of temperature on fetal growth independent of gestational age. Therefore we assume that associations estimated in our primary analysis of term births represent conservative estimates of the total effect of extreme temperatures on birth weight.

Geographic variation in the health effects of absolute temperatures may reflect adaptation and acclimatization to the local environment through the use of different building designs, interior temperature control (heating, cooling), behaviors (such as clothing type), and physiological adaptations (Hondula et al. 2015). Therefore, to characterize exposures to temperatures that better reflect local extremes, we converted absolute temperatures to percentiles based on regional temperature distributions. Our primary analysis used temperature distributions in three major climatic zones that may be less specific to local populations than temperature distributions in smaller regions. Associations with extreme temperature centiles were stronger when we repeated the analyses using temperature distributions in 49 natural zones, which suggests that using more localized percentiles may better capture etiologically relevant temperature exposures. Previous studies have estimated associations between pregnancy outcomes and average temperatures modeled as percentiles of temperature distributions within geographic and climatological regions (Sun et al. 2019) and hospital referral regions (Ha et al. 2017; Kloog et al. 2018). For example, Sun et al. reported that exposure to county-specific temperatures above the 90th percentile and below the 10th percentile vs. reference temperatures (the 40st–50th percentile category), were associated with 15 g (95% CI: −17 g, −13 g) and 6 g (95% CI: −8 g, −4 g) lower mean birth weights (standardized to an infant delivered at 40 weeks of gestation), respectively, among 29,597,735 singleton term live births born in 403 counties in the United States during the period 1989–2002 (Sun et al. 2019).

In our study, the strongest associations were observed during the third trimester for heat and cold. The three trimesters were adjusted simultaneously to reduce confounding by correlated exposures between trimesters due to seasonality (Wilson et al. 2017). The estimated changes in mean birth weight in association with temperatures during the first and second trimesters were quite small (∼10 g) and might not necessarily have clinical importance at the individual level but could be associated with a notable benefit at the population level (Doyle et al. 2006; Rose 2001). Previous studies that mutually adjusted for exposures during all three trimesters also reported stronger associations during the second and third trimesters vs. the first trimester (Ha et al. 2017; Kloog et al. 2018; Sun et al. 2019), whereas others (Yitshak-Sade et al. 2020) reported stronger associations with increased temperature during the first and third trimester, with the strongest association during the third trimester. Sun et al. (2019) reported that associations between birth weight and average temperatures during the second and third trimesters were similar to associations with average temperatures during the entire pregnancy, whereas associations with average temperatures during the first trimester were close to the null. Ha et al. (2017) reported that among 195,172 term infants from 12 U.S. sites, LBW was positively associated with exposure to low temperatures (<5th percentile) during the second and third trimester, and with exposure to high temperatures (>95th percentile) during the third trimester, in comparison with milder temperatures (defined as temperatures ranging from the 5th to the 95th percentiles). In a study of 56,141 singleton term live births in the southern part of Israel during the period 2004–2013, Kloog et al. (2018) reported nonsignificant associations between LBW and trimester-specific temperature quartiles (for the entire study area) based on mutually adjusted models, specifically, temperatures in the lowest quartile during the third trimester (OR = 1.17; 95% CI: 0.92, 1.49) and temperatures in the highest quartile during the second trimester (OR = 1.14; 95% CI: 0.92, 1.41), in comparison with the two intermediate quartiles. In a recent study of 640,659 singleton live births in the urban areas of Massachusetts during the period 2001–2011, Yitshak-Sade et al. (2020) reported significant associations between lower birth weight and exposure to higher temperatures, for all three trimesters, with the strongest associations observed during the third trimester. In the mutually adjusted models that included all other environmental and built environment exposures, the strongest associations were observed during the third trimester.

Pregnant women are a unique, vulnerable population affected by climate change (Kuehn and McCormick 2017; Zhang et al. 2017). The risk of "overheating" (experiencing high core body temperature) can occur during all stages of pregnancy due to hormonal changes, increased fat deposition, and associated decreases in the body surface-area-to-body-mass ratio, resulting in a reduced capacity to regulate body temperature (Rylander et al. 2013). Possible biological mechanisms and evidence from animal studies support the hypothesis that high temperatures may affect birth weight, gestational age, and development of the embryo (Bekkar et al. 2020). If sweating efficiency is inadequate, the body cannot cool down and can become dehydrated. With dehydration, uterine blood flow to the fetus can decrease and induce labor, often prematurely. In addition, heat exposure may also damage cells, the placenta, and the vascular system, resulting in insufficient fetal nutrition, increased risk of congenital malformations (Agay-Shay et al. 2013; Auger et al. 2017; Bennett 2010) and increased risk of stillbirths (Bekkar et al. 2020). However, exact mechanisms are uncertain (Konkel 2019). Less is known about possible mechanisms linking cold exposure to fetal growth. Cold ambient temperature causes veins and arteries to narrow and blood to become more viscous, increasing cardiac workload and leading to many of the same cardiovascular stresses as heat (Seltenrich 2015). It is biologically plausible that this may lead to oxidative stress and alterations in placental oxidative capacity that can ultimately lead to reduced fetal growth (Sun et al. 2019).

The identification of susceptible windows during pregnancy may clarify underlying mechanisms and potential strategies to reduce risks in pregnant women exposed to extreme temperatures. In our study, estimates based on adjusted DLNM of mean tBW suggested a potential window of vulnerability to cold from 3 to 36 GA-weeks, with the strongest association during GA-week 36, and potential windows of vulnerability to heat from GA-weeks 3–9 and 19–34, with the strongest association at GA-week 3. For tLBW, associations with cold temperatures were close to the null during all weeks. Adjusted ORs for heat and tLBW were not significant for exposure during any week, though the observed pattern suggests possible adverse associations after GA-week 28. Only two previous studies evaluated associations using distributed lag linear models (Jakpor et al. 2020) and nonlinear models (Wu et al. 2018). Wu et al. (2018) evaluated weekly specific temperature and fetal growth using DLNM method; however, they treated temperature as a confounder to air pollution and did not report the associations. A study of 4,771 singleton births in France also estimated associations between week-specific temperature exposures and tBW using a distributed lag model (Jakpor et al. 2020). A 5°C increase in mean temperature was not significantly associated with tBW for exposure during any GA-week, but results suggested possible associations between increased temperatures after GA-week 20 and lower mean birth weight. In contrast with our study, Jakpor et al. modeled temperature as a continuous (linear) variable, and adjusted their models for GA. In addition, they used an absolute exposure contrast vs. using relative temperature contrasts.

Adverse associations between heat during the third trimester and birth weight are plausible. Fetal weight gain occurs mainly in the third trimester (Kiserud et al. 2018), during which adverse exposures may lead to fetal growth retardation and weight loss. The evidence of adverse associations between birth weight and heat during the first weeks of gestation need further investigation. A previous study suggested that associations between poor first-trimester growth and lower birth weight may be caused by a suboptimal environment during the first trimester that limits subsequent fetal growth, or to a disorder of the placenta that is manifested throughout pregnancy (Smith et al. 1998).

The analysis by GA-weeks can provide important insights but it is challenging, because a large number of highly correlated variables (i.e., temperature in 34 consecutive weeks) is introduced into the model. Constraining the form of the weekly estimates with splines reduces precision problems, but problems associated with collinearity can still remain. In some instances analyses may suggest that some periods are more important than others when this is not the case (Basagaña and Barrera-Gómez 2021). Our large sample size reduces such problems, but still, weekly estimates should be interpreted with caution. Weekly estimates moved within a narrow range, and it was difficult to pinpoint with certainty an exact, specific period of increased estimated effects. Estimates from the DLNMs, models by trimester and models for the entire pregnancy cannot be directly compared because the temperature was averaged over different periods (entire pregnancy, trimesters, and GA-weeks) and further categorized to centiles. It is important to note that DLNM can also be used to calculate cumulative estimates over any period of choice. We believe that reporting estimates at different temporal levels can provide a more comprehensive approach to examining the underlying relationship between ambient exposures and pregnancy outcomes, rather than just focusing on one level, and recommend doing so in future studies. In our study, we observed the greatest discrepancies in associations between temperatures equal to or below the 10th percentile (vs. the 41st–50th percentile) and tLBW, which were positive and statistically significant for cold during the entire pregnancy and the third trimester but were essentially null for all weeks of gestation based on DLNMs. A similar discrepancy was also described by Jakpor et al. (2020), and this needs to be investigated in future studies.

One major advantage in our study is the use of a fine resolution scale (1-h and 1-km^2 resolution) for our spatiotemporal model for the temperature exposure, which may reduce exposure misclassification. Fewer than 20% (19.9%) of pregnancies in our study lacked accurate geocoding; therefore the spatial resolution of the temperature data was reduced for this subgroup. In our stratified analysis by geocoding level, effect estimates were similar for births geocoded at the settlement level vs. the home level or street level. Using the INCA model allowed us to estimate associations between the outcomes and average daily maximum and minimum temperatures during pregnancy, as well as average daily mean temperatures; the patterns of associations were similar for all three of the temperature metrics used. We plan to compare results using different spatiotemporal models in future research.

Observational epidemiological studies (in comparison with interventional or experimental studies) face considerable challenges of biases and confounding, as well as limited data availability. The current study is based on birth certificates and had the advantage of using a large number of birth records, thus reducing the uncertainties (larger standard errors) and selection bias more common in studies with a small sample size. A limitation of this type of study is that birth records are restricted to routinely recorded information, and thus it may not be possible to fully control for confounding variables. We adjusted for maternal education, occupation status, and area-level SES, though maternal occupation and education variables had a high percentage of missing data (up to 33.1%, resulting in 370,691 births with complete data for the primary analyses). We used multiple imputation to address this problem. This technique provides valid results under the missing at random (MAR) assumption (White et al. 2011). Associations were similar when estimated using complete-case analyses and imputed data set analyses, which suggests that using a complete case analysis for our primary analyses did not introduce selection bias. In our study, exposures were estimated based on the address reported at the time of delivery. A literature review revealed that up to 32% of mothers moved short distances during pregnancy (Bell and Belanger 2012). Residential mobility was found to be associated with errors in the estimates for air pollution and was associated with sociodemographic confounders (Hodgson et al. 2015). Findings from these previous studies may not apply to our population, and we were not able to assess residential mobility in our population. Personal activity patterns, such as time spent indoors vs. outdoors and time spent at work or home or the use of air conditioning and other methods for mitigating temperature, were not accounted for. We did not account for humidity or any other climatological variables and intend to incorporate these in our future studies. We also did not control for the correlation between siblings, which may affect the validity of our standard errors. However, we do not expect that properly accounting for siblings would change the study conclusions.

Conclusion

In this large, nationwide, retrospective cohort study of singleton term births in Israel during the period 2010–2014, consistent associations between extreme ambient temperature and mean birth weight and tLBW were observed, especially for exposure to heat during the second and third trimester. Due to climate change and the increase in the mean temperatures, public health adaptation strategies for climate change, on a national as well as on a community level, need to be developed. Furthermore, identifying windows of vulnerability to temperature can assist clinicians in constructing and refining the set of recommendations they already give to pregnant women.

Acknowledgments

This research was supported by the Israel Science Foundation (ISF) (grant no. 184/19).

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