Meteorological Conditions and Term Birthweight in the French EDEN-PELAGIE Consortium: Identifying Critical Exposure Windows Using Distributed Lag Models

Meteorological Conditions and Term Birthweight in the French EDEN-PELAGIE Consortium: Identifying Critical Exposure Windows Using Distributed Lag Models

by

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I have reviewed this thesis. It represents work done by the author under my supervision and guidance.

Faculty Supervisor's Signature

Abstract

Background/Aims

Heat stress during pregnancy may limit fetal growth, which has ramifications for health outcomes throughout the life course. However, current evidence on weather conditions and birthweight is mixed. This may be partly due to lack of temporal and spatial resolution in how exposures are measured and modelled. For example, prenatal weather exposure data are often obtained from monitoring stations (which may be sparse) and averaged over trimesters (which are fairly arbitrary time windows). We aim to clarify the impacts of mean temperature and relative humidity on term birthweight, by using a fine spatio-temporal model to assess temperature exposure and building distributed lag models to identify critical exposure windows during gestation. We also intend to investigate the role of weather variability by assessing the effects of standard deviation of temperature and relative humidity.

Methods

We analyzed data collected from a consortium of two French mother-child cohorts, EDEN and PELAGIE (n = 4771), between 2002 and 2006. Temperature exposure data were obtained from a satellite-based model with fine spatial resolution (1 km^2), and humidity data were obtained from Météo France monitors. Distributed lag models were constructed for term births, using weekly exposure data from the first 37 weeks of pregnancy. This analysis was also repeated with stratification by the sex of the infant. Results for each exposure (mean temperature, standard deviation of temperature, mean relative humidity, and standard deviation of relative humidity) were adjusted for the other exposures, gestational age, season and year of conception, recruitment center, and individual confounders.

Results

For standard deviation of temperature (1 °C increase), there was a critical exposure window between weeks 6 and 20, with a cumulative change in term birthweight of -65.2 g (95% CI: -101.9, -6.4). Upon stratification, the relationship between standard deviation of temperature and term birthweight was nonsignificant in girls, but in boys there was a critical exposure window from week 1 to 21 (-5.4 g, 95% CI: -10.7, -0.2). For mean humidity (5% increase), there was a critical exposure window between weeks 26 and 37, with a cumulative change in term birthweight of -28.2 g (95% CI: -49.2, -7.1). The critical exposure window occurred later and the association was stronger in boys (weeks 29 to 37; -37.3 g, 95% CI: -63.4, -11.1) than in girls (weeks 13 to

15; -5.4 g, 95% CI: -10.7, -0.2). There was no week with a statistically significant association between term birthweight and mean temperature or standard deviation of humidity.

Conclusions

We identified critical windows in gestation in which temperature variability and mean humidity were associated with decreased term birthweight. These windows varied by sex of the infant, suggesting possible differences in mechanism. Little is currently known about the impacts of temperature variability and humidity on fetal growth, and our findings indicate that more research is needed.

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Glossary of Abbreviations

AIC	Akaike information criterion
CI	Confidence interval
DLM	Distributed lag model
EDEN	*Etude des Déterminants pré et post natals du développement et de la santé de l'Enfant* (Study on the Pre- and Early Postnatal Determinants of Child Health and Development)
H	Mean relative humidity
ICAM-1	Intercellular adhesion molecule 1
IUGR	Intrauterine growth restriction
MODIS	Moderate Resolution Imaging Spectroradiometer
PELAGIE	*Perturbateurs Endocriniens: étude Longitudinale sur les Anomalies de la Grossesse l'Infertilité et l'Enfance* (Endocrine Disruptors: Longitudinal Study on Pathologies of Pregnancy, Infertility and Childhood)
SD	Standard deviation
SDH	Standard deviation of relative humidity
SDT	Standard deviation of temperature
T	Mean temperature

Introduction

Intrauterine growth restriction (IUGR), the failure of a fetus to reach its full growth potential, contributes significantly toward perinatal morbidity and mortality.[1] Even beyond the neonatal period, IUGR can have ramifications throughout the entire life course by increasing the risk of several cardiovascular and metabolic diseases.[2] A variety of maternal exposures during pregnancy have the potential to impact fetal growth, ranging from infections to stressful situations to environmental factors.[3,4] With climate change leading to rising average temperatures and volatile meteorological conditions, it is important to understand the impacts of temperature and humidity on health.

Reduced birthweight can be a manifestation of IUGR. Birthweight analyses can be particularly informative when limited to term births, so that reductions are clearly attributable to deficits in fetal growth rather than prematurity. However, the current evidence on temperature and birthweight is somewhat mixed.[5] Retrospective cohort studies conducted across the continental United States,[6] in the state of Massachusetts, USA,[7] in New York City, USA,[8] and in food-cropping communities in Kenya,[9] have found higher temperatures during pregnancy to be associated with decreased birthweight. Similarly, ecological studies by Matsuda et al. in Japan,[10] Wells and Cole across the globe,[11] Flouris et al. in Greece,[12] and Arroyo et al. in Madrid, Spain[13] have also linked hotter weather with decreased birthweight. A recent large retrospective study conducted in California by Basu et al.[14] found an association between increased long-term apparent temperature and term low birthweight (defined as <2500 g for births with gestational age between 37 and 44 weeks).

On the other hand, an ecological study of 19 African countries found an increase in birthweight with more hot days during pregnancy.[15] Also, retrospective cohort studies by Murray et al. in Northern Ireland[16] and Elter et al. in Marmara, Turkey[17] observed that lower temperatures in the second trimester may be linked with decreases in birthweight. Other studies have found that the direction of association varies depending on the trimester,[18] and some have reported no association at all between temperature and birthweight or low birthweight.[19–21]

Multiple reasons may account for the discrepancies between these findings, many of which stem from methodological differences. For instance, many studies have relied on temperature measurements taken from the nearest monitoring station, but spatial coverage can be sparse. This type of exposure error may bias effect estimates downwards, in certain cases.[22]

There have also been differences in the way temperature exposure is conceptualized. For example, while some have focused on heatwaves,[21] others have investigated daily minimum and maximum temperatures,[6,13,16] and several others have studied mean temperature over a given period.[19,20,23] Often temperature is averaged over the entire duration of gestation or over trimesters, which is somewhat arbitrary. There is currently no consensus on which periods of pregnancy might be particularly vulnerable to weather conditions, but these time windows are unlikely to fit neatly into trimesters. One recently developed strategy for addressing this problem is to build distributed lag models (DLMs), which may be used to identify critical windows in a data-driven way.[24] DLMs are suitable for studying time-varying associations, because they regress the outcome of interest on an exposure measured at intervals during the preceding time period (e.g. daily or weekly measurements).[25] Although this strategy has been applied to preterm birth[26,27] and low birthweight,[28] to our knowledge it has not been used to study the impact of meteorological conditions on term birthweight.

Besides differences in exposure assessment and analytical approach, location-specific differences in climate could lead to different patterns of effect (especially since acclimatization varies between populations).[29] The role of acclimatization is particularly noteworthy in the face of climate change, which may increase meteorological variability such that pregnant women cannot sufficiently acclimatize.[30] In their 2017 study on temperature anomalies and birth outcomes, Molina and Saldarriaga found that a temperature increase of one standard deviation over the local historical mean was associated with a decrease in birth weight.[31]

It is also worth considering the possible effects of other meteorological factors, such as humidity. Many studies have included humidity in models as a covariate, or studied the effect of heat index or apparent temperature (measures that reflect both temperature and relative humidity).[14,20] Since humidity limits the human body's ability to release heat, it can exacerbate the heat stress caused by high temperatures.[11] However, little is currently known about the possible effects of humidity itself on birth outcomes. A few studies have suggested that prenatal and postnatal humidity exposure could have an independent effect on DNA methylation; this raises the question of whether humidity may be directly linked to other health outcomes.[32,33]

In our study, we aim to clarify the impacts of mean temperature and relative humidity on term birthweight, by using distributed lag models to identify critical exposure windows during pregnancy. We also intend to investigate the role of meteorological variability by assessing the effects of standard deviation of temperature and relative humidity.

Methods

Study population

Data were obtained from a consortium of two French mother-child prospective cohorts, EDEN (**E**tude des **D**éterminants pré et post natals du développement et de la santé de l'**EN**fant) and PELAGIE (**P**erturbateurs **E**ndocriniens: étude **L**ongitudinale sur les **A**nomalies de la **G**rossesse, l'**I**nfertilité et l'**E**nfance). Both cohorts were formed to study the effects of prenatal exposures on child development and health, and their protocols have been described in detail elsewhere.[34,35] Figure 1 illustrates the composition of our study population.

For the EDEN cohort, 2,002 pregnant women were enrolled in the cities of Poitiers and Nancy between 2003 and 2006. They were recruited from the prenatal clinics of university hospitals before the 24th week of amenorrhea. Women were not included if they had multiple gestation, diabetes diagnosed before pregnancy, French illiteracy, or plans to move away from the area within three years.

The PELAGIE study recruited 3,421 pregnant women from three departments in the region of Brittany (Ille-et-Vilaine, Côtes d'Armor, and Finistère), from 2002 to 2006. These women were enrolled at prenatal care visits with obstetrician-gynecologists or ultrasonographers. The primary inclusion criteria were submitting the initial questionnaire before the 19th week of amenorrhea, and being pregnant at that time. For consistency with the EDEN cohort, women with multiple gestation were excluded from this study population. Similarly, women with a pre-existing diagnosis of diabetes were excluded.

After accounting for attrition, non-livebirths, and multiple gestation and pre-existing maternal diabetes (in PELAGIE), there were 1,907 children enrolled in EDEN and 3,322 children enrolled in PELAGIE. Mothers with gestational diabetes were excluded from our study population, as were mothers with gestational hypertension. Preterm births were also excluded from our analysis. In total, there were ultimately 4,589 mother-child pairs in the EDEN-PELAGIE Consortium for the purposes of this study.

Data collection for covariates and outcomes

In both cohorts, questionnaires and clinical examinations were used to collect sociodemographic and medical information, during and after pregnancy. Birthweight data were obtained from medical records.[36,37] Home addresses of the women at the time of delivery were collected and geocoded.

Exposure assessment

Temperature exposure estimates were generated by a hybrid spatio-temporal model, using Moderate Resolution Imaging Spectroradiometer (MODIS) satellite surface temperature data.[38]

Briefly, daily satellite surface temperature data (in 1 km^2 grid cells) were obtained, and calibrated with air temperature data from Météo France monitors within 1 km, with adjustment for spatio-temporal predictors. For grid cells where satellite surface temperature data were unavailable on a particular day, the model relied on the association on other days between the satellite-based predicted air temperature in that grid cell, and the measured air temperature from nearby monitoring stations (as well as temperature values in the surrounding grid cells). These daily model predictions were used to generate weekly temperature exposure estimates for each study participant, based on her home address at the time of delivery.

Relative humidity exposure estimates were obtained from the French national meteorological service, Météo France, using data from the monitoring station nearest to the home address of each woman.

Ethical approvals and informed consent

EDEN and PELAGIE were both approved by the relevant ethical committees: *la Commission Nationale de l'Informatique et des Libertés*, *le Comité Consultatif pour la Protection des Personnes dans la Recherche Biomédicale du Kremlin Bicêtre*, *le Comité Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la Santé*, and *le Comité d'Ethique de l'Inserm*. This particular study was reviewed by the Institutional Review Board of the Harvard T. H. Chan School of Public Health and deemed exempt per the federal criteria at 45 CFR 46.101(b)(4).

Statistical analyses

We performed regression analysis with generalized linear models, adjusted for the following possible confounders: gestational age (linear and quadratic), recruitment center location (Nancy, Poitiers, Brittany), season of conception, year of conception, sex of the newborn, and several maternal characteristics (height, pre-pregnancy weight [broken-stick/piecewise linear method, with a single knot near the median], parity, age at conception, educational level, and smoking status).[39,40] These covariates were selected *a priori*, based on biological and epidemiological reasoning and evidence in the literature. Gestational age was censored at 42 weeks, since professional consensus among French obstetricians favors induction of labor after that point.[41]

Main analytical strategy: Distributed lag models

Relationships between term birthweight and meteorological exposures were initially modelled with minimal adjustment, and then modelled in a fully-adjusted framework. The minimally-adjusted models were built for each exposure separately (mean temperature, standard deviation of temperature, mean humidity, and standard deviation of humidity), adjusting only for gestational age. Fully-adjusted models contained mean temperature, mean humidity, standard deviation of temperature, and standard deviation of humidity as simultaneous exposures, with adjustment for confounders.

Analyses were performed using data from term births only (at least 37 weeks gestational age). To create distributed lag models, an exposure matrix of the first 37 gestational weeks was constructed for each meteorological exposure.

The exposure-response relationship (reflecting the impact of exposure amount) was modelled linearly, and the lag-response relationship (reflecting the impact of exposure timing) was modelled with natural cubic splines. Degrees of freedom were tested from 2 to 6, and chosen by minimizing the Akaike information criterion (AIC) in minimal models for each exposure (Table 1). Then the selected values for degrees of freedom were used in building the fully-adjusted models, which contained all four exposures simultaneously. If the AIC was equally low with different degrees of freedom, e.g. same AIC with 2 or 3 degrees of freedom, the lowest value was chosen. Knots were set at equally spaced quantiles. We graphed these DLMs and used them to identify critical exposure windows during pregnancy.

To be thorough, we also tried using cubic b-splines and quadratic b-splines to model the lag-response relationship. Since this did not improve the AIC of fully-adjusted models, we proceeded with natural cubic splines. We also checked for non-linearity of the exposure-response relationship with natural cubic splines, again testing degrees of freedom from 2 to 6 and choosing the degrees of freedom that minimized the AIC in minimal models (Supplemental Table 1). However, the AIC of fully-adjusted models was consistently lower with a linear exposure-response relationship than with a nonlinear exposure-response relationship, so a linear exposure-response relationship was used in final models.

Sensitivity and secondary analyses

Since fetal weight gain accelerates in late pregnancy,[42] a secondary analysis was conducted to include late pregnancy exposures, using distributed lag models built with 42-week exposure matrices. However, since most term births occurred before 42 weeks, many women were missing exposure observations after delivery (between weeks 37 and 42). The statistical package we used to build distributed lag models, *dlnm*,[24] does not permit missing values in the exposure matrix (i.e. a participant missing any exposure observations would be completely removed from the analysis). To avoid this, for any women who delivered prior to 42 weeks, exposure after delivery was considered as 0, since any exposures after birth could not influence birth outcomes. We refer to the models in this secondary analysis as "partial exposure distributed lag models," since participants were permitted to have "incomplete" exposure histories (i.e. not all 42 weeks contained an actual temperature or humidity value; some weeks contained 0). Models in the primary analysis with 37-week exposure matrices are referred to here as "complete exposure distributed lag models," because every week in each exposure history contained an actual temperature or humidity value, with no artificial 0 values. (The complete exposure DLM approach is also described by Wilson et al. in their 2017 paper.)[43]

We also created average exposure models, with exposure data averaged over trimesters and the first 37 weeks of pregnancy, for comparison with the distributed lag models. As with the DLMs, we started with minimally-adjusted models and then created fully-adjusted models. Since meteorological exposures in each trimester were somewhat correlated with the same exposures in the other two trimesters, we used the Frisch-Waugh method to adjust for the influence of average exposure in the other trimesters. (Please see Supplemental Table 2 for the correlation coefficients for each exposure in different time windows.) Bell et al. have described the Frisch-Waugh method in a similar context in a study of ambient air pollution and low birth weight.[44] In short, we adjusted for correlation between exposure averages in each trimester as follows: $M_{1,j}^{i}$ = exposure to meteorological factor *j* over trimester 1 for birth *i*; residuals of the model $E\left[M_{2,j}^{i}\right] = \beta_1 + \beta_2 M_{1,j}^{i}$, which represents exposure to meteorological factor *j* over trimester 2 for birth *I*, adjusted for exposure over trimester 1; and residuals of the model $E\left[M_{3,j}^{i}\right] = \beta_3 + \beta_4 M_{1,j}^{i} + \beta_5 M_{2,j}^{i}$, which represents exposure to meteorological factor *j* over trimester 3 for birth *I*, adjusted for exposure over trimesters 1 and 2. The β values represent regression coefficients, with β_1 and β_3 as intercepts, β_2 as the association between exposure in trimesters 1 and 2, β_4 as the association between exposure in trimesters 1 and 3 adjusted for exposure in trimester 2, and β_5 as the association between exposure in trimesters 2 and 3 adjusted for exposure in trimester 1. This was then repeated using trimesters 2 and 3 as the initial reference trimester. For these trimester analyses, women were only included if temperature data were available from at least 50% of the days in the last trimester (to ensure that averages represented exposure over a long period of the trimester, not just a few days).

Finally, we repeated key analyses with stratification by sex of the infant, to investigate possible effect modification by sex.

Analyses were conducted with the R statistical software environment, version 3.4.0,[45] mainly using the *dlnm* package.[24] A significance level of α = 0.05 was used in interpreting results.

Results

Study population

Over half of the 4,589 women in this study lived in Brittany (64.9%), with the rest split fairly evenly between Poitiers and Nancy (17.6% and 17.5%, respectively) (Table 2). Most women (72.6%) were 25 to 34 years old at the time of delivery, and the majority (59.2%) had completed at least two years of university education (i.e. *baccalauréat* level +2 or higher). More than a quarter of participants (27.2%) reported tobacco use in early pregnancy. The mean gestational age at birth was 38.2 ± 1.2 weeks.

Mean temperature ± standard deviation over the entire pregnancy was 12.0 ± 2.1 °C, while mean humidity was 79.0 ± 4.2%. Both of these exposures were slightly higher in PELAGIE than in EDEN. Spearman correlations between exposures in each time window of pregnancy are provided in Supplemental Table 3, with the strongest correlation being -0.76 (between mean humidity and standard deviation of humidity in the first trimester).

Figure 2 illustrates the weekly exposure to mean temperature, standard deviation of temperature, mean humidity, and standard deviation of humidity over the first 37 weeks of pregnancy, averaged over all the participants in the study. On average, weekly standard deviation of temperature was around 2.0 °C, while weekly standard deviation of humidity was approximately 6.6%.

As Supplemental Table 4 shows, mean birthweight was higher in the PELAGIE cohort (3436 ± 439 g) than in the EDEN cohort (3357 ± 435 g in Poitiers, 3318 ± 429 g in Nancy; $p < 0.001$). Overall, the mean birthweight was 3402 ± 439 g. Supplemental Table 4 also contains the results of analyses of birthweight with other participant characteristics, adjusted only for gestational age. In general, higher maternal age, maternal education, and parity were associated with higher birthweight. Tobacco use was associated with lower birthweight, compared to no tobacco use.

Primary and secondary analyses

Figure 2 - Figure 6 present week-specific associations between each exposure and term birthweight, estimated using fully-adjusted DLMs over the first 37 weeks of gestation. Table 3 shows the cumulative change in term birthweight during time windows found to have a statistically significant association between the outcome and meteorological exposures in fully-adjusted models. (For findings from minimally-adjusted DLMs, please see Supplemental Figure 1 - Supplemental Figure 4 and Supplemental Table 5.) Primary results from the complete exposure DLMs (37-week exposure matrix) and secondary results from the partial exposure DLMs (42-week exposure matrix) are provided. Even with the longer exposure matrix of the partial exposure models, no weeks after the 37th week of pregnancy were found to have statistically significant associations between weather conditions and term birthweight (Table 3).

There was no week of pregnancy with a statistically significant association between mean temperature and birthweight in the complete exposure model (Figure 2a). The estimated association in the complete exposure model trended downwards throughout the first 37 weeks of pregnancy, but was always fairy close to 0. In secondary analysis with the partial exposure model, the curve was U-shaped with a positive association in weeks 1 to 14, a negative association in weeks 15 to 29, and a positive association in weeks 30 to 42. The overall association between temperature and term birthweight with the partial exposure model was statistically significant in weeks 1 to 3, with an estimated cumulative change in term birthweight of 12.3 g

(95% CI: 0.4, 24.2) for a 5 °C increase in mean temperature. In DLMs stratified by sex for both male and female infants, the estimated association between mean temperature and term birthweight in the complete exposure model trended downwards throughout the first 37 weeks of gestation (Figure 2c and Figure 2d). For boys, the association changed from positive to negative at week 27; for girls, it changed direction earlier at week 10.

The estimate for the association between standard deviation of temperature and term birthweight in the complete exposure analysis was negative throughout the first 37 weeks of pregnancy, though it trended steadily upwards towards 0 (Figure 4a). This relationship was statistically significant between weeks 6 and 20, with a cumulative change in term birthweight of -65.2 g (95% CI: -101.9, -6.4) for a 1 °C increase in standard deviation of temperature. The association between standard deviation of temperature and term birthweight in the partial exposure analysis was also negative at first, but became positive after week 32 (Figure 4b). Between weeks 1 and 15, this association was statistically significant, and the estimated cumulative change in term birthweight was -61.6 g (95% CI: -116.3, -6.8). After stratification by sex of the infant, the relationship in female infants was nonsignificant and close to 0 throughout the first 37 weeks of gestation (Figure 4d). In male infants, the relationship was negative throughout the first 37 weeks of gestation, but trended upwards towards 0 (Figure 4c). It was statistically significant from week 1 to 21, with a cumulative estimate of -5.4 g (95% CI: -10.7, -0.2).

Based on the complete exposure analysis, the estimated association between mean humidity and term birthweight was negative throughout the first 37 weeks of pregnancy (Figure 5a). The curve rose close to zero during the middle of pregnancy before becoming more negative towards the end of pregnancy. The relationship between mean humidity and term birthweight was statistically significant from week 26 to 37, with a cumulative change in term birthweight of -28.2 g (95% CI: -49.2, -7.1) for a 5% increase in mean relative humidity. In the partial exposure analysis, the relationship between mean humidity and term birthweight was also negative throughout pregnancy, gradually drawing closer to zero (Figure 5b). This association was statistically significant in weeks 13 to 28, and the cumulative change in term birthweight was -14.1 g (95% CI: -25.1, -3.1). In male infants, the estimated association between mean humidity and term birthweight was negative from week 1 to 7, positive from week 8 to 22, and negative again from week 23 to 37 (Figure 5c). This relationship was statistically significant from week 29 to 37, with a cumulative change in term birthweight of -37.3 g (95% CI: -63.4, -11.1). In female infants, the relationship was negative throughout the first 37 weeks of pregnancy, but was closer to zero towards the beginning and end of pregnancy (Figure 5d). Between weeks 13 and 15, there was a statistically significant cumulative change in term birthweight of -5.4 g (95% CI: -10.7, -0.2).

Figure 6 shows that the estimated association between standard deviation of humidity and term birthweight was not statistically significant in any week of pregnancy, in any of the DLMs. The estimated association became more negative over the first 37 weeks of pregnancy in the complete exposure analysis, whereas it became more positive over the entire pregnancy in the partial exposure analysis (Figure 6a and Figure 6b). However, in both cases the association was always close to zero. In analysis stratified by sex of the infant, for male infants the estimated association changed from positive to negative at week 19, and for female infants it changed from negative to positive at week 30 (Figure 5c and Figure 5d).

Supplemental Table 6 presents the cumulative change in term birthweight associated with various weather conditions over the course of each trimester and the first 37 weeks of pregnancy, from fully-adjusted complete exposure DLMs and from average exposure models. Estimates of association produced by distributed lag models were generally in the same direction as those produced by average exposure models, but with different magnitudes.

After adjusting for confounders and the other exposures, the distributed lag models showed a statistically significant decrease in term birthweight for a 1 °C increase in standard deviation of temperature over the first 37 weeks of pregnancy (-112.2 g, 95% CI: -217.5, -6.8), the first trimester (-54.4 g, 95% CI: -106.7, -2.2), and the second trimester (-38.2 g 95% CI: -75.3, -1.0). Based on these DLMs, there was also a statistically significant negative association between term birthweight and mean humidity in the first 37 weeks of pregnancy (-47.7 g, 95% CI: -77.3, -18.2) and the third trimester (-26.7 g, 95% CI: -46.9, -6.5).

Conversely, with the average exposure models, there was no statistically significant association between standard deviation of temperature and term birthweight in any time interval. Mean humidity in the third trimester was significantly associated with term birthweight (-33.6 g, 95% CI: -58.2, -9.0) in the average exposure model, but this was the only time window/exposure combination that produced statistically significant results with both the distributed lag model and the average exposure model. The average exposure models also showed a statistically significant increase in birthweight with a 5 °C rise in mean temperature during the first trimester (52.0 g, 95% CI: 10.4, 93.5), and a statistically significant decrease in the third trimester (-42.4 g, 95% CI: -78.0, -6.8). Finally, there was a statistically significant decrease in term birthweight (-12.1 g, 95% CI: -22.9, -1.3) for a 1% increase in standard deviation of humidity in the third trimester.

All of the results described above are from models with a nonlinear lag-response relationship (reflecting the impact of exposure timing) and a linear expose-response relationship (reflecting the impact of exposure amount). A nonlinear exposure-response relationship was not used in final models, but three-dimensional plots illustrating complete exposure DLMs with nonlinear lag-response and nonlinear exposure-response relationships are presented in Supplemental Figure 5 for reference.

Discussion, Conclusions, & Suggestions for Future Work

Main findings

In our primary analysis, critical windows of exposure were found for standard deviation of temperature and mean relative humidity, both of which were associated with a decrease in term birthweight. Critical exposure windows were not identified for mean temperature or standard deviation of humidity. Standard deviation of temperature was found to be negatively associated with term birthweight, with a critical window in weeks 6 to 20, from the middle of the first trimester to the middle of the second trimester. When this analysis was stratified by the sex of the infant, there was a critical window for standard deviation of temperature in the first 21 weeks of pregnancy for male infants, but no critical exposure window for female infants. With mean humidity, there was a critical window of exposure in weeks 26 to 37, which is the end of the second trimester and most of the third trimester. Stratifying this analysis by the sex of the infant revealed that the negative association between mean humidity and term birthweight was much larger in boys than girls. Also, the critical window for mean humidity in boys (weeks 29 to 37) was much later than in girls (weeks 13 to 15).

In the secondary analysis using partial exposure DLMs, no critical windows of exposure were identified after 37 weeks. This supports the use of 37-week complete exposure DLMs for our main analysis. Using 37-week exposure matrices so as to avoid setting exposure values after delivery to 0 is our preferred approach, because with temperature a 0 value does not truly represent the absence of exposure (i.e. 0 °C is a real, plausible temperature). The remainder of this discussion will therefore focus on the results of the complete exposure analysis.

Strengths and weaknesses

One major strength of this study is the fine spatial and temporal resolution of the temperature data used. By using satellite-based temperature data with high spatial resolution (1 km^2), we were able to reduce exposure error and the downward bias that could accompany it.[22,46] Furthermore, the use of distributed lag models allowed for fine temporal resolution of exposure modelling (i.e. daily temperature and humidity values were averaged by week, rather than by trimester). These models permitted us to identify critical windows of exposure during pregnancy with more precision than average exposure models. This could help inform our understanding of the mechanisms by which weather conditions can affect fetal growth.

Another strength is the study population itself, as the linking of two cohorts in the EDEN-PELAGIE consortium provides a large sample size of participants from across France. The locations involved have different geographic features and climatic conditions; for example, Brittany is more coastal than the other areas in this study, and is also warmer and more humid on average. Since our study population was drawn from multiple locations, our results reflect a wider range of exposures and are more generalizable than they would have been if participants came from only one region.

An important feature of our work is that we investigated the impacts of humidity itself, rather than only temperature, and that we studied weather variability using standard deviation. The impacts of these exposures have rarely been described in the previous literature, but in light of our findings, temperature variability and humidity may merit more attention moving forward.

A weakness of our study is that the humidity data were obtained from monitoring stations, and therefore did not have the same level of fine spatial resolution as the temperature data. Also, we did not monitor daily activity patterns and instead relied on participants' home addresses to estimate exposure, without accounting for how much time participants spent at home. People in the Western world tend to spend much of their time inside, but the temperature and humidity data we used reflected outdoor conditions, rather than indoor conditions. However, since air conditioning is not very common in France,[47] discrepancies between indoor and outdoor temperature and humidity were unlikely to have been very significant overall.

Another weakness of this study is that we were unable to adjust for certain factors known to influence birthweight, such as alcohol use,[48] and passive smoking,[49] since we did not have the data available. That said, we did adjust for several other demographic and socioeconomic factors. We also did not have data available to adjust for air pollution, which has been linked with decreased birthweight[50] and is often associated with temperature.[51] However, it is possible that adjusting for air pollution would have been inappropriate anyway. While temperature may confound the relationship between air pollution and birthweight, it may be less plausible for air pollution to confound the relationship between weather conditions and birthweight.[51]

Comparison with the literature

Unlike some previous studies,[7,17,18] we did not find an association between mean temperature and birthweight, either positively or negatively. One possible reason for this difference is that our outcome was actually *term* birthweight, so we focused solely on decreased size due to IUGR and not due to prematurity. However, the main reason is probably that we used distributed lag models rather than average exposure models in our main analysis, to reduce bias.[43] Kloog et al. also assessed term birthweight in their 2015 study of mean temperature and birth outcomes in Massachusetts, and they likewise used high resolution temperature data obtained from a satellite-based model.[7] However, they used average exposure models with various time windows before birth, not DLMs. They found that higher mean temperature in the third trimester was significantly associated with decreased term birthweight. Although the results of our main analysis with DLMs conflicted with this, the results of our secondary analysis with average exposure models were consistent with Kloog et al.

While several studies on weather and birth outcomes have adjusted for humidity to clarify the impacts of temperature, to our knowledge this is the first study to analyze the effect of humidity itself on term birthweight. Some prior studies have used measures that reflect both temperature and humidity. For example, Basu et al. reported that increased apparent temperature over the duration of gestation (particularly the third trimester) was associated with increased risk of term low birth weight in California.[14] The critical window of mean humidity exposure identified in our study was largely in the third trimester as well, which aligns with their findings. On the other hand, Son et al. did not find a statistically significant association between heat index and term low birthweight in Seoul, Korea.[20]

To our knowledge, this is also the first study to investigate the impacts of standard deviation of temperature and standard deviation of relative humidity on term birthweight (with standard deviation calculated within each week of participant exposure). Other studies have aimed to capture the impact of weather variability on birth outcomes in other ways. For example, Molina and Saldarriaga found that temperature anomalies of one standard deviation higher than the local historic mean temperature were associated with a decrease in birthweight, and that this association was particularly notable in the first trimester.[31] We likewise found that that temperature variability (standard deviation of temperature) was associated with decreased term birthweight, with a critical window in early to mid-pregnancy. However, in our study, we assessed temperature variability on a much shorter timescale (week by week) and did not focus on unusually high temperatures. Molina and Saldarriaga conducted their study in the Andean region and hypothesized that the observed association may have been related to declines in food security and healthcare utilization with greater temperature variability.[31] As for our study, temperature variability within a week in France would be less likely to cause large enough agricultural problems to impact food security in a major way, or to prevent women from accessing healthcare.

Discussion of methodology

To our knowledge, this is the first time distributed lag models have been used to study the association between weather conditions and term birthweight. This is an important development in research on this topic, as using average exposure models to study exposures during pregnancy can lead to bias. Wilson et al. demonstrated this in a 2017 simulation, where they assessed the impact of prenatal fine particulate matter exposure on children's body mass index z-score and fat mass in Massachusetts.[43] In their simulation, trimester average exposure models were biased and led to the identification of incorrect critical windows when the true windows did not match trimester boundaries. This was due to correlations between trimester average exposures, which arose from seasonal trends.

Similarly, when we compared results from distributed lag models to average exposure models, we found that they generally did not identify the same critical exposure windows. Most of the time window/exposure combinations found to be statistically significant with DLMs were not statistically significant with average exposure models. In this analysis, bias may have been somewhat reduced by the use of the Frisch-Waugh method to adjust for other trimester exposures. Even so, distributed lag models were still a more flexible and data-driven approach to identifying critical exposure windows.

Biological plausibility

Animal studies have shown chronic thermal stress in pregnancy to be associated with reduced birthweight, due to diminished uterine and umbilical blood flow and reduced placental weight.[52] Ovine studies suggest that this may happen in two phases, with early exposures leading to irreversible growth restriction, and later exposures influencing fetal growth separately.[52] However, the relevance of these potential mechanisms in humans is unclear.

Maternal fever in humans has been linked to perinatal morbidity and mortality, but it can be difficult to disentangle the effects of temperate elevation from those of the inciting infection and other metabolic changes that occur during fevers.[53] Fever represents a type of acute heat stress, which can trigger the heat shock response in the mammalian embryo or fetus, causing normal cell proliferation and protein synthesis to pause.[53] The biological impact of chronic heat stress on the developing human fetus is less clear, but would be valuable information for public health planning.

Some studies have reported associations between temperature changes and inflammatory markers, though not always in the same direction (i.e. some report increased inflammatory markers with cold temperatures, and some with hot temperatures).[54] This suggests the possibility that an inflammatory mechanism could be at play in the relationship between weather conditions and fetal growth. Another hypothesis is that ambient temperature could alter hormone patterns and affect birthweight as a result.[17] These potential mechanisms do not directly address the matter of temperature variability, as a concept separate from temperature itself. However, it is plausible that unrelenting temperature variation might interfere with the body's ability to recover from inflammatory changes or patterns of blood flow induced by heat stress.

Boys and girls are known to have different fetal growth patterns both early and late in gestation, and have also been found to have different levels of sensitivity to various prenatal exposures.[55,56] This is consistent with our identification of a critical exposure window for mean humidity in male but not female infants, and different critical windows in male and female infants for standard deviation of temperature. However, the exact biological mechanisms underlying these different development patterns have yet to be fully elucidated.

Humidity is known to reduce the body's ability to release heat, but the potential independent impacts of humidity on health are not well understood.[11] Bind et al. reported that relative humidity was associated with hypomethylation of the gene *ICAM-1* suggesting that it might lead to increased expression of the protein ICAM-1 (intercellular adhesion molecule 1), which is upregulated during inflammatory responses.[32] More research is certainly needed for clarification, but this hints at the possibility that inflammation could be involved in the relationship between humidity and fetal growth.

Suggestions for future work

In future, it could be illuminating to investigate the effect of heat waves using distributed lag models, to determine whether a sudden temperature spike is particularly concerning in certain periods of pregnancy. It could also be worthwhile to study the impacts of weather conditions on other adverse pregnancy outcomes using distributed lag models. For example, survival analysis using DLMs could be helpful for identifying critical windows of exposure for increased risk of preterm birth. Finally, in order to highlight the impact of exposures at the very end of pregnancy, an analysis of weather conditions and birthweight could be conducted using exposure matrices limited to the last portion of each woman's pregnancy. Although this would not allow for identification of critical windows in terms of gestational age, it could help clarify the importance of exposures during the period of rapid fetal weight gain at the end of pregnancy.

Summary

We have used distributed lag models to identify critical windows of exposure for standard deviation of temperature and mean relative humidity, both of which were associated with decreases in term birthweight. These particular exposures have rarely been investigated before in relation to birthweight. The critical exposure windows were different for standard deviation of temperature (early to mid-pregnancy) compared to humidity (mid- to late pregnancy), and did not fit neatly within trimesters. For mean relative humidity, the critical exposure window happened much later in male infants than in female infants, perhaps reflecting differences in fetal development between the sexes. Our analyses were conducted using exposure data with fine spatiotemporal resolution, enabling us to reduce exposure error and study the role of exposure timing with greater precision.

Tables & Figures

Table 1. Degrees of freedom minimizing the AIC for lag-response relationships between timing of meteorological exposure and term birthweight over 37 weeks (used in final models)

	Degrees of freedom
Mean temperature	2
Standard deviation of temperature	2
Mean humidity	3
Standard deviation of humidity	2

Table 2. Distribution of participant characteristics

Variable	**Consortium n** (%) or **Mean** (SD)	**EDEN n** (%) or **Mean** (SD)	**PELAGIE n** (%) or **Mean** (SD)	**p-value*** [χ2 or t-test†]
Study population	**4589** (100%)	**1611** (100%)	**2978** (100%)	--
EXPOSURES OVER ENTIRE PREGNANCY				
Temperature (°C)	**12.0** (2.1)	**11.6** (2.4)	**12.2** (1.9)	**<0.001**
Relative humidity (%)	**79.0** (4.2)	**77.6** (3.5)	**79.8** (4.3)	**<0.001**
OUTCOME				
Term birthweight (g)				
Mean birthweight in g, term births (SD)	**3402** (439)	**3338** (432)	**3436** (439)	**<0.001**
Missing	**4** (0.1%)	**3** (0.2%)	**1** (0.0%)	
PARTICIPANT CHARACTERISTICS				
Recruitment center				
Brittany (PELAGIE)	**2978** (64.9%)	**0** (0.0%)	**2978** (100.0%)	
Poitiers (EDEN)	**809** (17.6%)	**809** (50.2%)	**0** (0.0%)	**<0.001**
Nancy (EDEN)	**802** (17.5%)	**802** (49.8%)	**0** (0.0%)	
Maternal age at conception				
<25 years	**1611** (35.1%)	**317** (19.7%)	**351** (11.8%)	
25 - 29 years	**1836** (40.0%)	**613** (38.1%)	**1223** (41.1%)	
30 - 34 years	**1495** (32.6%)	**490** (30.4%)	**1005** (33.7%)	**<0.001**
≥35 years	**576** (12.6%)	**191** (11.9%)	**385** (12.9%)	
Missing	**14** (0.3%)	**0** (0.0%)	**14** (0.5%)	
Educational level				
Primary school or less	**72** (1.6%)	**56** (3.5%)	**16** (0.5%)	
Above primary school through *baccalauréat*	**1756** (38.3%)	**677** (42.0%)	**1079** (36.2%)	**<0.001**
Baccalauréat level +2 or more	**2717** (59.2%)	**849** (52.7%)	**1868** (62.7%)	
Missing	**44** (1.0%)	**29** (1.8%)	**15** (0.5%)	
Tobacco use in early pregnancy				
None	**3311** (72.2%)	**1187** (73.7%)	**2124** (71.3%)	
1 - 5 cigarettes/day	**569** (12.4%)	**175** (10.9%)	**394** (13.2%)	
6 - 10 cigarettes/day	**465** (10.1%)	**165** (10.2%)	**300** (10.1%)	**0.09**
>10 cigarettes/day	**214** (4.7%)	**82** (5.1%)	**142** (4.4%)	
Missing	**30** (0.7%)	**2** (0.1%)	**28** (0.9%)	
Parity				
0	**1993** (43.4%)	**705** (43.8%)	**1288** (43.3%)	
1	**1745** (38.0%)	**609** (37.8%)	**1136** (38.1%)	
2	**669** (14.6%)	**215** (13.3%)	**454** (15.2%)	**0.006**
≥3	**170** (3.7%)	**79** (4.9%)	**91** (3.1%)	
Missing	**12** (0.3%)	**3** (0.2%)	**9** (0.3%)	
Sex of infant				
Male	**2337** (50.9%)	**842** (52.3%)	**1495** (50.2%)	**0.19**
Female	**2252** (49.1%)	**769** (47.7%)	**1483** (49.8%)	

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Season of conception				
Winter	**1140** (24.8%)	**359** (22.3%)	**781** (26.2%)	
Spring	**1055** (23.0%)	**355** (22.0%)	**700** (23.5%)	**0.002**
Summer	**1258** (27.4%)	**459** (28.5%)	**799** (26.8%)	
Fall	**1136** (24.8%)	**438** (27.2%)	**698** (23.4%)	
Year of conception				
2002	**653** (14.2%)	**67** (4.2%)	**586** (19.7%)	
2003	**1731** (37.7%)	**648** (40.2%)	**1083** (36.4%)	**<0.001**
2004	**1553** (33.8%)	**597** (37.1%)	**956** (32.1%)	
2005	**652** (14.2%)	**299** (18.6%)	**353** (11.9%)	
Maternal pre-pregnancy weight				
Mean weight in kg (SD)	**60.5** (11.4)	**61.2** (11.7)	**60.1** (11.2)	**0.003†**
Missing	**23** (0.5%)	**14** (0.9%)	**9** (0.3%)	
Maternal height				
Mean height in cm (SD)	**163.9** (6.0)	**163.5** (6.2)	**164.1** (5.9)	**0.001†**
Missing	**34** (0.7%)	**22** (1.3%)	**12** (0.4%)	
Gestational age				
Mean gestational age in weeks (SD)	**38.2** (1.2)	**38.0** (1.8)	**38.3** (1.2)	**<0.001†**

* Indicates p-value of the comparison test between EDEN and PELAGIE.
† Indicates p-value from t-test. Unmarked p-values represent results of $\chi2$ tests.

Table 3. Cumulative change in term birthweight from fully-adjusted distributed lag models during gestational weeks that show statistically significant associations between term birthweight and meteorological exposures

	Complete exposure* distributed lag model		Partial exposure* distributed lag model	
	N	**Change (g)** (95% CI)	**N**	**Change (g)** (95% CI)
Mean temperature (5 °C)				
All infants: Weeks 1 - 3			*4347*	**12.3** (0.4, 24.2)
SD temperature (1 °C)				
All infants: Weeks 1 - 15			*4347*	**-61.6** (-116.3, -6.8)
All infants: Weeks 6 - 20	*3834*	**-65.2** (-101.9, -6.4)		
Male infants: Weeks 1 - 21	*1923*	**-124.5** (-228.0, -20.9)		
Mean relative humidity (5%)				
All infants: Weeks 13 - 28			*4347*	**-14.1** (-25.1, -3.1)
All infants: Weeks 26 - 37	*3834*	**-28.2** (-49.2, -7.1)		
Male infants: Weeks 29 - 37	*1923*	**-37.3** (-63.4, -11.1)		
Female infants: Weeks 13 - 15	*1911*	**-5.4** (-10.7, -0.2)		

** "Complete exposure" refers to distributed lag models based on 37-week exposure matrices, with a study population that included term births only (such that every participant had a complete exposure history, with an observation for each of the first 37 weeks of pregnancy). "Partial exposure" refers to distributed lag models based on 42-week exposure matrices. For women who gave birth between 37 and 42 weeks, exposures after birth were set to 0.*
Note: These results are adjusted for the other exposures and the following participant characteristics: gestational age, maternal factors (age, height, weight, education, tobacco use, and parity), sex of child (except in models stratified by sex), season and year of conception, and recruitment center.

Figure 1. Composition of study population

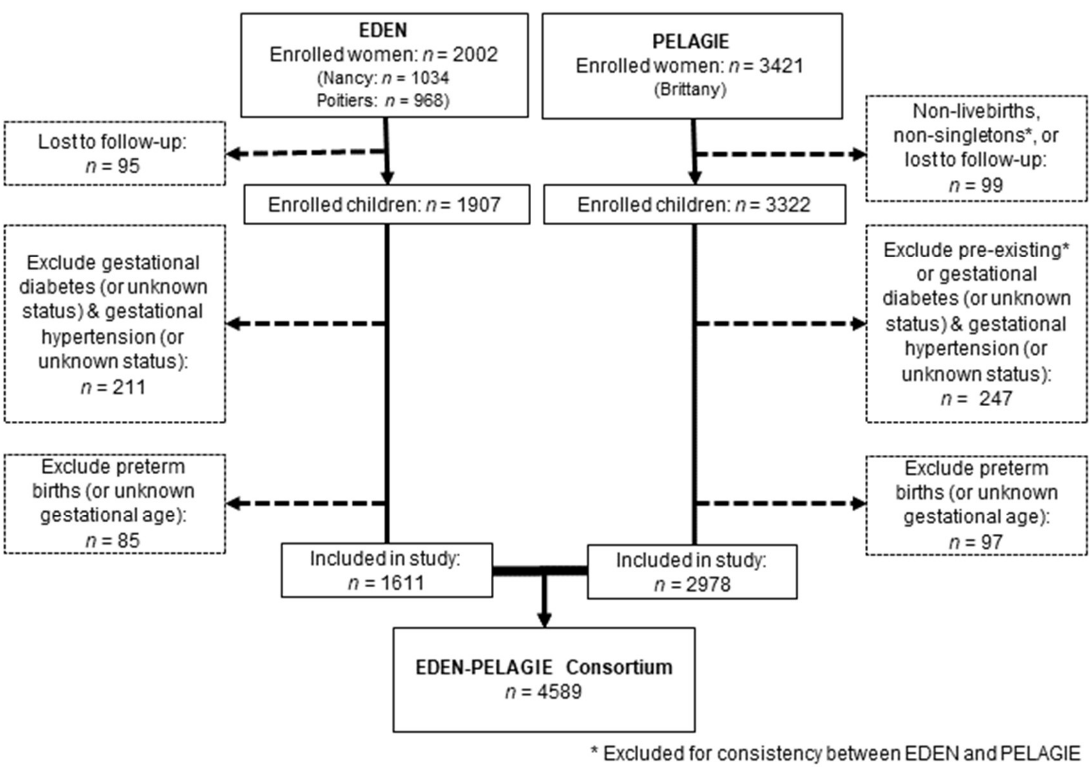


Figure 2. Weekly exposures over the first 37 weeks of pregnancy, averaged over all the participants in the study. [A] Mean temperature. [B] Standard deviation of temperature. [C] Mean humidity. [D] Standard deviation of humidity.

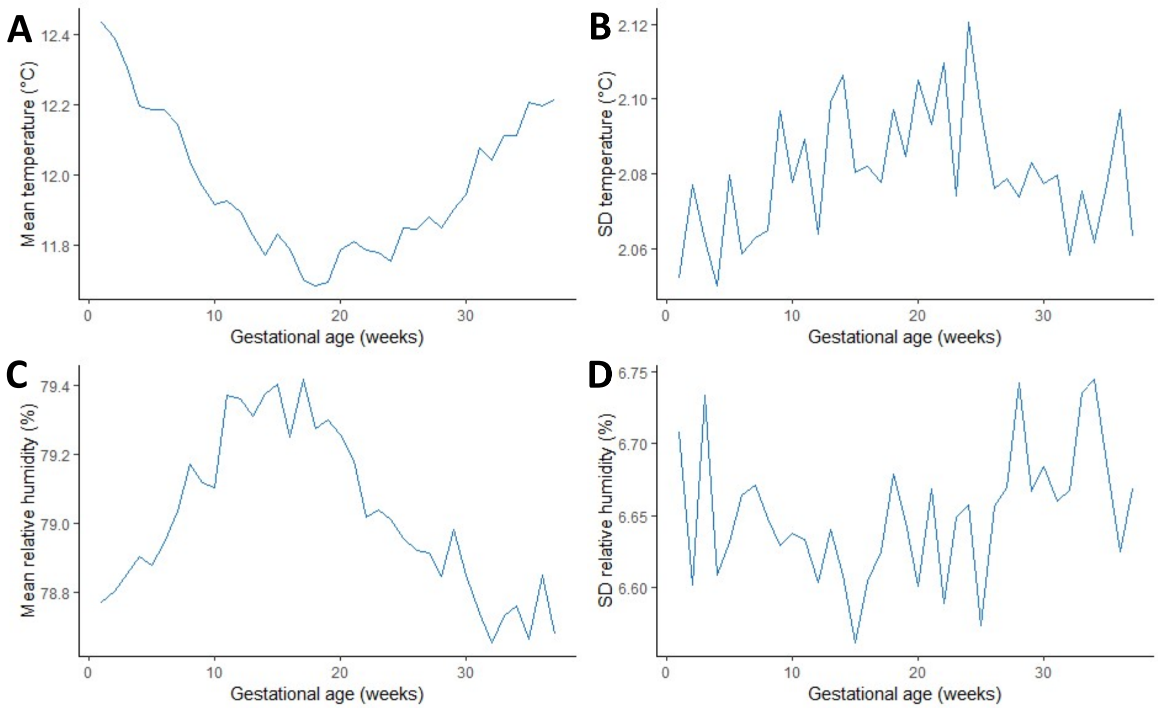
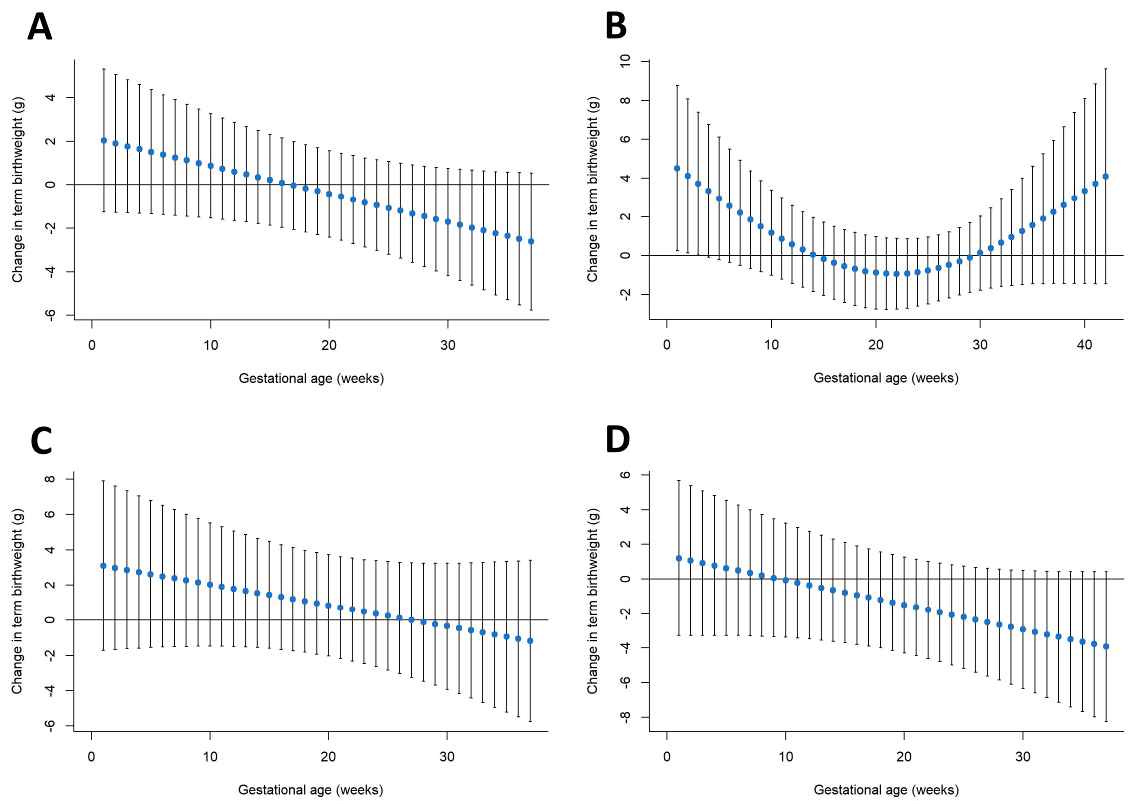
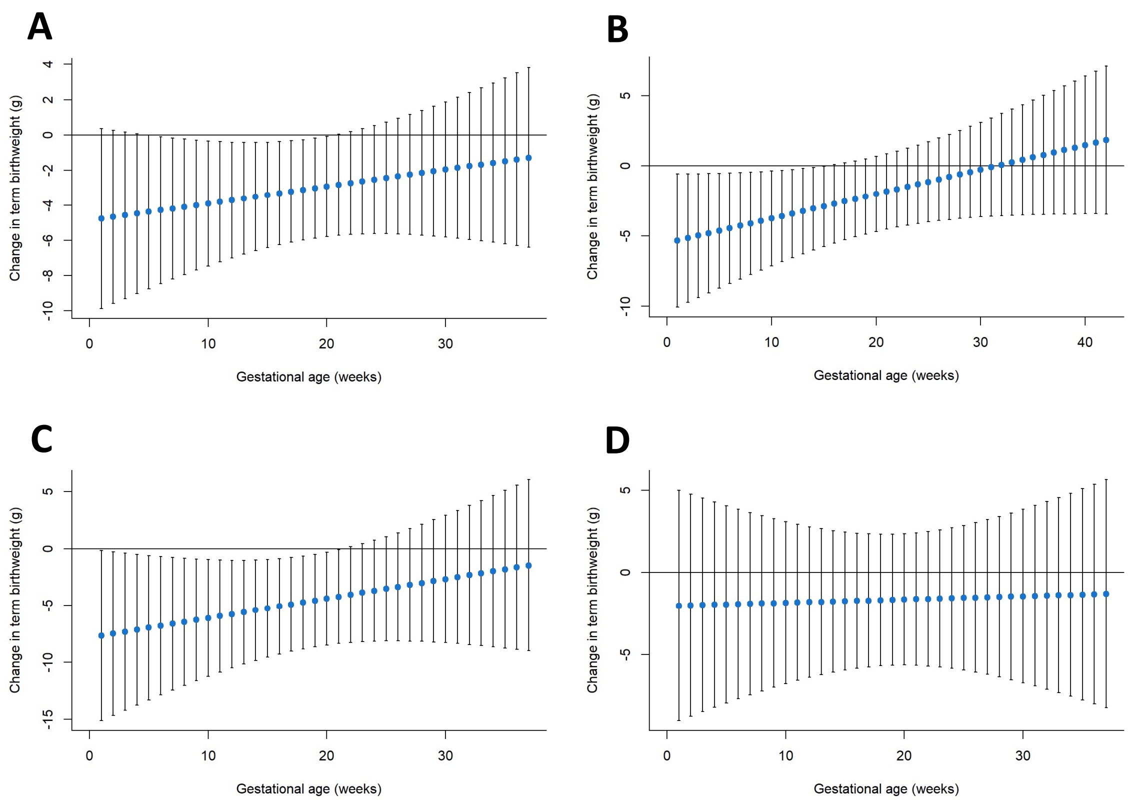


Figure 3. Change in term birthweight associated with a 5 °C increase in mean temperature in fully-adjusted distributed lag models. [A] Association between term birthweight and mean temperature over the first 37 weeks of pregnancy, using complete exposure model. [B] Association between term birthweight and mean temperature over 42 weeks of pregnancy, using partial exposure model. [C] Association in male infants between term birthweight and mean temperature over the first 37 weeks of pregnancy, using complete exposure model. [D] Association in female infants between term birthweight and mean temperature over the first 37 weeks of pregnancy, using complete exposure model.



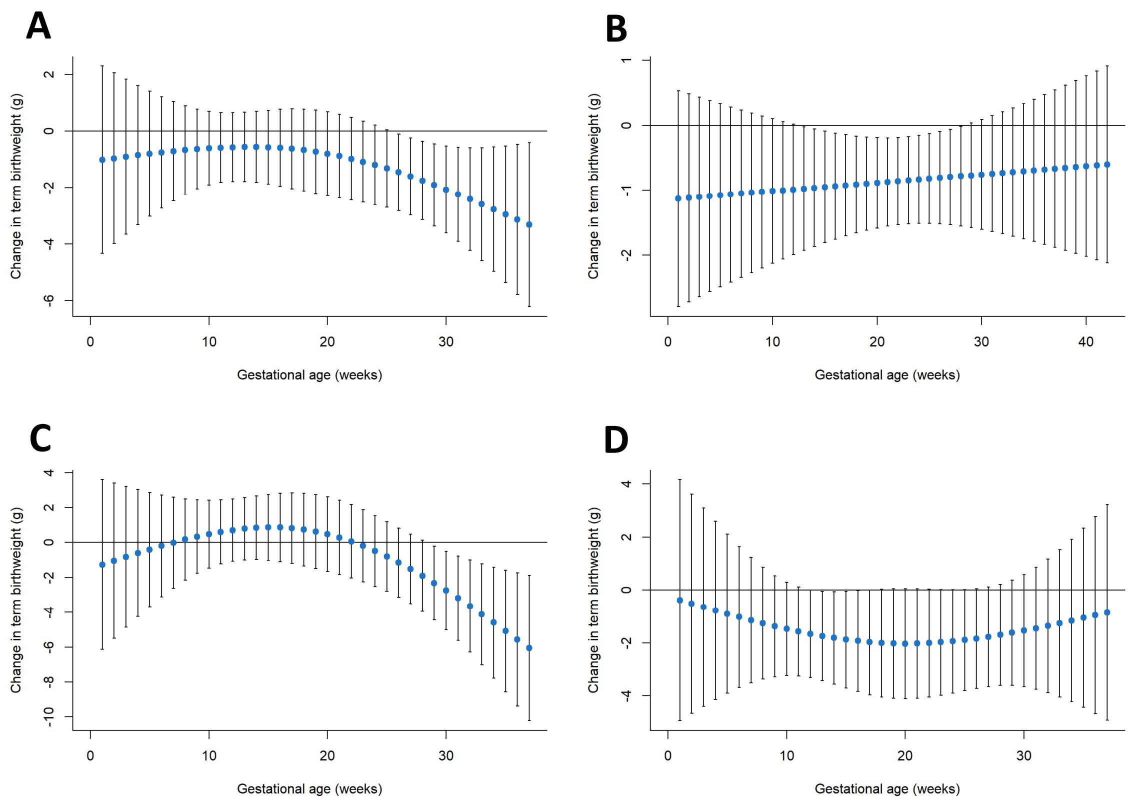
Note: These results are adjusted for the other exposures and the following participant characteristics: gestational age, maternal factors (age, height, weight, education, tobacco use, and parity), sex of child (except in models stratified by sex), season and year of conception, and recruitment center. Error bars represent 95% confidence intervals.

Figure 4. Change in term birthweight associated with a 1° C increase in standard deviation of temperature in fully-adjusted distributed lag models. [A] Association between term birthweight and standard deviation of temperature over the first 37 weeks of pregnancy, using complete exposure model. [B] Association between term birthweight and standard deviation of temperature over 42 weeks of pregnancy, using partial exposure model. [C] Association in male infants between term birthweight and standard deviation of temperature over the first 37 weeks of pregnancy, using complete exposure model. [D] Association in female infants between term birthweight and standard deviation of temperature over the first 37 weeks of pregnancy, using complete exposure model.



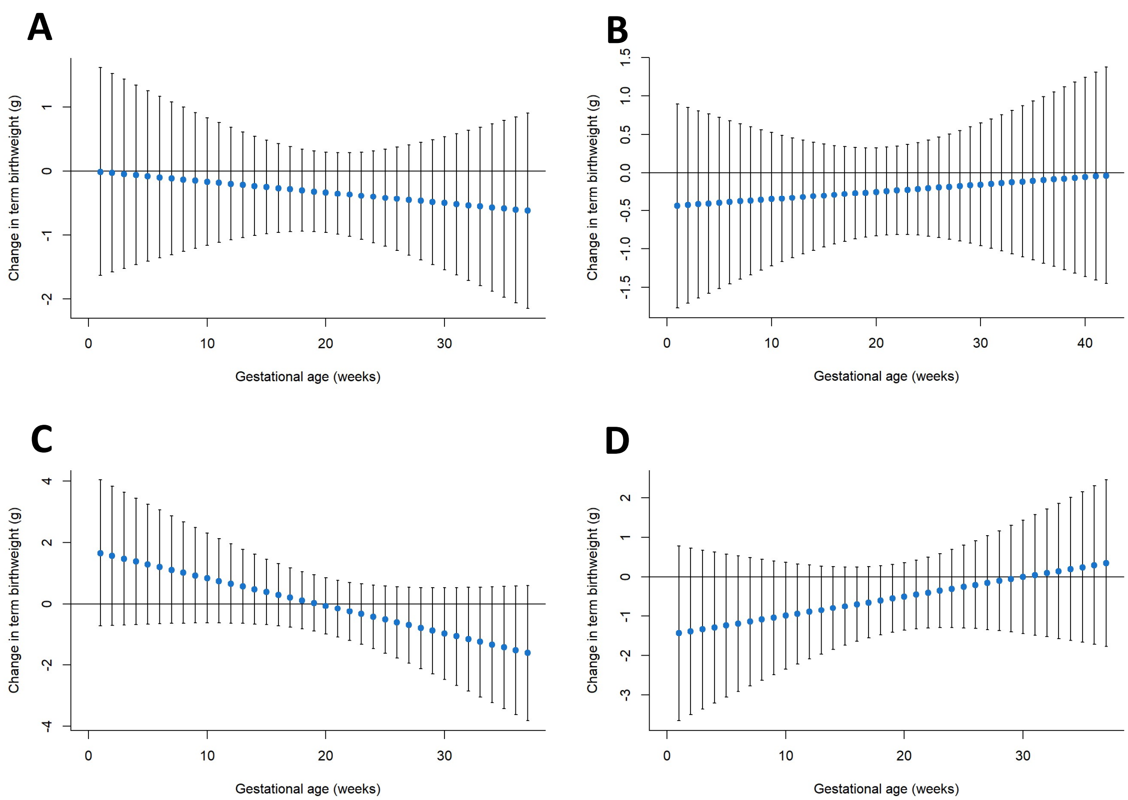
Note: These results are adjusted for the other exposures and the following participant characteristics: gestational age, maternal factors (age, height, weight, education, tobacco use, and parity), sex of child (except in models stratified by sex), season and year of conception, and recruitment center. Error bars represent 95% confidence intervals.

Figure 5. Change in term birthweight associated with a 5% increase in mean relative humidity in fully-adjusted distributed lag models. [A] Association between term birthweight and mean humidity over the first 37 weeks of pregnancy, using complete exposure model. [B] Association between term birthweight and mean humidity over 42 weeks of pregnancy, using partial exposure model. [C] Association in male infants between term birthweight and mean humidity over the first 37 weeks of pregnancy, using complete exposure model. [D] Association in female infants between term birthweight and mean humidity over the first 37 weeks of pregnancy, using complete exposure model.



Note: These results are adjusted for the other exposures and the following participant characteristics: gestational age, maternal factors (age, height, weight, education, tobacco use, and parity), sex of child (except in models stratified by sex), season and year of conception, and recruitment center. Error bars represent 95% confidence intervals.

Figure 6. Change in term birthweight associated with a 1% increase in standard deviation of relative humidity in fully-adjusted distributed lag models. [A] Association between term birthweight and standard deviation of humidity over the first 37 weeks of pregnancy, using complete exposure model. [B] Association between term birthweight and standard deviation of humidity over 42 weeks of pregnancy, using partial exposure model. [C] Association in male infants between term birthweight and standard deviation of humidity over the first 37 weeks of pregnancy, using complete exposure model. [D] Association in female infants between term birthweight and standard deviation of humidity over the first 37 weeks of pregnancy, using complete exposure model.



Note: These results are adjusted for the other exposures and the following participant characteristics: gestational age, maternal factors (age, height, weight, education, tobacco use, and parity), sex of child (except in models stratified by sex), season and year of conception, and recruitment center. Error bars represent 95% confidence intervals.

Supplemental Materials

Supplemental Table 1. Degrees of freedom minimizing the AIC for nonlinear exposure-response relationship between meteorological conditions and birthweight over 37 weeks (not in final models)

	Degrees of freedom
Mean temperature	2
Standard deviation of temperature	6
Mean humidity	3
Standard deviation of humidity	4

Supplemental Table 2. Spearman correlations between same exposures in different time windows

Exposure windows	Mean temperature	Standard deviation of temperature	Mean humidity	Standard deviation of humidity
1st trimester & 2nd trimester	-0.02 *p = 0.16*	-0.20 *p < 0.001*	0.16 *p < 0.001*	0.19 *p < 0.001*
1st trimester & 3rd trimester	-0.90 *p < 0.001*	0.19 *p < 0.001*	-0.32 *p < 0.001*	-0.32 *p < 0.001*
2nd trimester & 3rd trimester	0.31 *p < 0.001*	-0.05 *p < 0.001*	0.39 *p < 0.001*	0.39 *p < 0.001*

Supplemental Table 3. Spearman correlations between different exposures in same time windows

Exposures*	First 37 weeks of pregnancy	1st trimester	2nd trimester	3rd trimester
T & SDT	0.12	-0.19	-0.14	-0.25
T & H	-0.51	-0.61	-0.64	-0.64
T & SDH	0.11	0.30	0.32	0.33
SDT & H	-0.39	-0.15	-0.15	-0.13
SDT & SDH	0.50	0.38	0.37	0.32
H & SDH	-0.64	-0.76	-0.75	-0.74

Note: p-values for all correlations <0.001.

** T = mean temperature, SDT = standard deviation of temperature, H = mean humidity, & SDH = standard deviation of humidity*

Supplemental Table 4. Crude associations of birthweight with participant characteristics

Variable	Consortium n (%)	Mean birthweight (g) (SD)	Coefficient (95% CI)	p-value
Study population	**4589** (100%)	**3402** (439)	--	--
Recruitment center				
Brittany (PELAGIE)	**2978** (64.9%)	**3436** (439)	*Baseline*	**<0.001**
Poitiers (EDEN)	**809** (17.6%)	**3357** (435)	**-79.4** (-113.4, -45.4)	
Nancy (EDEN)	**802** (17.5%)	**3318** (429)	**-118.5** (-152.5, -84.4)	
Maternal age				
<25 years	**668** (14.6%)	**3325** (428)	*Baseline*	**<0.001**
25 - 29 years	**1836** (40.0%)	**3401** (427)	**75.4** (36.7, 114.2)	
30 - 34 years	**1495** (32.6%)	**3416** (451)	**91.1** (51.2, 131.0)	
≥35 years	**576** (12.6%)	**3452** (447)	**126.7** (77.9, 175.4)	
Missing	**14** (0.3%)	**3580** (602)		
Educational level				
Primary school or less	**72** (1.6%)	**3237** (494)	*Baseline*	**<0.001**
Above primary school through *baccalauréat*	**1756** (38.3%)	**3380** (452)	**143.3** (39.8, 246.8)	
Baccalauréat level +2 or more	**2717** (59.2%)	**3420** (429)	**182.4** (79.6, 285.1)	
Missing	**44** (1.0%)	**3416** (371)		
Tobacco use in early pregnancy				
None	**3311** (72.2%)	**3421** (433)	*Baseline*	**<0.001**
1 - 5 cigarettes/day	**569** (12.4%)	**3384** (443)	**-37.2** (-76.2, 1.7)	
6 - 10 cigarettes/day	**465** (10.1%)	**3311** (457)	**-110.4** (-153.0, -67.9)	
>10 cigarettes/day	**14** (4.7%)	**3346** (464)	**-74.9** (-135.4, -14.3)	
Missing	**30** (0.7%)	**3398** (430)		
Parity				
0	**1993** (43.4%)	**3343** (427)	*Baseline*	**<0.001**
1	**1745** (38.0%)	**3424** (443)	**80.6** (52.6, 108.6)	
2	**669** (14.6%)	**3493** (429)	**149.8** (111.6, 187.9)	
≥3	**170** (3.7%)	**3508** (479)	**164.9** (96.7, 233.1)	
Missing	**12** (0.3%)	**3285** (461)		
Sex of infant				
Male	**2337** (50.9%)	**3467** (447)	*Baseline*	**<0.001**
Female	**2252** (49.1%)	**3334** (42)	**-132.4** (-157.5, -107.2)	
Season of conception				
Winter	**1140** (24.8%)	**3402** (451)	*Baseline*	**0.44**
Spring	**1055** (23.0%)	**3417** (430)	**14.2** (-22.6, 51.0)	
Summer	**1258** (27.4%)	**3403** (442)	**0.7** (-34.5, 35.9)	
Fall	**1136** (24.8%)	**3386** (433)	**-16.6** (-52.7, 19.5)	
Missing				
Year of conception				
2002	**653** (14.2%)	**3427** (413)	*Baseline*	**0.12**
2003	**1731** (37.7%)	**3383** (445)	**-44.1** (-83.7, -4.5)	
2004	**1553** (33.8%)	**3409** (439)	**-18.7** (-58.9, 21.5)	
2005	**652** (14.2%)	**3410** (449)	**-17.4** (-65.1, 30.3)	
Maternal pre-pregnancy weight				
Number of observations	**4566** (99.5%)			
Missing	**23** (0.5%)			
Broken stick model: <60 kg			**22.3** (19.5, 22.4)	**<0.001**
Broken stick model: ≥60 kg			**1.9** (0.4, 3.4)	**0.016**
Maternal height				
Number of observations	**4555** (99.3%)			
Missing	**34** (0.7%)			
Mean height in cm.			**17.1** (14.8, 19.3)	**<0.001**
Gestational age				
Number of observations	**4589** (100%)			
Mean gestational age in weeks			**1087.7** (535.5, 1639.8)	**<0.001**
Square of mean gestation age in weeks			**-12.7** (-20.0, -5.4)	**0.001**

Note: Adjusted for gestational age. Separate model for each exposure.

Supplemental Table 5. Cumulative change in term birthweight from minimally-adjusted distributed lag models during gestational weeks that show statistically significant associations between term birthweight and meteorological exposures

	Complete exposure* distributed lag model		Partial exposure* distributed lag model	
	N	**Change (g)** (95% CI)	**N**	**Change (g)** (95% CI)
Mean temperature (5 °C)				
Weeks 1 - 9	*3834*	**2.7** (-2.4, 7.8)		
Weeks 1 - 19			*4347*	**27.1** (-16.3, 70.5)
SD temperature (1 °C)				
Weeks 1 - 28	*3834*	**-97.1** (-182.2, -11.9)	*4347*	**-83.1** (-164.7, -1.6)
Mean relative humidity (5%)				
Weeks 22 - 37	*3834*	**-32.7** (-56.6, -8.8)		
Weeks 22 - 42			*4347*	**-14.5** (-33.8, 4.8)

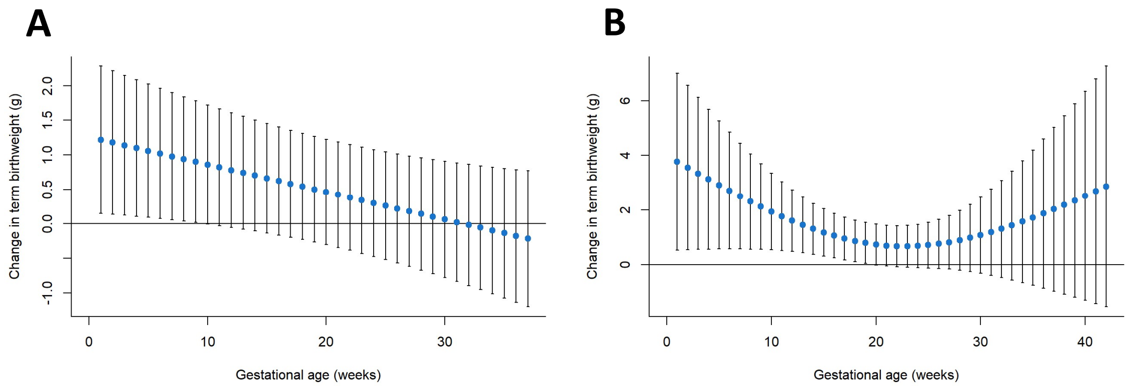
** "Complete exposure" refers to distributed lag models based on 37-week exposure matrices, with a study population that included term births only (such that every participant had a complete exposure history, with an observation for each of the first 37 weeks of pregnancy). "Partial exposure" refers to distributed lag models based on 42-week exposure matrices. For women who gave birth between 37 and 42 weeks, exposures after birth were set to 0.*
Note: These results are adjusted for gestational age only. Separate model for each exposure.

Supplemental Table 6. Comparison of average exposure models and distributed lag models: Results of fully-adjusted models of the association between weather conditions and birthweight

	N	Distributed lag model* **Change (g)** (95% CI)	Average exposure model* **Change (g)** (95% CI)
First 37 weeks of pregnancy	*3834*		
Mean temperature (5 °C)		**-11.0** (-84.7, 62.7)	**-6.78** (-64.0, 50.5)
SD temperature (1 °C)		**-112.2** (-217.5, -6.8)	**-2.2** (-17.5, 13.1)
Mean relative humidity (5%)		**-47.7** (-77.3, -18.2)	**-18.0** (-45.3, 9.3)
SD relative humidity (1%)		**-11.7** (-35.1, 11.6)	**4.0** (-8.9, 16.9)
1st trimester	*3834*		
Mean temperature (5 °C)		**16.2** (-18.3, 50.7)	**52.0** (10.4, 93.5)
SD temperature (1 °C)		**-54.5** (-106.7, -2.2)	**16.2** (-3.2, 35.6)
Mean relative humidity (5%)		**-9.6** (-32.8, 13.6)	**2.3** (-23.0, 27.6)
SD relative humidity (1%)		**-1.5** (-17.0, 14.0)	**-2.4** (-13.8, 9.0)
2nd trimester	*3834*		
Mean temperature (5 °C)		**-5.5** (-31.4, 20.4)	**-18.5** (-53.1, 16.0)
SD temperature (1 °C)		**-38.2** (-75.3, -1.0)	**-11.9** (-30.7, 6.9)
Mean relative humidity (5%)		**-11.4** (-28.7, 5.8)	**-18.1** (-41.4, 5.3)
SD relative humidity (1%)		**-4.3** (-12.5, 3.8)	**-1.3** (-13.1, 10.5)
3rd trimester (until week 37)			
Mean temperature (5 °C)	*3834*	**-21.7** (-50.8, 7.4)	**-50.8** (-87.0, -14.7)
SD temperature (1 °C)		**-19.5** (-65.5, 26.4)	**11.6** (-9.7, 32.9)
Mean relative humidity (5%)		**-26.7** (-46.9, -6.5)	**-33.6** (-58.2, -9.0)
SD relative humidity (1%)		**-5.9** (-18.8, 7.0)	**-12.1** (-22.9, -1.3)

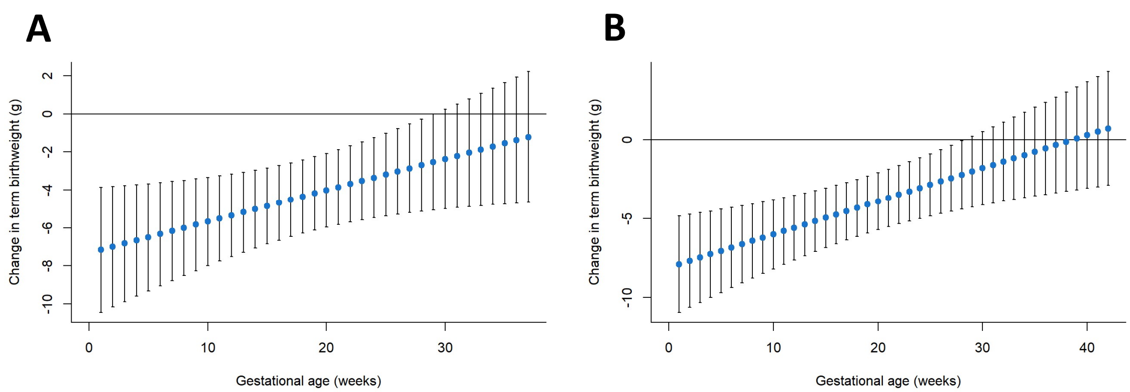
**Adjusted for the other exposures and the following participant characteristics: gestational age, maternal factors (age, height, weight, education, tobacco use, and parity), sex of child, season and year of conception, and recruitment center.*

Supplemental Figure 1. Change in term birthweight associated with a 5 °C increase in mean temperature in minimally-adjusted distributed lag models. [A] Association between term birthweight and mean temperature over the first 37 weeks of pregnancy, using complete exposure model. [B] Association between term birthweight and mean temperature over 42 weeks of pregnancy, using partial exposure model.



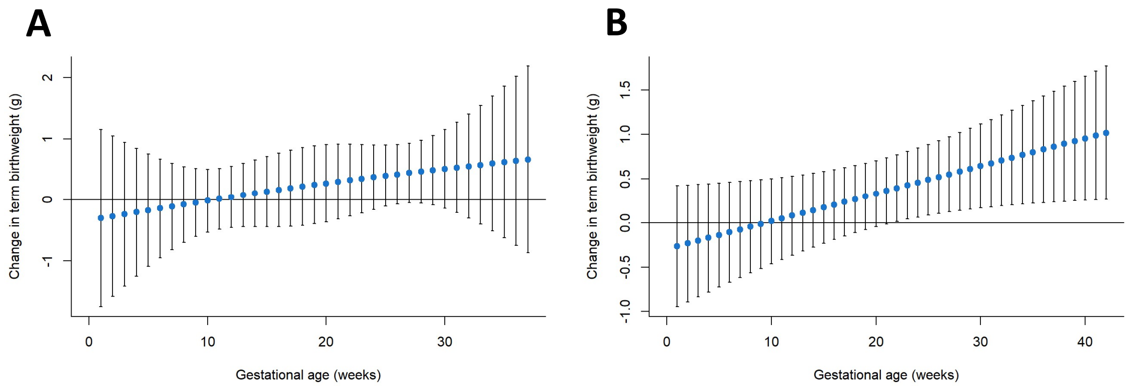
Note: Adjusted for gestational age only. Error bars represent 95% confidence intervals.

Supplemental Figure 2. Change in term birthweight associated with a 1 °C increase in standard deviation of temperature in minimally-adjusted distributed lag models. [A] Association between term birthweight and mean temperature over the first 37 weeks of pregnancy, using complete exposure model. [B] Association between term birthweight and mean temperature over 42 weeks of pregnancy, using partial exposure model.



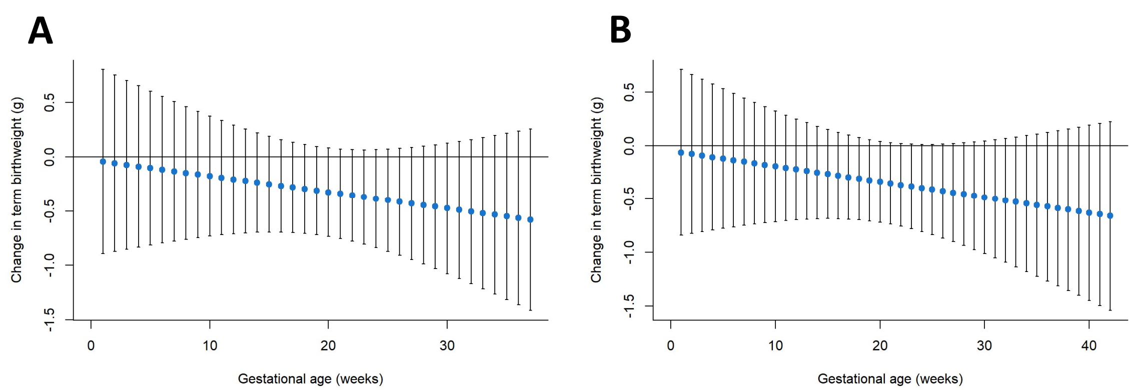
Note: Adjusted for gestational age only. Error bars represent 95% confidence intervals.

Supplemental Figure 3. Change in term birthweight associated with a 5% increase in mean relative humidity in minimally-adjusted distributed lag models. [A] Association between term birthweight and mean temperature over the first 37 weeks of pregnancy, using complete exposure model. [B] Association between term birthweight and mean temperature over 42 weeks of pregnancy, using partial exposure model.



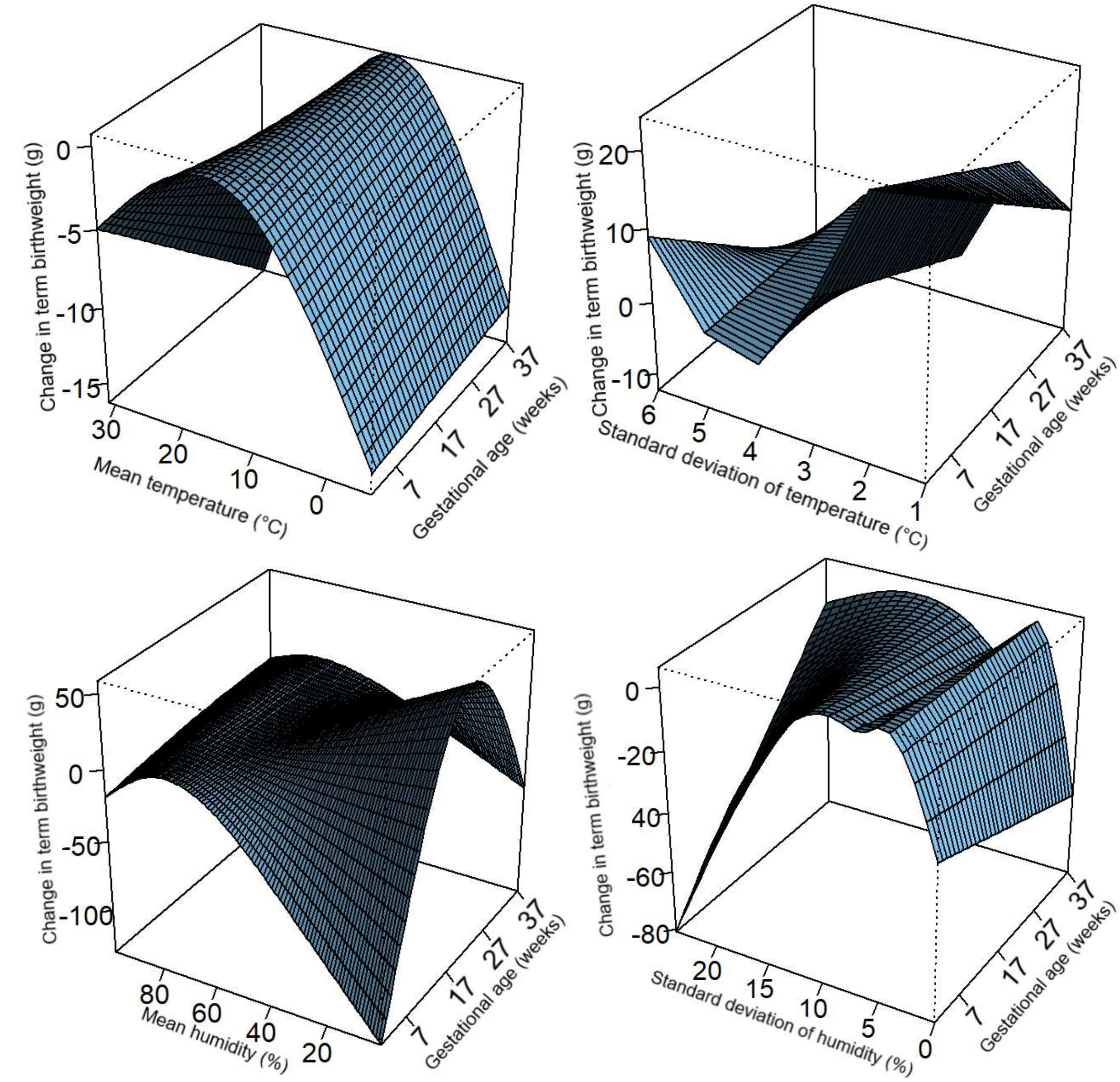
Note: Adjusted for gestational age only. Error bars represent 95% confidence intervals.

Supplemental Figure 4. Change in term birthweight associated with a 1% increase in standard deviation of humidity in minimally-adjusted distributed lag models. [A] Association between term birthweight and mean temperature over the first 37 weeks of pregnancy, using complete exposure model. [B] Association between term birthweight and mean temperature over 42 weeks of pregnancy, using partial exposure model.



Note: Adjusted for gestational age only. Error bars represent 95% confidence intervals.

Supplemental Figure 5. Exposure-lag-response plots for relationship between meteorological exposures during the first 37 weeks of pregnancy and term birthweight. [A] Mean temperature. [B] Standard deviation of temperature. [C] Mean humidity. [D] Standard deviation of humidity.



Note: These results are adjusted for the other exposures and the following participant characteristics: gestational age, maternal factors (age, height, weight, education, tobacco use, and parity), sex of child, season and year of conception, and recruitment center.

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