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Term birthweight and critical windows of prenatal exposure to average meteorological conditions and meteorological variability

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ABSTRACT

Background: Heat stress during pregnancy may limit fetal growth, with ramifications throughout the life course. However, critical exposure windows are unknown, and effects of meteorological variability have not been investigated.

Objectives: We aimed to identify sensitive windows for the associations of mean and variability of temperature and humidity with term birthweight.

Methods: We analyzed data from two French mother–child cohorts, EDEN and PELAGIE (n = 4771), recruited in 2002–2006. Temperature exposure was assessed using a satellite-based model with daily 1-km² resolution, and relative humidity exposure data were obtained from Météo France monitors. Distributed lag models were constructed using weekly means and standard deviation (SD, to quantify variability) from the first 37 gestational weeks. Analyses were then stratified by sex. Results for each exposure were adjusted for the other exposures, gestational age at birth, season and year of conception, cohort and recruitment center, and individual confounders.

Results: There was no evidence of association between term birthweight and mean temperature. We identified a critical window in weeks 6–20 for temperature variability (cumulative change in term birthweight of –54.2 g [95% CI: –102, –6] for a 1 °C increase in SD of temperature for each week in that window). Upon stratification by sex of the infant, the relationship remained for boys (weeks 1–21, cumulative change: –125 g [95% CI: –228, –21]). For mean humidity, there was a critical window in weeks 26–37, with a cumulative change of –28 g (95% CI: –49, –7) associated with a 5% increase in humidity for each week. The critical window was longer and had a stronger association in boys (weeks 29–37; –37 g, 95% CI: –63, –11) than girls (week 14; –1.8 g, 95% CI: –3.6, –0.1).

Discussion: Weekly temperature variability and mean humidity during critical exposure windows were associated with decreased term birthweight, especially in boys.

1. Introduction

Intrauterine growth restriction (IUGR)¹, the failure of a fetus to

reach its full growth potential, contributes significantly toward perinatal morbidity and mortality (Pallotto and Kilbride 2006). Even beyond the neonatal period, IUGR can have ramifications throughout the

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¹ Abbreviations: AIC = Akaike information criterion, CI = confidence interval, DLM = distributed lag model, IUGR = intra-uterine growth restriction, MODIS = Moderate Resolution Imaging Spectroradiometer, SD = standard deviation

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entire life course by increasing the risk of several cardiovascular and metabolic diseases (Fowden et al. 2006). A variety of maternal exposures during pregnancy have the potential to impact fetal growth, ranging from infections to stressful situations to environmental factors (Longo et al. 2014; Romo et al. 2009). With climate change leading to rising average temperatures and volatile meteorological conditions, it is important to understand the impacts of temperature and humidity on fetal growth.

Reduced birthweight can be a manifestation of IUGR. The current evidence on temperature and birthweight is somewhat mixed (Zhang et al. 2017). While some retrospective cohort studies (Bakhtsiyarava et al. 2018; Deschênes et al. 2009; Kloog et al. 2015; Li et al. 2018; Ngo and Horton 2016) and ecological studies (Arroyo et al. 2016; Basu et al. 2018; Flouris et al. 2009; Matsuda et al. 1998; Wells and Cole 2002) have linked hotter weather to a reduction in birthweight, others have noted higher birthweight with more frequent hot days (Grace et al. 2015), or lower birthweight with decreasing temperatures (Elter et al. 2004; Murray et al. 2000). A recent large cohort study found that hotter-than-average temperatures and colder-than-average temperatures were both associated with decreased term birthweight (though the reduction was smaller with colder-than-average temperatures), suggestive of an inverse U-shaped relationship (Sun et al. 2019). Similarly, another recent cohort study found that term low birth weight was associated with both hot and cold temperatures, compared to mild temperatures (Ha et al. 2017). Still others have found that the direction of association varies depending on the trimester of exposure (Lawlor et al. 2005), and some have reported no association at all between temperature and birthweight or low birthweight (Díaz et al., 2016; Son et al. 2019; Tustin et al. 2004).

Multiple reasons may account for the discrepancies between these findings. Studies conducted under different climates investigate different temperature ranges, and if the dose–response relationship is not linear (as is often the case with temperature), this could lead to apparent differences in results. Another possible explanation is that location-specific differences in climate could lead to different patterns of effect, especially since acclimatization varies between populations (Kuehn and McCormick 2017). 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 (Bathiany et al. 2018). An increase in temperature variability implies that women will experience temperature fluctuation over relatively short periods of time. Hence, the adverse health effects of climate change could be related to an increase in short-term variability of temperature rather than to a warmer average temperature to which women might be able to adapt in the long term (McGeehin and Mirabelli 2001). Yet there is currently limited evidence about the effects of temperature variability on pregnancy outcomes (Molina and Saldarriaga 2017).

Besides location-specific differences in climate, the disparate findings in the literature may also be related to methodological differences in exposure assessment and analytical approach. For instance, many studies have relied on temperature measurements taken from the nearest monitoring station, but spatial coverage can be sparse. This may lead to exposure misclassification. The issue is compounded by the fact that most studies assess outside temperature, which may strongly differ from personal exposure, depending on the area-specific rate of air conditioning and habits related to window opening. There have also been differences in the way temperature exposure is conceptualized. For example, while some have focused on heatwaves (Díaz et al., 2016), others have investigated daily or weekly minimum and maximum temperatures (Arroyo et al. 2016; Deschênes et al. 2009; Li et al. 2018; Murray et al. 2000), and several others have studied mean temperature over a given period (Kloog et al. 2018; Son et al. 2019; Tustin et al. 2004). 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. Furthermore, the approach that considers trimester average exposures separately to estimate associations with health outcomes has been shown to be biased, and mutual adjustment for trimester-specific exposures may not be enough to eliminate bias (Wilson et al. 2017b). 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 (Gasparrini 2014). 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) (Wilson et al. 2017a). Although this strategy has been applied to preterm birth (Cox et al. 2016; Vicedo-Cabrera et al. 2014), to our knowledge it has not been used to study the impact of meteorological conditions on term birthweight.

Humidity limits the human body's ability to release heat, and can exacerbate the heat stress caused by high temperatures (Wells and Cole 2002). 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) (Basu et al. 2018; Son et al. 2019). However, little is currently known about the possible effects of humidity itself on birth outcomes.

We aimed to clarify the association between mean temperature and relative humidity and term birthweight (i.e. among infants born after 37 completed gestational weeks), by using a fine spatio-temporal model for temperature exposure and building distributed lag models to identify critical windows of exposure. Furthermore, we investigated the role of meteorological variability.

2. Methods

2.1. Study population

Data were obtained from a consortium of two French mother–child prospective cohorts, EDEN (Etude des Déterminants pré et post natales du développement et de la santé de l'ENfant) and PELAGIE (Perturbateurs Endocriniens: étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité et l'Enfance). 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 (Heude et al. 2016; Petit et al. 2012).

For the EDEN cohort, 2,002 pregnant women were enrolled in the cities of Poitiers and Nancy between 2003 and 2006 (Fig. 1). They were recruited from the prenatal clinics of university hospitals before the 24th week of amenorrhea. Women were not included if they had 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 their first prenatal care visit 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.

After accounting for multiple gestation, non-livebirths, and attrition, there were 1,907 children enrolled in EDEN and 3,322 children enrolled in PELAGIE (Fig. 1). For the purposes of our study, women with multiple gestation, diabetes diagnosed before pregnancy, gestational diabetes, and gestational hypertension were excluded, to avoid potential confounding. Preterm births (gestational age at birth < 37 weeks) 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.

2.2. Data collection for covariates and outcomes

In both cohorts, questionnaires and clinical examinations were used to collect sociodemographic and medical information, during and after

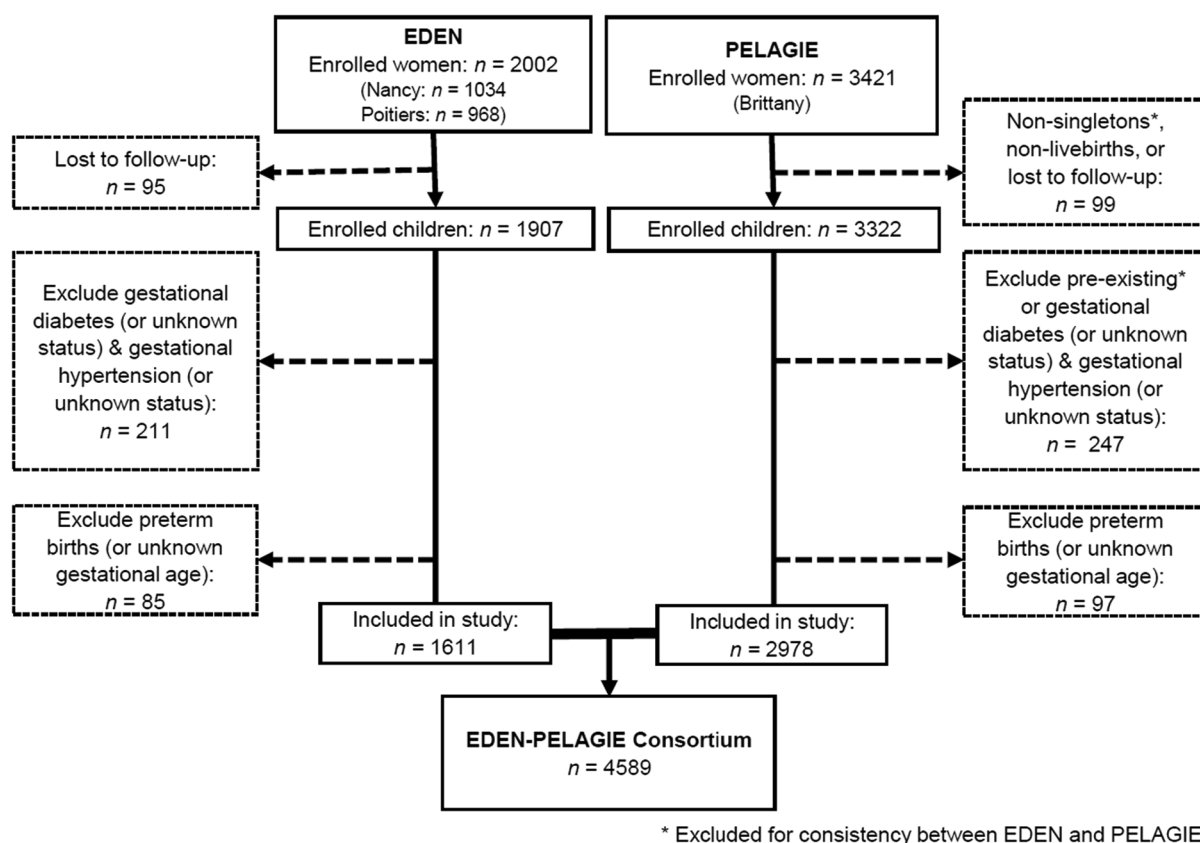


Fig. 1. Composition of study population.

pregnancy. Birthweight data were obtained from medical records (Chevrier et al. 2011; Kadawathagedara et al. 2016). In EDEN, newborn birth weight was measured with Seca electronic scales (Hamburg, Germany: Seca 737 in Nancy and Seca 335 in Poitiers; precision 10 g). The PELAGIE study covered the whole region of Brittany (3 departments: Ille-et-Vilaine, Côtes d'Armor, and Finistère), which includes many clinics and university hospitals, which used their own weighing scales. Home addresses of the women were collected and geocoded, at the time of inclusion for PELAGIE (mean gestational age 11.7 weeks) and at the time of birth for EDEN.

2.3. Exposure assessment

Temperature exposure estimates were generated by a hybrid spatio-temporal model, using Moderate Resolution Imaging Spectroradiometer (MODIS) satellite surface temperature data (Kloog et al. 2017). Briefly, daily satellite surface temperature data (in 1 km² 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 temperature exposure estimates for each gestational week for every study participant, based on her home address.

Humidity was defined as relative humidity, which reflects the level of moisture contained in the air compared to the maximum amount of moisture that could be present at a given temperature (US National Oceanic and Atmospheric Administration 2013). The 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.

Exposure estimates for mean temperature, standard deviation of temperature, mean humidity, and standard deviation of humidity, were calculated for each participant within each week of pregnancy.

2.4. 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'Éthique 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).

2.5. Statistical analyses

We performed regression analysis for this cohort study with generalized linear models, adjusted for the following possible confounders: gestational age at birth, cohort and recruitment center (Nancy, Poitiers, Brittany), season of conception, sex of the newborn, and several maternal characteristics (height, pre-pregnancy weight, parity, age at conception, educational level, and smoking status) (Kramer 1987; Strand et al. 2011). These covariates were selected *a priori*, based on biological and epidemiological reasoning and evidence in the literature. Gestational age at birth was censored at 42 weeks, since professional consensus among French obstetricians favors induction of labor after that point (Vayssière et al. 2013).

2.5.1. Main analytical strategy: Distributed lag models

Relationships between term birthweight and meteorological

Table 1
Distribution of participant characteristics.

Variable	Consortium n (%) or Mean (SD)	EDEN n (%) or Mean (SD)	PELAGIE n (%) or Mean (SD)	p-value [χ^2 ^a or t-test ^b]
Study population	4589 (100%)	1611 (100%)	2978 (100%)	–
Temperature over entire pregnancy (°C)	12.0 (2.1)	11.6 (2.4)	12.2 (1.9)	< 0.001 ^b
Humidity over entire pregnancy (%)	79.0 (4.2)	77.6 (3.5)	79.8 (4.3)	< 0.001 ^b
Term birthweight (g)				< 0.001 ^b
Mean birthweight in g, term births (SD)	3402 (4 3 9)	3338 (4 3 2)	3436 (4 3 9)	
Missing	4 (0.1%)	3 (0.2%)	1 (0.0%)	
Recruitment center				< 0.001 ^a
Brittany (PELAGIE)	2978 (64.9%)	0 (0.0%)	2978 (100.0%)	
Poitiers (EDEN)	809 (17.6%)	809 (50.2%)	0 (0.0%)	
Nancy (EDEN)	802 (17.5%)	802 (49.8%)	0 (0.0%)	
Maternal age at conception				< 0.001 ^a
< 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%)	
≥ 35 years	576 (12.6%)	191 (11.9%)	385 (12.9%)	
Missing	14 (0.3%)	0 (0.0%)	14 (0.5%)	
Educational level				< 0.001 ^a
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%)	
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				0.09 ^a
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%)	
> 10 cigarettes/day	214 (4.7%)	82 (5.1%)	142 (4.4%)	
Missing	30 (0.7%)	2 (0.1%)	28 (0.9%)	
Parity				0.006 ^a
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%)	
≥ 3	170 (3.7%)	79 (4.9%)	91 (3.1%)	
Missing	12 (0.3%)	3 (0.2%)	9 (0.3%)	
Sex of infant				0.19 ^a
Male	2337 (50.9%)	842 (52.3%)	1495 (50.2%)	
Female	2252 (49.1%)	769 (47.7%)	1483 (49.8%)	
Season of conception				0.002 ^a
Winter	1140 (24.8%)	359 (22.3%)	781 (26.2%)	
Spring	1055 (23.0%)	355 (22.0%)	700 (23.5%)	
Summer	1258 (27.4%)	459 (28.5%)	799 (26.8%)	
Fall	1136 (24.8%)	438 (27.2%)	698 (23.4%)	
Year of conception				< 0.001 ^a
2002	653 (14.2%)	67 (4.2%)	586 (19.7%)	
2003	1731 (37.7%)	648 (40.2%)	1083 (36.4%)	
2004	1553 (33.8%)	597 (37.1%)	956 (32.1%)	
2005	652 (14.2%)	299 (18.6%)	353 (11.9%)	
Maternal pre-pregnancy weight				0.003 ^b
Mean weight in kg (SD)	60.5 (11.4)	61.2 (11.7)	60.1 (11.2)	
Missing	23 (0.5%)	14 (0.9%)	9 (0.3%)	
Maternal height				0.001 ^b
Mean height in cm (SD)	163.9 (6.0)	163.5 (6.2)	164.1 (5.9)	
Missing	34 (0.7%)	22 (1.3%)	12 (0.4%)	
Gestational age at birth				< 0.001 ^b
Mean gestational age at birth in weeks (SD)	38.2 (1.2)	38.0 (1.8)	38.3 (1.2)	

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 at birth. Fully-adjusted models contained mean temperature, mean humidity, standard deviation of temperature, and standard deviation of humidity as simultaneous exposures, with adjustment for the aforementioned possible confounders. (As seen in Table A1, these meteorological exposures were not highly correlated with each other within each week of pregnancy; the Spearman correlation coefficients ranged from –0.55 to 0.47.) We used distributed lag models with an exposure matrix of the first 37 gestational weeks for each meteorological exposure. Exposures after 37 weeks were not addressed in the main analysis, but were included in a sensitivity analysis as described later.

The exposure–response relationship 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 minimally-adjusted models for each exposure (Table A2). 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 number of degrees of freedom was chosen. Knots were set at equally spaced quantiles. We graphed these fully-adjusted DLMs and used them to identify critical exposure windows during pregnancy.

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 (Table A3). The AIC of fully-adjusted models was consistently lower with a linear exposure–response relationship than with a non-linear exposure–response relationship. Also, we performed likelihood ratio tests for departure from linearity using fully-adjusted models, as shown in Table A4. The results were consistent with linearity ($p > 0.05$), so a linear exposure–response relationship was used in final models.

2.5.2. Sensitivity and secondary analyses

Since fetal weight gain accelerates in late pregnancy (Cunningham et al. 2018), 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 distributed lag modelling technique does not permit missing values in the exposure matrix, such that a participant missing any exposure observations must be completely removed from the analysis. To avoid this, for any woman who delivered prior to 42 weeks, exposure after delivery was set to the median of exposures in previous weeks (specific to each woman). We refer to the models in this secondary analysis as “partial exposure distributed lag models,” since participants were permitted to have exposure histories only partly filled with actual weekly exposures, and “missing” values after birth replaced with median exposure values. 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 estimate, with no imputed median values.

We also created models using average exposure windows (exposure data averaged over trimesters and the first 37 weeks of pregnancy), for comparison with the distributed lag models and to illustrate the possible bias of these types of analyses (Wilson et al. 2017b). Since meteorological exposures in each trimester were somewhat correlated with the same exposures in the other two trimesters (particularly for mean temperature in the 1st and 3rd trimesters), we used the Frisch-Waugh method to adjust for the influence of average exposure in the other trimesters. (Please see Table A5 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 (Bell et al. 2007).

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 (R Core Team 2017), mainly using the *dlm* package (Gasparrini 2014). A significance level of $\alpha = 0.05$ was used in interpreting results.

3. Results

3.1. Study population

Approximately two-thirds 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 1). 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). The mean gestational age at birth among the term births was 38.2 ± 1.2 weeks.

Mean temperature \pm standard deviation over the entire pregnancy was 12.0 ± 2.1 °C, while mean humidity was $79.0 \pm 4.2\%$. Both of these exposures were slightly higher in PELAGIE than in EDEN. On average, weekly standard deviation of temperature (mean \pm standard deviation) was 2.1 °C \pm 0.02, while weekly standard deviation of humidity was $6.65\% \pm 0.05$.

Fig. 2 illustrates the distribution of mean temperature and mean humidity over time, by location of recruitment center.

As Table A6 shows, mean term 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 term birthweight was 3402 ± 439 g. Table A6 also contains the results of analyses of term birthweight with other participant characteristics, adjusted only for gestational age at birth. In general, higher maternal age, maternal education, and parity were associated with higher term birthweight. Tobacco use was associated with lower term birthweight.

3.2. Associations between term birthweight and temperature and relative humidity

There was no week of pregnancy with a statistically significant association between mean temperature and term birthweight in the complete exposure model, partial exposure model, or sex-stratified complete exposure model (Fig. 3). In all of these models, the estimated association trended downwards but was always fairly close to 0.

In the complete exposure model, partial exposure model, and sex-stratified complete exposure model, the estimate for the association between standard deviation of temperature and term birthweight was negative but steadily upwards towards 0 (Fig. 4). Based on the complete exposure model, this relationship was statistically significant between weeks 6 and 20. Over this critical period, there was a cumulative change in term birthweight of -54.2 g (95% CI: $-101.9, -6.4$) for a 1 °C increase in standard deviation of temperature in every week from week 6 to 20. After stratification by sex of the infant, the relationship in female infants was nonsignificant, but the relationship in male infants was statistically significant from week 1 to 21. The cumulative change in term birthweight was -124.5 g (95% CI: $-228.0, -20.9$) (Table 2).

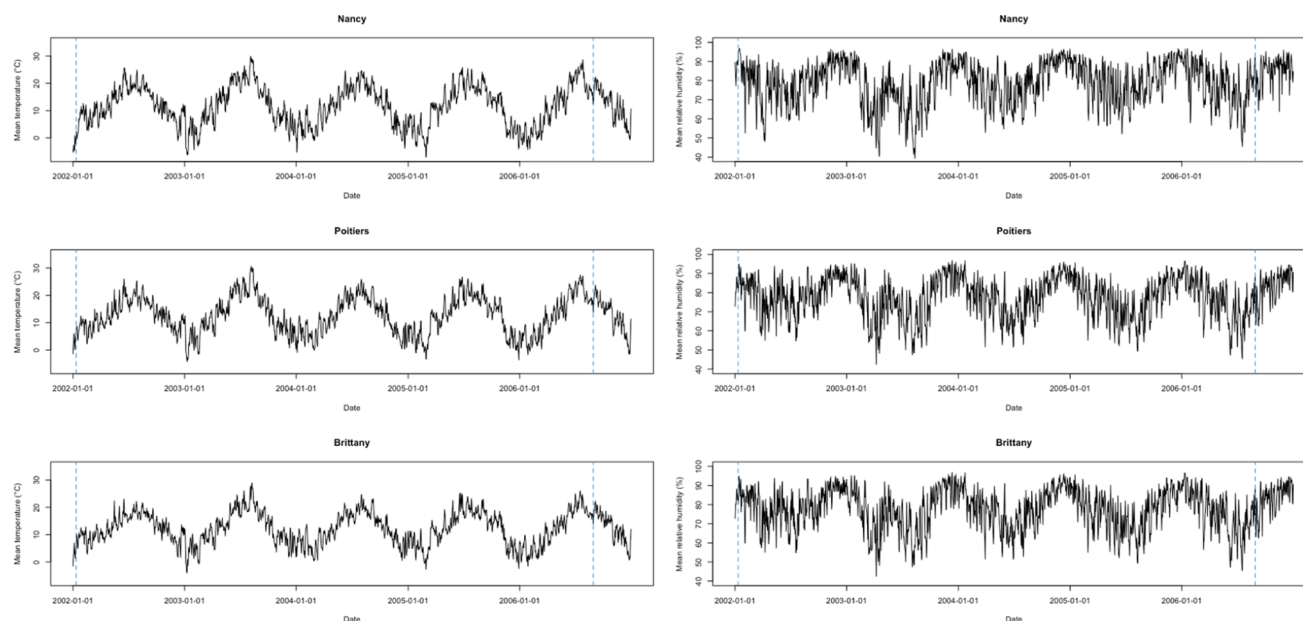
Based on the complete exposure analysis and the partial exposure analysis, the estimated association between mean humidity and term birthweight was negative throughout pregnancy (Fig. 5a, Fig. 5b). In the complete exposure analysis, the relationship between mean humidity and term birthweight was statistically significant from week 26 to 37. There was a cumulative change in term birthweight of -28.2 g (95% CI: $-49.2, -7.1$) for a 5% increase in mean humidity for each week of that critical window (Table 2). In male infants, this relationship was statistically significant from week 29 to 37, and the cumulative change in term birthweight was -37.3 g (95% CI: $-63.4, -11.1$) (Table 2). 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 (Fig. 5d). There were borderline significant associations between approximately week 13 and week 25. At week 14, this association was statistically significant, with a change in term birthweight of -1.8 g (95% CI: $-3.6, -0.1$) for a 5% increase in mean humidity (Table 2).

Fig. 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. In analysis stratified by sex of the infant, for male infants the estimated association downtrended over pregnancy, whereas for female infants it uptrended (Fig. 6c, Fig. 6d).

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 in Table 2 and Fig. 3d - Fig. 6d. Even with the longer exposure matrix of the partial exposure models, no week after the 37th week of pregnancy was found to have statistically significant associations between weather conditions and term birthweight.

The above findings are from fully-adjusted DLMS, while results from minimally-adjusted DLMS are provided in Figure A1 - Figure A4 and Table A7.

Table A8 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 the fully-adjusted



Note: Dotted lines represent date of first conception and last delivery in the study population

Fig. 2. Mean temperature and humidity estimates at home addresses of study participants over time, by recruitment center location.

complete exposure DLMs and the trimester average exposure approach. Estimates of association produced by distributed lag models were generally in the same direction as those produced by trimester average exposure models, but with different magnitudes. However, it is worth noting that the effect sizes from these models are not directly comparable, because the exposures of interest are averaged over different time periods (weekly vs. over a trimester or entire pregnancy). Results that were statistically significant in the DLMs were typically not statistically significant in the trimester average exposure models, and vice versa. In particular, the trimester average exposure approach identified statistically significant associations for mean temperature during trimesters 1 and 3, but no strong association with temperature variability (Table A8). This is the opposite of the pattern observed with the cumulative change (Table A8) and critical weeks (Fig. 3, Fig. 4) estimated by the distributed lag models.

4. Discussion

4.1. Main findings

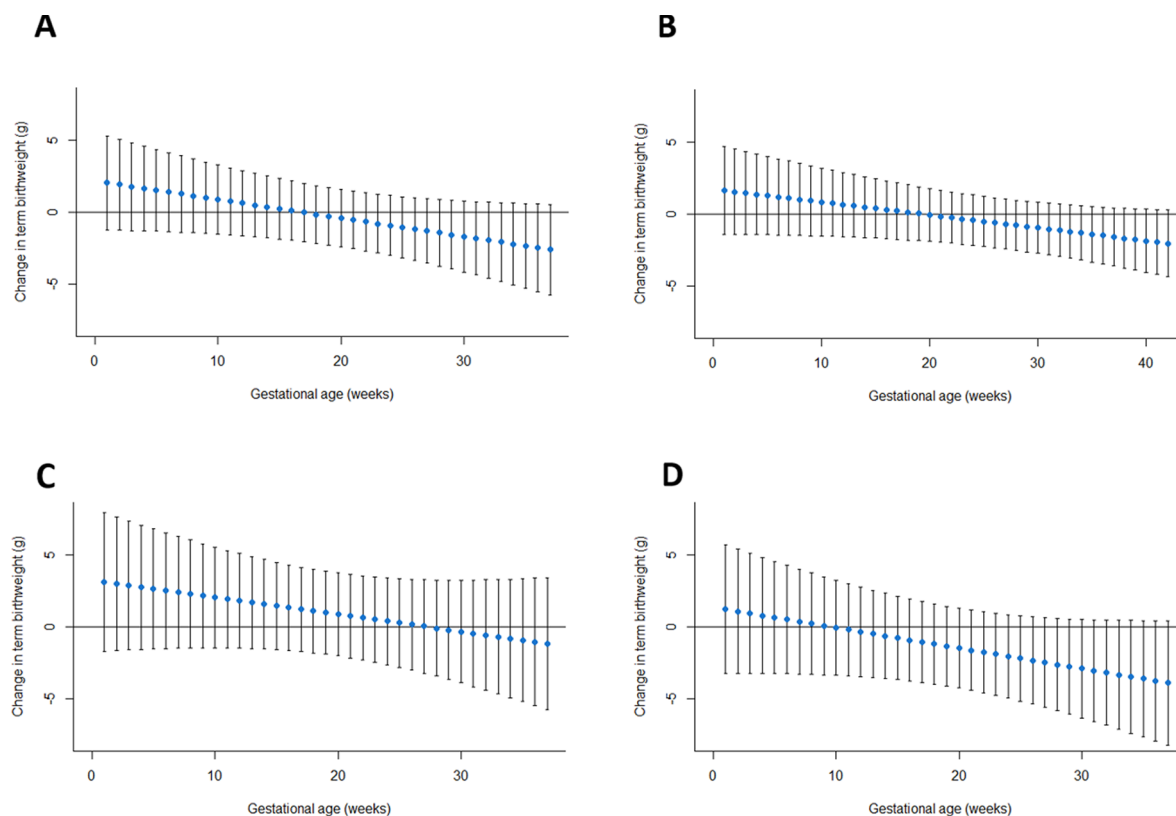
In our primary analysis, critical windows of exposure were found for weekly standard deviation of temperature from week 6 to 20 (middle of the first trimester to middle of the second trimester) and for weekly mean humidity from week 26 to 37 (late in the second trimester to late in the third trimester), both of which were negatively associated with term birthweight. Stratifying these analyses by the sex of the infant suggested that these negative associations were much larger in boys than girls. In fact, there was a significant negative association with standard deviation of temperature in the first 21 weeks of pregnancy for male infants, but no critical exposure window for female infants. The critical window for mean humidity in boys (week 29 to 37) was longer than in girls (week 14). No critical exposure window was identified for mean temperature or standard deviation of humidity.

Regarding clinical significance, although an estimated average change of 50 g in birth weight might be seen as somewhat small, it could reflect suboptimal development and carry some clinical significance for at-risk infants. For comparison, the general difference observed in birth weight between boys and girls is around 100 g (132 g in the present study, please see Table A6), which is considered to

represent true physiological differences. We limited our study to term births to avoid confounding, but one might expect the same critical windows to exist for pre-term births (if these critical windows arise from particular stages in fetal development). For infants who are pre-term or small for gestational age, small changes in birthweight may be more meaningful. Furthermore, when considered across an entire population where almost all pregnant women are exposed to these meteorological factors, these small changes might shift the birth weight distribution towards the left and thus increase the number of low birth weight (< 2500 g) babies, which has major impact in terms of public health as these babies are at higher risk for perinatal morbidity and mortality and developmental issues.

4.2. Discussion of methodology

To our knowledge, this is the first time that 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 trimester average exposures to study health effects of environmental exposures 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 (Wilson et al. 2017b). In their simulation, results of regressions relying on trimester average exposure were biased, particularly when adjustment was not made for exposures in the other trimesters, 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. In our analysis, the bias of the trimester average exposure approach may have been somewhat reduced by the use of the Frisch-Waugh method to adjust for other trimester exposures. In fact, our distributed lag models and more classical regression models were in agreement regarding a possible adverse effect of third trimester humidity exposure on term birthweight. Regarding temperature effects, when we compared results from distributed lag models to those of the trimester average exposure approach, 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 the trimester average



Note: These results are adjusted for the other exposures (SD temperature, mean humidity, and SD humidity) and the following participant characteristics: gestational age at birth, 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.

Fig. 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.

exposure approach. It should be noted though that for a given trimester of exposure, the distributed lag model and the trimester average exposure approach do not estimate the same effect. For example, for mean temperature the distributed lag model assesses the cumulative effect of a 5 °C increase in every week throughout the whole lag period of the given trimester, while the trimester average exposure approach assesses the effect of a 5 °C increase on average in the given trimester. Even so, distributed lag models were a more flexible and data-driven approach to identifying critical exposure windows.

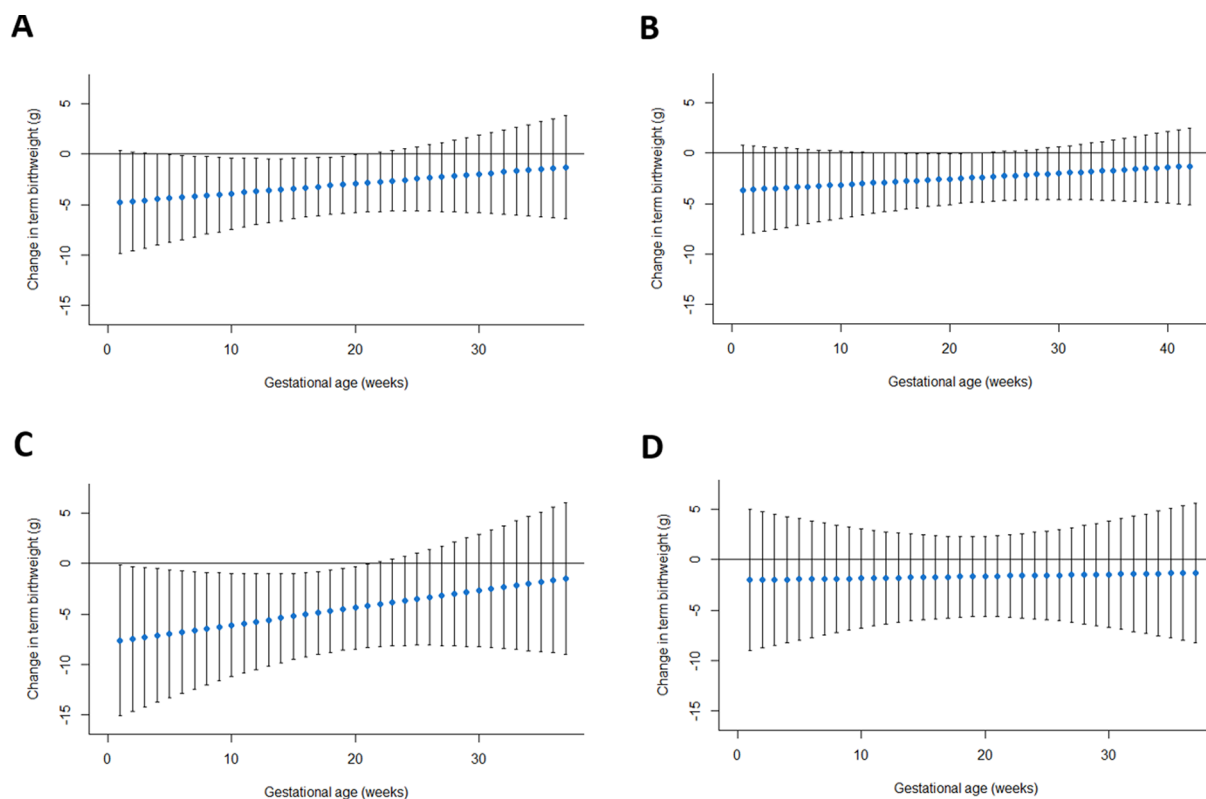
The main analysis only looked for critical windows of exposure during the first 37 weeks of pregnancy. In the secondary analysis using partial exposure DLMs, we examined the entire 42 weeks of pregnancy but did not identify any critical windows of exposure after 37 weeks. This supports the theory that most likely, no critical windows were missed by the 37-week complete exposure DLMs. For this study we favor using 37-week exposure matrices, as this avoids the need for median imputation of post-birth exposures. This discussion will therefore focus on the results of the complete exposure analysis.

4.3. Strengths and weaknesses

One major strength of this study is the fine spatial and temporal resolution of the temperature exposure data used. By using a satellite-based temperature model with high spatial resolution (1 km²), we were

able to reduce exposure error and the downward bias that could accompany it (Zanobetti et al. 2017; Zeger et al. 2000). Furthermore, the use of distributed lag models allowed for fine temporal resolution of exposure modelling. These models permitted us to identify critical windows of exposure during pregnancy with more precision than the trimester average exposure approach. Another 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 weekly 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 we did not account for daily activity patterns or changes in residence during pregnancy, and instead relied on participants' home addresses at time of inclusion (PELAGIE) or at birth (EDEN) to estimate exposure. Based on the literature, we would expect about 20% of women to have changes in residence during pregnancy (Bell and Belanger 2012). Since women are more likely to move during the second trimester of pregnancy (Bell and Belanger 2012), measurement error in exposure estimates is more likely towards the end of pregnancy for PELAGIE and towards the beginning of the pregnancy for EDEN. Of note, residential mobility during pregnancy is often fairly local (e.g. < 10 km), such that even women who moved during pregnancy may not have had large changes in meteorological



Note: These results are adjusted for the other exposures (mean temperature, mean humidity, and SD humidity) and the following participant characteristics: gestational age at birth, 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.

Fig. 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.

exposure (Bell and Belanger 2012). In this study we would expect residential mobility to lead to nondifferential exposure misclassification, causing our results to be biased towards the null.

As for other weaknesses of this study, the humidity data were

obtained from monitoring stations, and therefore did not have the same level of fine spatial resolution as the temperature data. We did not adjust for air pollution, which has been linked with decreased birthweight (Stieb et al. 2012) and is often associated with temperature

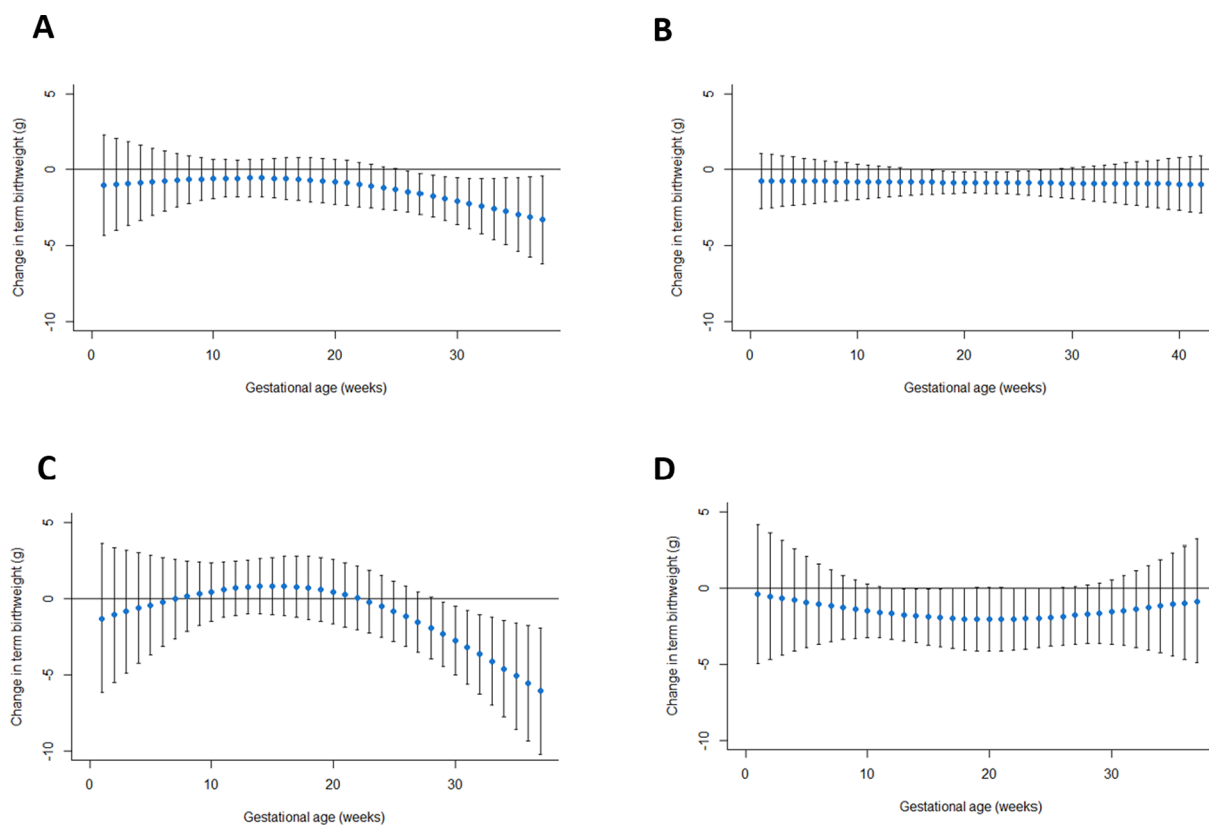
Table 2

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 ^a distributed lag model		Partial exposure ^a distributed lag model	
	N	Change (g) (95% CI)	N	Change (g) (95% CI)
SD temperature (1 °C)				
All infants: Weeks 6–20	3834	−54.2 (−101.9, −6.4)		
Male infants: Weeks 1–21	1923	−124.5 (−228.0, −20.9)		
Mean humidity (5%)				
All infants: Weeks 17–26			4347	−9.4 (−17.1, −1.7)
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: Week 14	1911	−1.8 (−3.6, −0.1)		

Note: These results are adjusted for the other exposures and the following participant characteristics: gestational age at birth, 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.

^a “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 the median of prior exposures (specific to each woman).



Note: These results are adjusted for the other exposures (mean temperature, SD temperature, and SD humidity) and the following participant characteristics: gestational age at birth, 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.

Fig. 5. Change in term birthweight associated with a 5% increase in mean 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.

(Buckley et al. 2014). However, air pollution might be on the causal pathway between temperature exposure and term birthweight, so adjusting for air pollution would potentially have been inappropriate (Buckley et al. 2014).

We can expect some small measurement error from the weighing scales, which is likely to be nondifferential and therefore produce bias toward the null. Our study identified significant vulnerable windows to temperature variability and mean humidity in association with decreased birthweight, which suggests that the measurement error and corresponding bias were minimal.

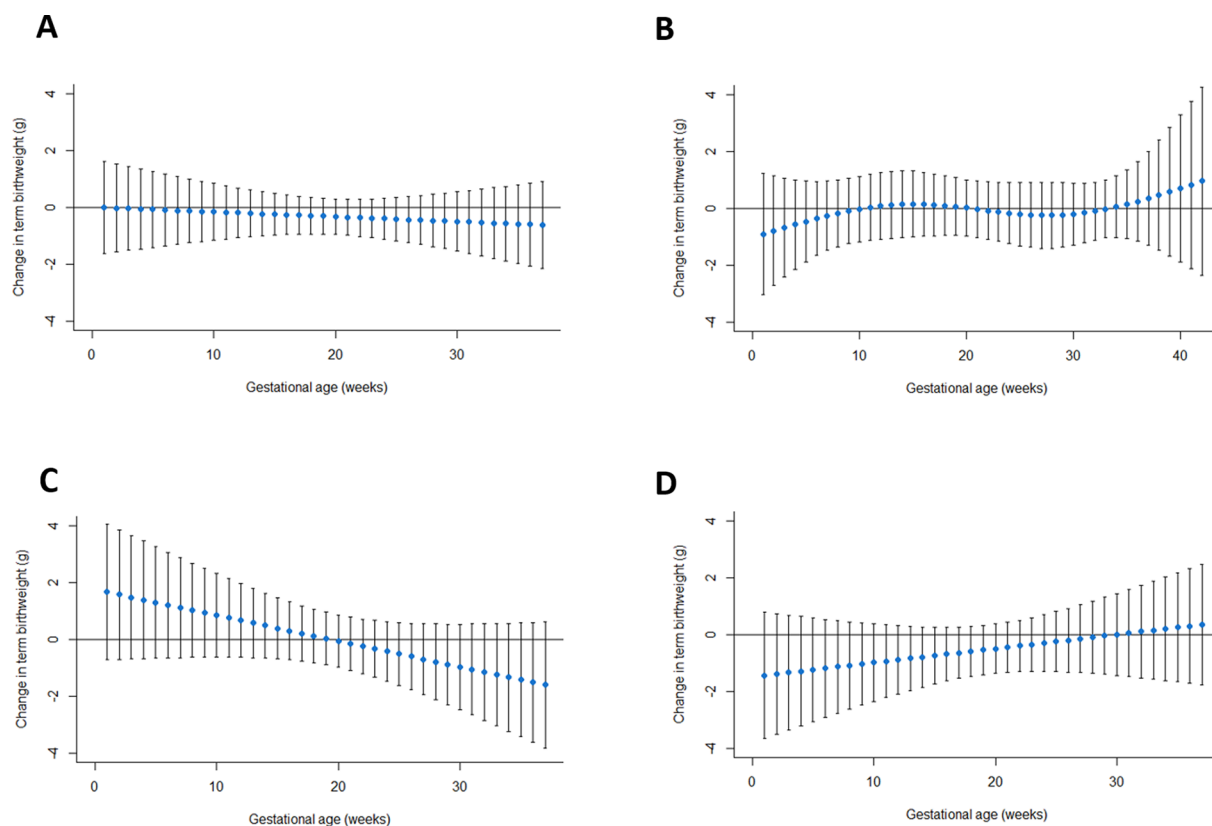
4.4. Comparison with the literature

Unlike some previous studies (Elter et al. 2004; Kloog et al. 2015; Lawlor et al. 2005; Sun et al. 2019), we did not find an association between mean temperature and birthweight, either positively or negatively. This is likely because we used distributed lag models rather than trimester average exposure models in our main analysis, to reduce bias (Wilson et al. 2017b). Kloog et al. also assessed term birthweight in their 2015 study of mean temperature and birth outcomes in Massachusetts, and they similarly used high resolution temperature data obtained from a satellite-based model (Kloog et al. 2015). However, they used models relying on various predefined time windows before birth, not DLMs. They found that higher mean temperature in the third

trimester was significantly associated with decreased term birthweight. Although probably biased, the results of our secondary analysis relying on trimester average exposures were consistent with those reported by Kloog et al.

Some prior studies have described a nonlinear relationship between temperature and birthweight, and the relationship between temperature and other health outcomes like mortality has been described as V-, J- or U-shaped (Armstrong 2006; Basu et al. 2018; Kloog et al. 2018; Sun et al. 2019). However, both AIC and formal likelihood ratio testing supported modelling our data with a linear exposure–response relationship. Although we do not yet have an explanation for this relative inconsistency, it suggests that the relationship between temperature variability and term birthweight would be linear, which might be relevant from a physiological point of view. As for humidity, we observed a linear relationship between mean humidity and term birthweight.

While several studies on weather and birth outcomes have adjusted for humidity to clarify the impacts of temperature (Li et al. 2018; Rashid et al. 2017), to our knowledge this is the first study to report 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 (Basu et al. 2018). The critical window of mean humidity exposure identified



Note: These results are adjusted for the other exposures (mean temperature, SD temperature, and mean humidity) and the following participant characteristics: gestational age at birth, 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.

Fig. 6. Change in term birthweight associated with a 1% increase in standard deviation of 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.

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 (Son et al. 2019).

To our knowledge, this is also the first study to investigate the impacts of variability in temperature and relative humidity on term birthweight, with standard deviations 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 monthly 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 (Molina and Saldarriaga 2017). We likewise found 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 shorter timescale (week by week).

4.5. Biological plausibility

Animal studies have shown chronic thermal stress in pregnancy to cause reduced birthweight in many species, due to diminished uterine and umbilical blood flow and reduced placental weight (Wells 2002).

However, the relevance of these potential mechanisms in humans is unclear. Some studies have reported associations between temperature changes and inflammatory markers. Although many of these have noted greater evidence of inflammation with reductions in temperature (Basu et al. 2017; Halonen et al. 2010; Hong et al. 2012; Schneider et al. 2008), some have also found decreased inflammatory markers with lower temperatures (Hampel et al. 2010) or increased inflammatory markers with higher temperatures (Wilker et al. 2012). This suggests the possibility that an inflammatory mechanism could be at play in the relationship between weather conditions and fetal growth. Also, heat stress can induce oxidative stress, and placental oxidative stress has been implicated as a possible contributor to intrauterine growth restriction (Dennerly 2010; Fujimaki et al. 2011; Takahashi 2012). These potential mechanisms do not directly address temperature variability, as a concept separate from average 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 thermal stress. Furthermore, thermoregulation and acclimation to significant rapid changes in temperature may be less efficient in pregnant women, given the cardiovascular demands and other physiologic changes involved in pregnancy.

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 (Wells and Cole 2002). Bind et al. reported that relative

humidity was associated with blood 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 (Bind et al. 2014). In pregnant women, associations have been shown between relative humidity during the second trimester and the month preceding birth and placental DNA methylation in several genomic regions (Abraham et al. 2018). More research is certainly needed, but this hints at the possibility that epigenetic programming might be involved in the relationship between humidity and fetal growth. In our study, reduced term birthweight was associated with increased mean humidity during the end of the pregnancy, which corresponds to the developmental period where the baby gains the most weight (Smith 2004).

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 stressors (Jedrychowski et al. 2009; Vik et al. 2003). 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 weekly temperature variation. Our results suggest that male infants might be more vulnerable regarding the effects of temperature and humidity on term birthweight than female infants. The exact biological mechanisms underlying these different development patterns have yet to be fully elucidated. That said, studies have suggested that placentas for boys may be more efficient but have less reserve than placentas for girls. In other words, although placentas for boys may allow them to grow faster than girls from a very early stage, boys may also be at higher risk of impaired growth if fetal nutrition (delivered via the placenta) is compromised (Eriksson et al. 2010; Forsén et al. 1999). This raises the question of whether boys might be more susceptible to placental oxidative stress or impaired function induced by heat stress, which would be consistent with our results. Interestingly, though not statistically significant, the association between term birth weight and standard deviation of humidity downtrended over time in boys and uptrended over time in girls. Also, for mean humidity the lag-response relationship had an inverse U-shape in boys and a very shallow U-shape in girls. If confirmed by future studies, this may suggest multiple mechanisms at play in the link between meteorological conditions and fetal development, perhaps predominating at different times in male and female infants.

5. Summary

By estimating effects of both mean and variability of temperature and humidity simultaneously, this study adds to the evidence of a significant association between term birthweight and temperature and humidity exposure, especially temperature variability. A key contribution of this study is the identification of critical windows for adverse effects on term birthweight, with regards to increased temperature variability (early to mid-pregnancy) and mean humidity (mid- to late pregnancy). Our results suggest that temperature variability could be an important risk factor for reductions in term birthweight. Boys seemed to be more likely to have an association between reduced term birthweight and increased exposure to temperature variability and mean humidity. These findings have significant implications not only for the health of newborns, but also for health across the lifespan, as reduced birthweight is associated with chronic diseases in childhood and adulthood. Identification of time window- and sex-specific associations provide insights into the identification of vulnerable subgroups and the underlying mechanisms linking meteorological conditions and birthweight.

CRedit authorship contribution statement

Otana Jakpor: Conceptualization, Methodology, Formal analysis, Writing - original draft, Funding acquisition. **Cécile Chevrier:**

Conceptualization, Methodology, Writing - review & editing. **Itai Kloog:** Methodology, Writing - review & editing. **Meriem Benmerad:** Data curation, Writing - review & editing. **Lise Giorgis-Allemand:** Data curation, Writing - review & editing. **Sylvaine Cordier:** Methodology, Writing - review & editing. **Emie Seyve:** Methodology, Software, Writing - review & editing. **Ana Maria Vicedo-Cabrera:** Methodology, Software, Writing - review & editing. **Rémy Slama:** Writing - review & editing. **Barbara Heude:** Writing - review & editing. **Joel Schwartz:** Conceptualization, Methodology, Supervision, Writing - review & editing. **Johanna Lepeule:** Conceptualization, Methodology, Writing - review & editing, Supervision, Project administration, Funding acquisition.

Declaration of Competing Interest

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

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.envint.2020.105847>.

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