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# Early delivery following chronic and acute ambient temperature exposure: a comprehensive survival approach

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## Abstract

**BACKGROUND:** Ambient temperature, particularly heat, is increasingly acknowledged as a trigger of preterm delivery, but study designs have been limited and results mixed. We aimed to comprehensively evaluate the association between ambient temperature throughout pregnancy and preterm delivery.

**METHODS:** We estimated daily temperature throughout pregnancy using a cutting-edge spatiotemporal model for 5,347 live singleton births from three prospective cohorts in France, 2002-2018. We performed Cox regression (survival analysis) with distributed lags to evaluate time-varying associations with preterm birth simultaneously controlling for exposure during the first 26 weeks and last 30 days of pregnancy. We examined weekly mean, daytime, night-time, and variability of temperature, and heatwaves accounting for adaptation to location and season.

**RESULTS:** Preterm birth risk was higher following cold (5<sup>th</sup> vs 50<sup>th</sup> percentile of mean temperature) 7-9 weeks after conception [relative risk (RR) 1.3, 95% confidence interval (CI) 1.0-1.6 for 2°C vs 11.6°C] and 10-4 days before delivery (1.6 [1.1-2.1] for 1.2°C vs 12.1°C). Night-time heat (95<sup>th</sup> vs 50<sup>th</sup> percentile of minimum temperature; 15.7°C vs 7.4°C) increased risk when exposure occurred within five weeks of conception (2.0 [1.05-3.8]) or 20-26 weeks after conception (2.9 [1.2-6.8]). Overall and daytime heat (high mean and maximum temperature) showed consistent effects. We found no clear associations with temperature variability or heatwave indicators, suggesting they may be less relevant for preterm birth.

**CONCLUSION:** In a temperate climate, night-time heat and chronic and acute cold exposures were associated with increased risk of preterm birth. These results suggest night-time heat as a relevant indicator. In the context of rising temperatures and more frequent weather hazards, these results should inform public health policies to reduce the growing burden of preterm births.

## Keywords

preterm birth, heat, cold, exposure windows

## Key Messages

- We examined chronic and acute windows of susceptibility to temperature during pregnancy in France
- Cold and night-time heat increased the risk of preterm birth
- Cold was harmful during weeks 7-9 after conception and days 10-4 before delivery
- Night-time heat was harmful during weeks 1-5 and weeks 20-26 after conception

## Introduction

Climate change already affects human health, and continued increases in mean temperature and the frequency and intensity of extreme weather events will magnify morbidity and mortality impacts.<sup>1</sup> A growing body of research suggests that extreme ambient temperatures can increase the risk of adverse birth outcomes such as preterm birth.<sup>2,3</sup> Preterm birth (delivery at <37 weeks amenorrhea) is the leading cause of under-5 mortality worldwide<sup>4</sup> and increases the risk of adverse health outcomes throughout childhood and into adulthood.<sup>5</sup> Globally, about 11% of births are preterm, and the rate is increasing in many countries.<sup>6</sup> In France, the rate of preterm birth increased from 5.4% in 1995 to 7.5% in 2016.<sup>7</sup> The drivers of these trends remain unclear,<sup>8</sup> but exposure to extreme and variable temperatures may contribute and is expected to increase as climate change progresses.<sup>9</sup>

The biological pathways underlying associations between temperature and preterm birth remain unclear. Chronic exposure throughout pregnancy could increase the risk of preterm delivery and acute exposure could trigger preterm delivery. Pregnant women have increased fat deposition, decreased surface area to mass ratio, weight gain, and higher metabolic heat production (as the foetus contributes), which could make them more susceptible to heat. Heat may cause the release of cytokines involved in labour induction such as prostaglandin and oxytocin,<sup>10</sup> and their concentration in the blood might be increased by heat-induced dehydration.<sup>11</sup> Dehydration and shifting of blood flow to the skin to dissipate heat could limit oxygen supply to the foetus,<sup>12</sup> and heat shock proteins might cause inflammation.<sup>13</sup> Heat may also be linked to preeclampsia.<sup>14</sup> Fewer mechanisms have been proposed for cold, but thermoregulatory responses can cause peripheral vasoconstriction and increase blood pressure and viscosity, which might restrict blood flow to the placenta or contribute to gestational hypertension.<sup>13</sup>

Many previous studies of temperature and preterm birth focused only on the last days of pregnancy (acute exposure), and most reported that high temperatures or heatwaves were associated with decreased gestational duration or increased risk of preterm or early term birth.<sup>12,15–17</sup> Fewer studies have examined chronic exposure earlier in pregnancy, and results have been less consistent: chronic heat and cold may increase the risk of preterm birth in some populations,<sup>18–22</sup> but may protect or have no effect in others.<sup>19,20,23,24</sup> These mixed findings could in part be due to misidentification of critical windows in studies that did not fully account for correlation in exposure between trimesters.<sup>25</sup> Since windows of susceptibility may not align with trimesters,<sup>24</sup> some recent studies have examined narrower exposure windows such as months or weeks,<sup>20,24,26</sup> but the timing of critical windows remains unclear. Previous studies mostly estimated temperature exposure for all inhabitants of a city or region based on one or a few monitoring stations. This can lead to exposure error that biases associations towards the null,<sup>27</sup> particularly for rural populations, which may live far from monitors, and for urban residents, who may be affected by urban heat islands. To address this, a few recent studies estimated exposure with spatiotemporally resolved models coupled to home addresses.<sup>19,22,26,28</sup> Previous studies also considered various exposure indicators such as mean, minimum, maximum, and apparent temperature. Some reported stronger associations for certain indicators<sup>16,29</sup> while others found that all indicators gave similar results.<sup>30</sup> Mortality studies suggest that temperature variability may have health impacts<sup>31</sup> and that acclimation to location and season may modify associations,<sup>32</sup> but few studies have examined these in relation to preterm birth.

A recent review highlighted these methodological disparities and recommended that future studies consider cold as well as heat, focus on identifying windows of susceptibility using more accurate exposure data, and use methods such as survival analysis that account for time-varying associations with birth outcomes.<sup>2</sup> In this study, we estimated daily temperature exposure throughout pregnancy for three French prospective mother-child cohorts using a cutting-edge spatiotemporal model (spatial unit 200 m to 1 km) coupled to participants' exact home addresses. We performed a survival analysis using Cox proportional hazards models with distributed lags to evaluate the time-varying nonlinear association between temperature and preterm birth. We simultaneously considered chronic and acute exposures by exploring gestational-week specific temperatures and daily temperatures preceding delivery. We further examined several exposure indicators: overall (mean), daytime (maximum), and night-time (minimum) temperature, temperature variability, and a heatwave index that accounts for acclimation to location and season.

## Methods

### Study population

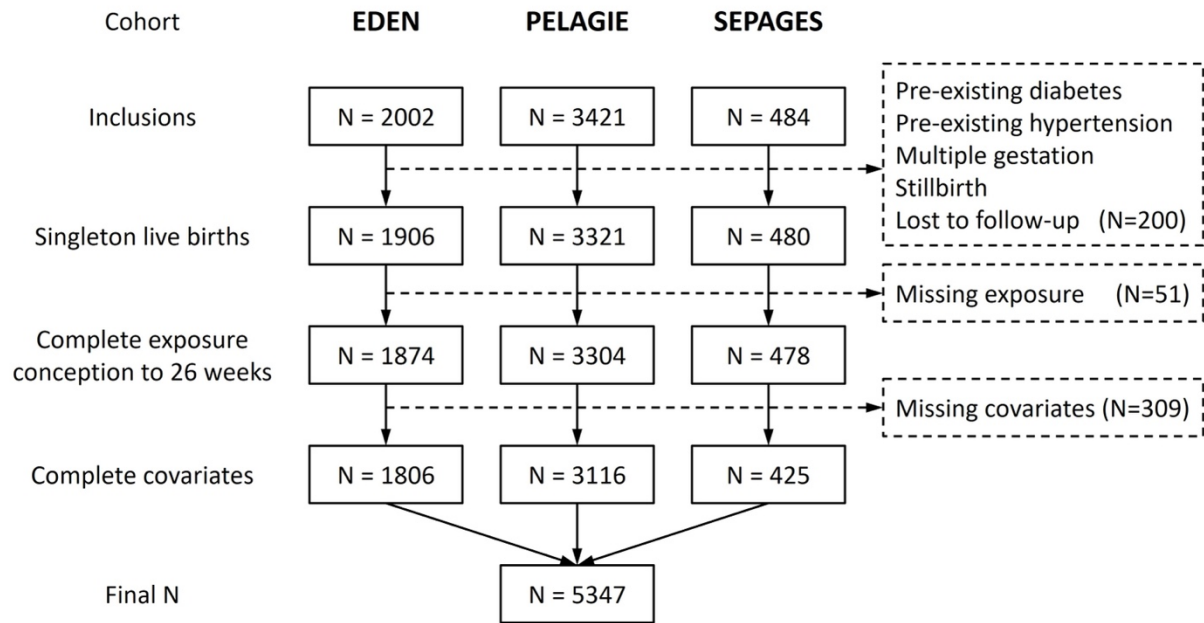
We obtained data from three French prospective mother-child cohorts that were designed to study the effects of prenatal environmental exposures on child development and health: EDEN (Étude des Déterminants pré et post natus du développement et de la santé de l'Enfant),<sup>33</sup> PELAGIE (Perturbateurs Endocriniens : étude Longitudinale sur les Anomalies de la Grossesse, l'Infertilité, et l'Enfance),<sup>34</sup> and SEPAGES (Suivi de l'Exposition à la Pollution Atmosphérique durant la Grossesse et Effets sur la Santé).<sup>35</sup> Briefly, EDEN included 2002 women recruited between 2003 and 2006 at <24 weeks amenorrhea in the metropolitan areas of Poitiers and Nancy; PELAGIE included 3421 women recruited between 2002 and 2006 at <19 weeks amenorrhea in the Brittany region; SEPAGES included 484 women recruited between 2014 and 2017 at <19 weeks amenorrhea in the metropolitan area of Grenoble (Supplementary Figure S1).

All three cohorts collected medical and sociodemographic information via clinical examinations and questionnaires during and after pregnancy. Exact home addresses (including any changes during pregnancy) were geocoded. For 43% of PELAGIE participants, only the municipality or neighbourhood of residence at inclusion (on average 10.4 weeks after conception) was available; we assumed these women did not move during pregnancy.

We excluded multiple gestation, non-livebirths, pre-existing diabetes or hypertension, and participants lost to follow-up before delivery. To ensure complete equal-length exposure histories, we further excluded participants missing covariates (described below) or missing exposure for more than one day in any of the 26 weeks following conception (among these were five extremely preterm births at <28 weeks amenorrhea; all remaining participants had exposure for the 30 days ending at delivery). This left 5,347 mother-child pairs (Figure 1).

### Outcome definition

Duration of pregnancy (conception to birth) was assessed in days using both the reported date of the last menstrual period (LMP) and the estimate from the first trimester ultrasound (when LMP was not reported or when the two differed by more than 30 days). When neither of these were available ( $n = 3$  in EDEN;  $n = 84$  in PELAGIE), we used the obstetrician's estimate of gestational age at delivery. We defined preterm birth as delivery at <37.0 weeks amenorrhea (<35.0 weeks since conception).<sup>36</sup>



**Figure 1.** Flow chart of the study population.

## Exposure assessment

We estimated daily ambient temperature at women's home address using a multi-resolution hybrid spatiotemporal model.<sup>37</sup> The model estimates daily minimum, maximum, and mean air temperature from 2000 to 2018 at a 1 km spatial resolution across France and at a 200 m spatial resolution over urban areas with >50,000 inhabitants. Briefly, it uses a multi-stage ensemble approach combining linear mixed models, random forests, and gradient boosting to calibrate air temperature measured at meteorological stations with satellite-derived land surface temperature, elevation, and other spatiotemporal predictors. The model performs well, with cross-validated  $R^2$  better than 0.9 and mean absolute error of about 1°C. We used 200 m temperature for women in urban areas covered by the model ( $n = 1,741$ ; 33%) and 1 km temperature otherwise.

We calculated five indicators of exposure based on each woman's daily temperature profile from conception to delivery: 1) weekly mean temperature (Tmean), a marker of overall exposure; 2) weekly average of daily maximum temperature (Tmax), a marker of daytime exposure because temperature is usually highest in the afternoon; 3) weekly average of daily minimum temperature (Tmin), a marker of night-time exposure because temperature is typically lowest before sunrise; 4) weekly temperature variability ( $T_{SD}$ , the standard deviation of daily mean temperature), a marker of exposure to temperature swings; and 5) daily Excess Heat Factor (EHF), a marker of exposure to extreme heat that accounts for both spatial and seasonal acclimation.<sup>38</sup> Supplementary Material Part A details the EHF calculation.

## Main analysis

We used Cox proportional hazards models with duration of pregnancy (weeks since conception) as the time variable and birth as the outcome (censored at 35 weeks after conception). We fit a separate model for each of the five exposure indicators (Tmean, Tmin, Tmax, TSD, EHF). We accounted for the time-varying effects of exposure using a distributed lag nonlinear model (DLNM)<sup>39</sup> with two exposure matrices: the 26 weeks following conception (weekly chronic exposure) and the 30 days ending at delivery (daily acute exposure). We censored chronic exposure at 26 weeks to avoid excluding a substantial fraction of preterm births. We modelled both the exposure-response and the lag-response relationship using natural cubic splines with equally spaced knots and three degrees of freedom (chosen by testing 3-6 degrees of freedom for the lowest value that minimized the Akaike information criterion). The reference temperatures for each model were the median exposure (50<sup>th</sup> percentile) of the study population during each of the chronic and acute periods.

We adjusted all models for possible confounders or predictors of the outcome selected *a priori* based on the literature and our reasoning: cohort recruitment area (Nancy / Poitiers / Côtes-d'Armor / Finistère / Ille-et-Vilaine / Grenoble), season of conception (Winter / Spring / Summer / Fall), urbanicity (city centre / suburban / rural), normalized difference vegetation index (NDVI; a measure of vegetation density), child sex, and maternal characteristics (age at conception, height, pre-pregnancy body mass index [BMI], parity, education, and smoking during pregnancy [none / active smoker]). **Table 1** lists the levels of the covariates. We did not adjust for gestational hypertension or preeclampsia as these may mediate the association between temperature and preterm birth. Nor did we adjust for air pollution, as it is on the causal pathway between temperature and preterm birth.<sup>40</sup> Urbanicity was based on data from the French National Institute of Statistics and Economics for the home address at birth. We calculated mean NDVI from Landsat satellite data<sup>41</sup> in a 500 m buffer around the home address during summer (June-August) of the year of birth. Our intent was to capture total vegetated area (rather than temporal changes in vegetation extent and greenness) and to minimize the influence of missing data due to snow and cloud cover during colder seasons. Previous studies of preterm birth estimated NDVI on a single summer day,<sup>42-47</sup> reported very high correlation between seasonal and annual NDVI,<sup>48</sup> or reported consistent effects for every month.<sup>49</sup> We considered NDVI missing if it was unavailable over more than 25% of the buffer.

200 **Table 1.** Characteristics of the study population by cohort ( $n = 5347$ ).

	Consortium <i>n (%) or mean (sd)</i>	EDEN <i>n (%) or mean (sd)</i>	PELAGIE <i>n (%) or mean (sd)</i>	SEPAGES <i>n (%) or mean (sd)</i>
Participants	5347 (100%)	1806 (33.8%)	3116 (58.3%)	425 (7.8%)
Preterm births	232 (4.3%)	103 (5.7%)	110 (3.5%)	19 (4.5%)
Duration of pregnancy <sup>a</sup> (weeks)	37.9 (1.7)	37.7 (1.8)	38.1 (1.6)	37.7 (1.5)
Temperature <sup>b</sup> (°C)	11.8 (3.6)	11.3 (4.1)	12.1 (3.2)	12 (4.4)
Temperature variability <sup>c</sup> (°C)	2.0 (0.3)	2.2 (0.2)	1.9 (0.3)	2.1 (0.2)
Excess Heat Factor <sup>d</sup>	0.7 (1.1)	0.8 (1.3)	0.6 (0.9)	0.7 (1.0)
Child sex				
Boy	2737 (51.2%)	940 (52%)	1572 (50.4%)	225 (52.9%)
Girl	2610 (48.8%)	866 (48%)	1544 (49.6%)	200 (47.1%)
Parity				
0	2374 (44.4%)	794 (44.0%)	1386 (44.5%)	194 (45.6%)
1	2021 (37.8%)	670 (37.1%)	1166 (37.4%)	185 (43.5%)
≥2	952 (17.8%)	342 (18.9%)	564 (18.1%)	46 (10.8%)
Maternal age at conception (years) <sup>e</sup>	30 (4.5)	29.4 (4.9)	29.9 (4.3)	32.5 (3.9)
Maternal height				
135-175 cm	4612 (86.3%)	1561 (86.4%)	2719 (87.3%)	332 (78.1%)
170-190 cm	735 (13.7%)	245 (13.6%)	397 (12.7%)	93 (21.9%)
Maternal pre-pregnancy BMI				
<18.5 kg/m <sup>2</sup>	412 (7.7%)	157 (8.7%)	229 (7.3%)	26 (6.1%)
18.5 – 25 kg/m <sup>2</sup>	3844 (71.9%)	1177 (65.2%)	2346 (75.3%)	321 (75.5%)
>25 kg/m <sup>2</sup>	1091 (20.4%)	472 (26.1%)	541 (17.4%)	78 (18.4%)
Maternal education				
Baccalaureate or less	1987 (37.2%)	840 (46.5%)	1125 (36.1%)	22 (5.2%)
Baccalaureate +1 or +2 years	1373 (25.7%)	415 (23.0%)	906 (29.1%)	52 (12.2%)
≥ Baccalaureate +3 years	1987 (37.2%)	551 (30.5%)	1085 (34.8%)	351 (82.6%)
Smoking status during pregnancy				
None	4006 (74.9%)	1347 (74.6%)	2257 (72.4%)	402 (94.6%)
Active smoker	1341 (25.1%)	459 (25.4%)	859 (27.6%)	23 (5.4%)
NDVI <sup>e</sup>	0.50 (0.11)	0.46 (0.10)	0.52 (0.10)	0.49 (0.16)
Urbanicity				
City-centre	896 (16.8%)	191 (10.6%)	547 (17.6%)	158 (37.2%)
Small city-centre or suburban	2021 (37.8%)	879 (48.7%)	918 (29.5%)	224 (52.7%)
Rural	2430 (45.4%)	736 (40.8%)	1651 (53%)	43 (10.1%)
Season of conception				
Winter	1321 (24.7%)	431 (23.9%)	762 (24.5%)	128 (30.1%)
Spring	1211 (22.6%)	371 (20.5%)	751 (24.1%)	89 (20.9%)
Summer	1477 (27.6%)	527 (29.2%)	860 (27.6%)	90 (21.2%)
Autumn	1338 (25.0%)	477 (26.4%)	743 (23.8%)	118 (27.8%)
Cohort recruitment area				
Nancy	940 (17.6%)	940 (52%)	0 (0%)	0 (0%)
Poitiers	866 (16.2%)	866 (48%)	0 (0%)	0 (0%)
Côtes-d'Armor	898 (16.8%)	0 (0%)	898 (28.8%)	0 (0%)
Finistère	157 (2.9%)	0 (0%)	157 (5.0%)	0 (0%)
Ille-et-Vilaine	2061 (38.5%)	0 (0%)	2061 (66.1%)	0 (0%)
Grenoble	425 (7.9%)	0 (0%)	0 (0%)	425 (100%)

BMI, body mass index; NDVI, normalized difference vegetation index.

<sup>a</sup> From conception to delivery.

<sup>b</sup> Mean during the 26 weeks following conception.

<sup>c</sup> Mean weekly standard deviation during the 26 weeks following conception.

<sup>d</sup> Mean during days 30-181 after conception (up to 26 weeks following conception).

<sup>e</sup> Coded as a continuous variable.

To better understand the associations with temperature and evaluate the robustness of our findings, we repeated our analyses 1) including the 309 participants (of which 16 preterm births) that were missing covariates, which we imputed using the cohort recruitment area-specific median or mode; 2) using temperature estimated at a 1 km spatial resolution for all participants (rather than using 200 m temperature for the 33% of participants that lived in large urban areas); 3) adjusting for year of conception in addition to the main covariates; and 4) including  $T_{SD}$  as a simultaneous exposure along with each of  $T_{min}$ ,  $T_{mean}$ ,  $T_{max}$ , and EHF ( $T_{SD}$  was the only uncorrelated exposure indicator).

We used the fitted models to estimate the relative risk (RR) of preterm birth and 95% confidence interval (CI) associated with moderate (10<sup>th</sup>, 90<sup>th</sup> percentiles), severe (5<sup>th</sup>, 95<sup>th</sup> percentiles), and extreme (1<sup>st</sup>, 99<sup>th</sup> percentiles) exposure compared to the median exposure (50<sup>th</sup> percentile) during the chronic and acute periods. We report both the cumulative risk associated with exposure throughout the entire duration of a critical window and the mean risk associated with exposure on only a single week or day during each window. We calculated mean risk by averaging the risk of all individual weeks or days in each window. We conducted all statistical analyses using R version 4.1.0<sup>50</sup> with the packages survival v3.2-11<sup>51</sup> and dlnm v2.4.6.<sup>52</sup>

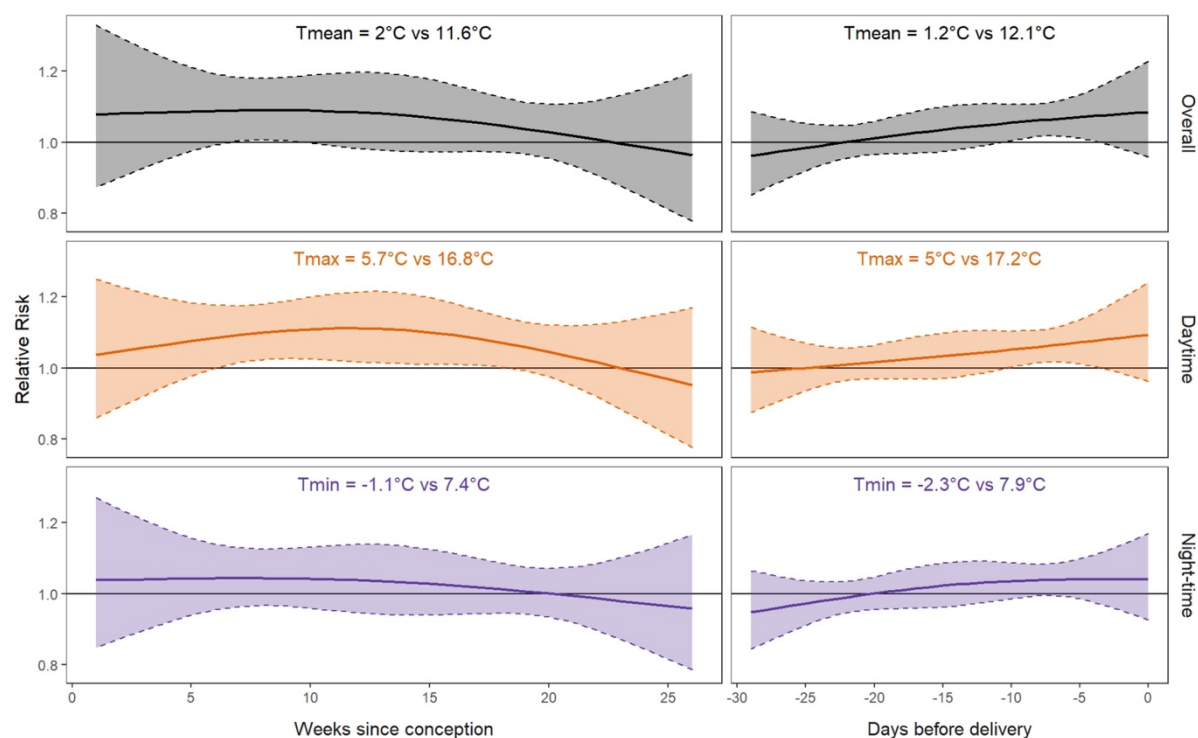
## Results

Over half (58%) of the women lived in Brittany; 18% lived in Nancy, 16% in Poitiers, and 8% in Grenoble (**Table 1**). Almost half (45%) lived in a rural area. Most women (72%) were 25 to 34 years old at conception, had completed at least one year of post-secondary education (63%), and were multiparous (56%). A quarter (25%) of women smoked during pregnancy.

Mean duration of pregnancy (conception to delivery) was 37.9 weeks and 4.3% of births were preterm. Mean temperature  $\pm$  standard deviation during the 26 weeks following conception was  $11.8 \pm 3.6^{\circ}\text{C}$ ; the standard deviation of weekly temperature averaged  $2.0 \pm 0.3^{\circ}\text{C}$ . Mean EHF was  $0.7 \pm 1.1$  over days 30 to 181 since conception. **Supplementary Figure S2** shows the distribution of mean temperature and EHF over time for each cohort and **Supplementary Table S1** summarizes the distribution of the exposure indicators.

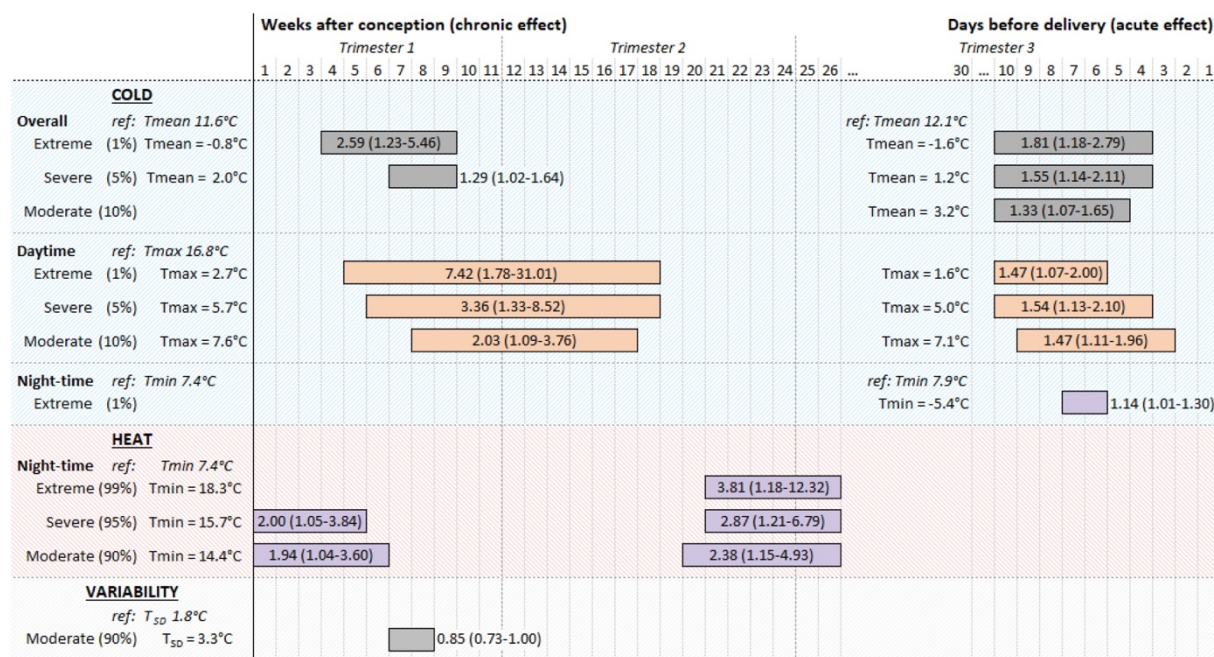
## Cold

Severe cold (5<sup>th</sup> vs 50<sup>th</sup> percentile of  $T_{mean}$ ) during weeks 7-9 after conception and days 10-4 before delivery increased the risk of preterm birth (**Figure 2**). A mean temperature of  $2^{\circ}\text{C}$  throughout weeks 7-9 after conception was associated with RR for preterm birth of 1.29 (95%



**Figure 2.** Adjusted relative risk (solid line) and 95% confidence interval (shaded area) for preterm birth associated with severe cold during the 26 weeks following conception (left) and the 30 days ending at delivery (right). Top: overall cold (5th percentile of Tmean); middle: daytime cold (5th percentile of Tmax); bottom: night-time cold (5th percentile of Tmin). Reference is 50th percentile of temperature. Models included exposure throughout pregnancy, area, season of conception, urbanicity, NDVI, child sex, and maternal characteristics (age at conception, height, pre-pregnancy BMI, parity, education, smoking during pregnancy). BMI, body mass index; NDVI, normalized difference vegetation index; Tmax, daily maximum temperature; Tmean, daily mean temperature; Tmin, daily minimum temperature.

CI: 1.02-1.64) compared to the reference temperature of 11.6°C (**Figure 3**). A mean temperature of 1.2°C throughout days 10-4 before delivery had RR of 1.55 (95% CI: 1.14-2.11) compared to 12.1°C. Considering a single week or day during each critical window, the mean RR for preterm birth was about 1.09 (95% CI: 1.01-1.18) following severe cold on one of weeks 7-9 after conception; the mean RR for preterm birth was about 1.06 (95% CI: 1.01-1.12) following severe cold on one of days 10-4 before delivery (**Supplementary Figure S3**). For extreme cold (1<sup>st</sup> percentile of Tmean), the critical windows were 4-9 weeks after conception and 10-4 days before delivery; the only critical window for moderate cold (10<sup>th</sup> percentile of Tmean) was 10-5 days before delivery (**Figure 3**). Chronic daytime cold (low Tmax) showed a longer critical window than chronic overall cold (low Tmean) (**Figure 2**), while night-time cold (low Tmin) was only significant when it was extreme (1<sup>st</sup> percentile) 7-6 days before delivery (**Figure 3**).

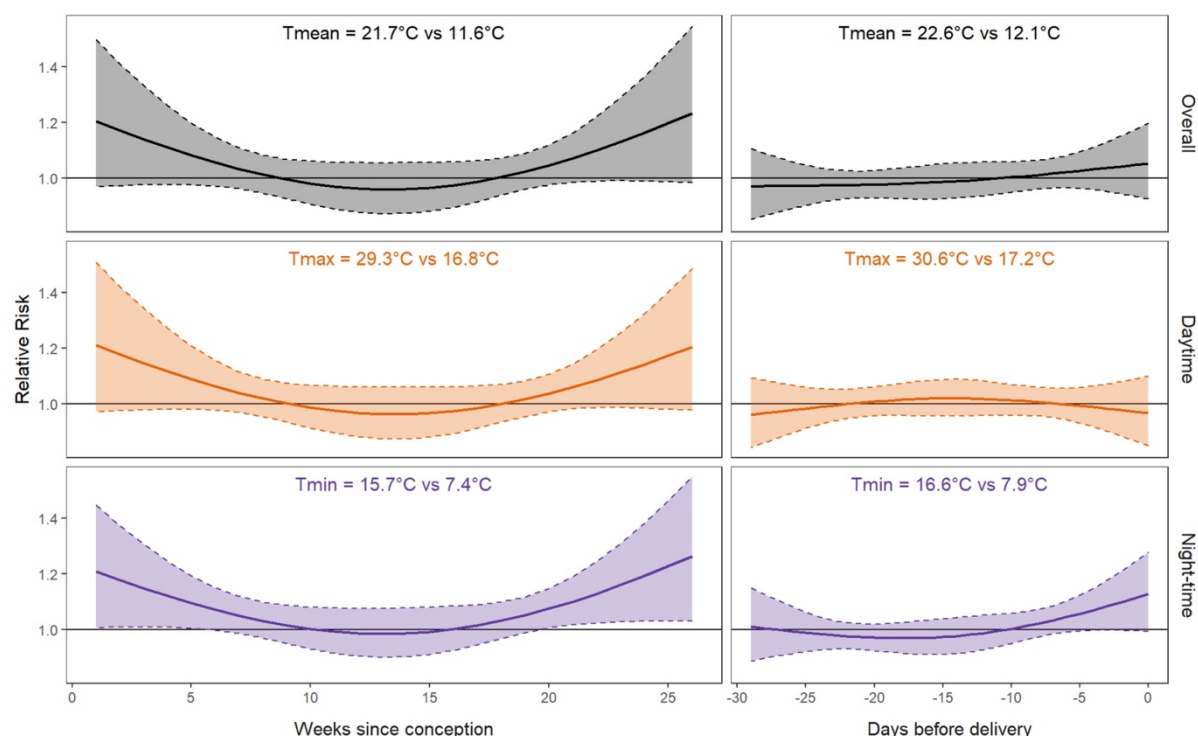


**Figure 3.** Cumulative adjusted relative risk (RR) for preterm birth associated with ambient temperature exposure throughout an entire critical window. Bars show timing of critical windows; bar labels show cumulative RR (95% confidence interval). Models included exposure throughout pregnancy, area, season of conception, urbanicity, NDVI, child sex, and maternal characteristics (age at conception, height, pre-pregnancy BMI, parity, education, smoking during pregnancy). BMI, body mass index; NDVI, normalized difference vegetation index; Tmax, daily maximum temperature; Tmean, daily mean temperature; Tmin, daily minimum temperature.

Imputing missing covariates did not substantially change the associations; nor did adjusting for year of conception or including T<sub>SD</sub> as a simultaneous exposure. Using only 1 km temperature made the critical windows shorter or widened the confidence intervals. Maternal education was the only variable that did not satisfy the proportional hazards assumption; stratifying the Cox models on education did not substantially alter our results.

## Heat

Heat (high Tmean) during the first weeks following conception, the second half of the second trimester, and the last days before delivery seemed to correspond with an increased risk of preterm birth (**Figure 4**). We identified critical windows for severe night-time heat (95<sup>th</sup> vs 50<sup>th</sup> percentile of Tmin; 15.7°C vs 7.4°C) during weeks 1-5 after conception (RR: 2.00; 95% CI: 1.05-3.84) and 20-26 weeks after conception (RR: 2.87; 95% CI: 1.21-6.79) (**Figure 3**, **Figure 4**). Focusing on a single week during each critical window, an average minimum temperature of 15.7°C during any one of weeks 1-5 or weeks 21-26 after conception was associated with mean RR of about 1.16 (95% CI: 1.02-1.34) (**Supplementary Figure S3**).



**Figure 4.** Adjusted relative risk (solid line) and 95% confidence interval (shaded area) for preterm birth associated with severe heat during the 26 weeks following conception (left) and the 30 days ending at delivery (right). Top: overall heat (95th percentile of Tmean); middle: daytime heat (95th percentile of Tmax); bottom: night-time heat (95th percentile of Tmin). Reference is 50th percentile of temperature. Models included exposure throughout pregnancy, area, season of conception, urbanicity, NDVI, child sex, and maternal characteristics (age at conception, height, pre-pregnancy BMI, parity, education, smoking during pregnancy). BMI, body mass index; NDVI, normalized difference vegetation index; Tmax, daily maximum temperature; Tmean, daily mean temperature; Tmin, daily minimum temperature.

Moderate (90<sup>th</sup> percentile) night-time heat showed a somewhat smaller effect during the same windows, while extreme (99<sup>th</sup> percentile) night-time heat showed a larger effect but only 21-26 weeks after conception (**Figure 3**). Sensitivity analyses did not substantially alter the results.

#### Temperature variability and Excess Heat Factor

There was no clear association between temperature variability and risk of preterm birth. Moderately variable temperature (90<sup>th</sup> vs 50<sup>th</sup> percentile of T<sub>SD</sub>; 3.3°C vs 1.8°C) 7-8 weeks after conception may have had a protective effect (**Supplementary Figure S4**), but the association did not clearly differ from null (RR: 0.85; 95% CI: 0.73-1.00). There were no critical windows for other exposure levels, and sensitivity analyses showed similar results.

There was no association between EHF and preterm birth (**Supplementary Figure S5**).

## 300 Discussion

301 Our results are based on a state-of-the-art approach combining survival analysis with daily  
302 residence-based temperature exposure, controlling for both chronic (weekly for the 26 weeks  
303 following conception) and acute (daily for the 30 days ending at delivery) exposure, and  
304 accounting for lagged nonlinear effects. Pregnant women were susceptible to cold from the  
305 middle of the first to the middle of the second trimester and about one week before delivery.  
306 Women were susceptible to heat during the five weeks following conception and the end of the  
307 second trimester. Night-time heat (high  $T_{min}$ ) seemed to increase preterm birth risk more than  
308 daytime (high  $T_{max}$ ) or overall (high  $T_{mean}$ ) heat, while night-time cold seemed less harmful  
309 than daytime or overall cold.

### 310 Cold

311 We found a critical window for chronic cold 4-9 weeks after conception. Women were more  
312 sensitive to daytime cold: the critical window continued until 18 weeks after conception. We  
313 found no critical window for chronic night-time cold. Women may have been less exposed to  
314 night-time cold as they were likely inside a heated home.

315 Few previous studies examined cold early during pregnancy in temperate climates, with most  
316 finding protective effects.<sup>19,20,23,24</sup> Consistent with our results, a study in the USA found that  
317 cold during the two weeks before or five weeks after conception increased the risk of preterm  
318 birth, and studies in China reported increased risk from entire-pregnancy cold in temperate<sup>19</sup>  
319 and cold areas.<sup>20</sup> Compared to previous studies, we examined narrower windows (single weeks  
320 during the first two trimesters), estimated residence-based temperature (rather than using city-  
321 wide or regional temperature), and adjusted for temperature later in pregnancy, which may have  
322 improved our ability to detect critical windows.

323 We also found a critical window for acute cold 10-4 days before delivery. Previous studies of  
324 acute cold in temperate climates have reported conflicting results of no association with preterm  
325 birth,<sup>20,22,53,54</sup> a decreased risk,<sup>24</sup> or oscillating positive and negative associations.<sup>12,16</sup> Most of  
326 these studies considered only the last seven days or four weeks of pregnancy, which may have  
327 limited their ability to detect a critical window starting about 10 days before delivery, and most  
328 did not adjust for temperature earlier in pregnancy as we did.

## 329 Heat

330 We found critical windows for chronic heat during the five weeks after conception and 20-26  
331 weeks after conception. The association was clearest for night-time heat, but the shape of the  
332 lag-response curve was similar for overall and daytime heat. Heatwave mortality studies have  
333 suggested that hot nights following hot days may be particularly dangerous because they limit  
334 the ability to recover from daytime exposure,<sup>55,56</sup> and recent studies in California and Belgium  
335 found a clearer association with preterm birth for night-time than daytime heat.<sup>16,29</sup> Our study  
336 may have been particularly suited to examining night-time heat because we estimated  
337 residence-based exposure using a model that captures the higher night-time temperatures of  
338 urban heat islands.<sup>37</sup> Taken together, these results suggest that future studies should consider  
339 night-time heat indicators in order to clarify the effects of heat during pregnancy, particularly  
340 in countries such as France where only about 13% of homes have air conditioning.<sup>57</sup>

341 Many studies have reported that heat in the last days of pregnancy may trigger preterm  
342 delivery,<sup>2,3</sup> although a few have reported no effect in cold or cool climates.<sup>12,20,22,53</sup> In our study,  
343 heat during the last five days of pregnancy may have increased risk of preterm birth, but the  
344 association was unclear. This might be because we adjusted for temperatures earlier in  
345 pregnancy whereas most previous studies did not. Our residence-based exposure estimates may  
346 also be less accurate during the final days of pregnancy for some women who may have been  
347 admitted to maternity units before the day of delivery.

## 348 Temperature variability and acclimation

349 Temperature variability and acclimation to location and season have been shown to affect the  
350 risk of mortality,<sup>31,32</sup> but few studies have examined them in relation to birth outcomes. A recent  
351 study in the Andes associated more variable temperature with lower birth weight,<sup>58</sup> and a study  
352 in France using a subset of our study population associated more variable temperature during  
353 weeks 4-18 after conception with lower term birth weight.<sup>59</sup>

354 We did not find an association between preterm birth and the variability of temperature. Nor  
355 did we find an association with EHF, a heatwave index that accounts for acclimation to both  
356 location and season. This might be related to the fact that we only found critical windows for  
357 night-time heat (high T<sub>min</sub>) whereas EHF is based on T<sub>mean</sub>. Our sample size may also have  
358 limited our ability to examine an infrequent acute exposure such as EHF. We also adjusted for  
359 EHF earlier in pregnancy, which may have reduced the effect of EHF shortly before delivery;  
360 previous heatwave studies only examined exposure during the last week of pregnancy.<sup>30,60</sup>

Overall, our findings suggest that daily mean, minimum, and maximum temperature may be more relevant for preterm birth than temperature variability or heatwaves.

### Strengths and limitations

We estimated outdoor temperature at women's home address, but women likely spent time indoors (particularly at night) and at other locations (particularly early in pregnancy). We also lacked complete address history for a quarter of participants (all from the PELAGIE cohort); for these women we used municipality or neighbourhood of residence at inclusion (mean 10.4 weeks after conception), which may have increased exposure measurement error and biased our associations towards null.

DLNM requires complete equal-length exposure histories, so we only considered exposure during the 26 weeks following conception and the 30 days ending at delivery. This could have led us to miss critical windows early in the third trimester (e.g. weeks 27-30 after conception). A recent study in Rome and Barcelona found that acute heat was more harmful earlier in the third trimester,<sup>17</sup> so future studies should investigate critical windows in the first half of the third trimester. Such studies might stratify preterm birth by gestational age,<sup>17</sup> or use alternate designs such as natural experiments.<sup>61</sup> Our study's relatively small population precluded stratification and is another limitation.

Although we adjusted for major confounders including maternal smoking, age, parity, and pre-pregnancy BMI, we were unable to adjust for some possible confounders such as household income (although we used education as a proxy), noise, and light at night. We also did not account for humidity, which may modify the physiological effects of heat.<sup>62</sup> However, the evidence for humidity is mixed: some studies found it did not substantially modify the association between temperature and mortality<sup>63,64</sup> or birth outcomes<sup>30</sup> while others suggested a significant role<sup>59</sup> or that humidity's importance varies between locations.<sup>65</sup>

Despite these limitations, our study has several strengths. Pooling three cohorts from different regions of France allowed us to increase the study population and capture greater climatic variability while maintaining detailed health data and similar lifestyles across participants. We estimated exposure at participants' home address with a spatiotemporally resolved temperature model. This likely reduced exposure error for the 45% of women that lived in rural areas, which often have few weather monitors, and the 33% of women that lived in large urban areas, where we were able to use 200 m temperature estimates that better capture urban heat islands and fine-scale spatial patterns. One previous study of temperature and birth weight found that

associations disappeared when using coarser monitor-based exposure rather than residence-based exposure.<sup>22</sup> Consistently, our sensitivity analyses using 1 km rather than 200 m temperature for urban women showed similar trends as the main analysis but the associations were weakened and critical windows shortened.

We performed a survival analysis with pregnancy duration as the time variable, which is the most effective method to study time-varying exposures in cohorts.<sup>66,67</sup> It also avoids possible confounding by temporal trends in conception rates and accounts for the fact that the risk of preterm birth increases exponentially later in pregnancy.<sup>68</sup> To avoid underestimating gestational age in the case that temperature affects foetal growth during the first trimester, we preferred gestational duration calculated from the last menstrual period rather than from measurements performed at the first ultrasound. We accounted for lags in the effect of exposure, examined narrow windows, and adjusted our estimates of chronic effects (during the 26 weeks following conception) for acute effects (during the 30 days preceding delivery) and vice versa. We further adjusted for potential confounders such as season of conception, maternal age, education, and smoking, but did not adjust for air pollution because it may be on the causal pathway from temperature to preterm birth.<sup>40</sup> Future research may investigate the possible synergistic effects of air pollution and temperature.<sup>60,69,70</sup>

## Conclusion

Our results indicate that, in a temperate climate, cold between the middle of the first and second trimesters may increase the risk of preterm birth and cold late in pregnancy may trigger preterm birth with a lag time of about one week. Night-time heat may be harmful during the five weeks following conception and the 6<sup>th</sup> month of pregnancy. We found inconclusive evidence for heat as a short-term trigger of preterm birth. In the context of the demonstrated and increasing risks of climate change and preterm birth's association with poorer health in childhood and adulthood, health professionals and policy makers should use these findings to increase awareness of the risks of extreme temperature for pregnant women.

## Ethics approval

EDEN, PELAGIE and SEPAGES were 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, le Comité de Protection des Personnes Sud-Est V, and le Comité d'Éthique de l'Inserm. All participating women gave informed written consent for themselves and their children.

## Data availability

The data underlying this article will be shared on reasonable request to the corresponding author with permission of the EDEN, PELAGIE, and SEPAGES steering committees.

## Supplementary data

Supplementary data are available at *IJE* online.

## Author contributions

IH helped design the study, prepared data, performed analyses, interpreted the results, and wrote the manuscript. MR helped design the study, prepared data, performed analyses, helped interpret the results, and edited the manuscript. AG helped design the study, prepared data, helped interpret the results, and edited the manuscript. ES prepared data and edited the manuscript. BH prepared data and edited the manuscript. RS edited the manuscript. SLC prepared data and edited the manuscript. IP edited the manuscript. CC prepared data and edited the manuscript. IK helped direct the study and edited the manuscript. JL designed and directed the study, helped interpret the results, and edited the manuscript.

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## Conflict of interest

None declared.

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