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1 Early delivery following chronic and acute in utero ambient  
2 temperature exposure: a comprehensive survival approach

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23

## 24 Abstract

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

29 **METHODS:** We estimated daily temperature throughout pregnancy using a cutting-edge  
30 spatiotemporal model for 5,347 live singleton births from three prospective cohorts in France,  
31 2002-2018. We performed Cox regression (survival analysis) with forward (weekly from  
32 conception) and backward (30 days before delivery) distributed lags to evaluate time-varying  
33 associations with preterm birth. We examined weekly mean, daytime, night-time, and  
34 variability of temperature, and heatwaves accounting for adaptation to location and season.

35 **RESULTS:** Preterm birth risk was higher following cold (5<sup>th</sup> vs 50<sup>th</sup> percentile of mean  
36 temperature) 7-9 weeks after conception [relative risk (RR) 1.3, 95% confidence interval (CI)  
37 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).  
38 Night-time heat (95<sup>th</sup> vs 50<sup>th</sup> percentile of minimum temperature; 15.7°C vs 7.4°C) increased  
39 risk when exposure occurred within five weeks of conception (2.0 [1.05-3.8]) or 20-26 weeks  
40 after conception (2.9 [1.2-6.8]). Overall and daytime heat (high mean and maximum  
41 temperature) showed consistent effects. We found no clear associations with temperature  
42 variability or heatwave indicators, suggesting they may be less relevant for preterm birth.

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

## 48 Keywords

49 preterm birth, heat, cold, exposure windows

50

## 51 Key Messages

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

## 57 Introduction

58 Climate change already affects human health, and continued increases in mean temperature  
59 and the frequency and intensity of extreme weather events will magnify morbidity and  
60 mortality impacts.<sup>1</sup> A growing body of research suggests that extreme ambient temperatures  
61 can increase the risk of adverse birth outcomes such as preterm birth.<sup>2,3</sup> Preterm birth  
62 (delivery at <37 weeks amenorrhea) is the leading cause of under-5 mortality worldwide<sup>4</sup> and  
63 increases the risk of adverse health outcomes throughout childhood and into adulthood.<sup>5</sup>  
64 Globally, about 11% of births are preterm, and the rate is increasing in many countries.<sup>6</sup> In  
65 France, the rate of preterm birth increased from 5.4% in 1995 to 7.5% in 2016.<sup>7</sup>

66 The biological pathways underlying associations between temperature and preterm birth  
67 remain unclear. Chronic exposure throughout pregnancy could increase the risk of preterm  
68 delivery and acute exposure could trigger preterm delivery. Pregnant women have increased  
69 fat deposition, decreased surface area to mass ratio, weight gain, and higher metabolic heat  
70 production (as the foetus contributes), which could make them more susceptible to heat. Heat  
71 may cause the release of cytokines involved in labour induction such as prostaglandin and  
72 oxytocin,<sup>8</sup> and their concentration in the blood might be increased by heat-induced  
73 dehydration.<sup>9</sup> Dehydration and shifting of blood flow to the skin to dissipate heat could limit  
74 oxygen supply to the foetus,<sup>10</sup> and heat shock proteins might cause inflammation.<sup>11</sup> Heat may  
75 also be linked to preeclampsia.<sup>12</sup> Fewer mechanisms have been proposed for cold, but  
76 thermoregulatory responses can cause peripheral vasoconstriction and increase blood pressure  
77 and viscosity, which might restrict blood flow to the placenta or contribute to gestational  
78 hypertension.<sup>11</sup>

79 Many previous studies of temperature and preterm birth focused only on the last days of  
80 pregnancy (acute exposure), and most reported that high temperatures or heatwaves were

81 associated with decreased gestational duration or increased risk of preterm or early term  
82 birth.<sup>10,13–15</sup> Fewer studies have examined chronic exposure earlier in pregnancy, and results  
83 have been less consistent: chronic heat and cold may increase the risk of preterm birth in  
84 some populations,<sup>16–20</sup> but may protect or have no effect in others.<sup>17,18,21,22</sup> These mixed  
85 findings could in part be due to misidentification of critical windows in studies that did not  
86 fully account for correlation in exposure between trimesters.<sup>23</sup> Also, windows of susceptibility  
87 may not align with trimesters,<sup>22</sup> but very few studies have examined narrow exposure  
88 windows. Previous studies mostly estimated temperature exposure for all inhabitants of a city  
89 or region based on one or a few monitoring stations. This can lead to exposure error that  
90 biases associations towards the null,<sup>24</sup> particularly for rural populations, which may live far  
91 from monitors, and for urban residents, who may be affected by urban heat islands. To  
92 address this, a few recent studies estimated exposure with spatiotemporally resolved models  
93 coupled to home addresses.<sup>17,20,25,26</sup> Previous studies also considered various exposure  
94 indicators such as mean, minimum, maximum, and apparent temperature. Some reported  
95 stronger associations for certain indicators<sup>14,27</sup> while others found that all indicators gave  
96 similar results.<sup>28</sup> Mortality studies suggest that temperature variability may have health  
97 impacts<sup>29</sup> and that acclimation to location and season may modify associations,<sup>30</sup> but few  
98 studies have examined these in relation to preterm birth.

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

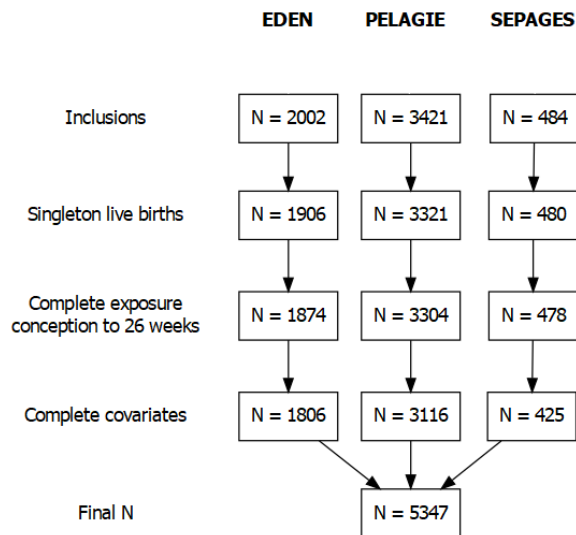
## 112 Methods

### 113 Study population

114 We obtained data from three French prospective mother-child cohorts that were designed to  
115 study the effects of prenatal environmental exposures on child development and health:  
116 EDEN (Étude des Déterminants pré et post natals du développement et de la santé de  
117 l'Enfant),<sup>31</sup> PELAGIE (Perturbateurs Endocriniens : étude Longitudinale sur les Anomalies de  
118 la Grossesse, l'Infertilité, et l'Enfance),<sup>32</sup> and SEPAGES (Suivi de l'Exposition à la Pollution  
119 Atmosphérique durant la Grossesse et Effets sur la Santé).<sup>33</sup> Briefly, EDEN included 2002  
120 women recruited between 2003 and 2006 at <24 weeks amenorrhea in the metropolitan areas  
121 of Poitiers and Nancy; PELAGIE included 3421 women recruited between 2002 and 2006 at  
122 <19 weeks amenorrhea in the Brittany region; SEPAGES included 484 women recruited  
123 between 2014 and 2017 at <19 weeks amenorrhea in the metropolitan area of Grenoble  
124 (Figure S1).

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

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



136  
137 Figure 1. Flow chart of the study population.

138 [Outcome definition](#)

139 Duration of pregnancy (conception to birth) was assessed using both the reported date of the  
140 last menstrual period (LMP) and the estimate from the first trimester ultrasound (when LMP  
141 was not reported or when the two differed by more than 30 days). When neither of these were  
142 available ( $n = 3$  in EDEN;  $n = 84$  in PELAGIE), we used the obstetrician's estimate of  
143 gestational age at delivery. We defined preterm birth as delivery at  $<37$  weeks amenorrhea  
144 ( $<35$  weeks since conception).

145 [Exposure assessment](#)

146 We estimated daily ambient temperature at women's home address using a multi-resolution  
147 hybrid spatiotemporal model.<sup>34</sup> The model estimates daily minimum, maximum, and mean air  
148 temperature from 2000 to 2018 at a 1 km spatial resolution across France and at a 200 m  
149 spatial resolution over urban areas with  $>50,000$  inhabitants. Briefly, it uses a multi-stage  
150 ensemble approach combining linear mixed models, random forests, and gradient boosting to  
151 calibrate air temperature measured at meteorological stations with satellite-derived land  
152 surface temperature, elevation, and other spatiotemporal predictors. The model performs well,  
153 with cross-validated  $R^2$  better than 0.9 and mean absolute error of about  $1^\circ\text{C}$ . We used 200 m  
154 temperature for women in urban areas covered by the model ( $n = 1,741$ ; 33%) and 1 km  
155 temperature otherwise.

156 We calculated five indicators of exposure based on each woman's daily temperature profile  
157 from conception to delivery: 1) weekly mean temperature (Tmean), a marker of overall

158 exposure; 2) weekly average of daily maximum temperature ( $T_{max}$ ), a marker of daytime  
159 exposure because temperature is usually highest in the afternoon; 3) weekly average of daily  
160 minimum temperature ( $T_{min}$ ), a marker of night-time exposure because temperature is  
161 typically lowest before sunrise; 4) weekly temperature variability ( $T_{SD}$ , the standard deviation  
162 of daily mean temperature), a marker of exposure to temperature swings; and 5) daily Excess  
163 Heat Factor (EHF), a marker of exposure to extreme heat that accounts for both spatial and  
164 seasonal acclimation.<sup>35</sup> Supplemental appendix A details the EHF calculation.

## 165 Main analysis

166 We used Cox proportional hazards models with duration of pregnancy (weeks since  
167 conception) as the time variable and birth as the outcome (censored at 35 weeks after  
168 conception). We fit a separate model for each of the five exposure indicators ( $T_{mean}$ ,  $T_{min}$ ,  
169  $T_{max}$ ,  $T_{SD}$ , EHF). We accounted for the time-varying effects of exposure using a distributed  
170 lag nonlinear model (DLNM)<sup>36</sup> with two exposure matrices: the 26 weeks following  
171 conception (weekly chronic exposure) and the 30 days ending at delivery (daily acute  
172 exposure). We censored chronic exposure at 26 weeks to avoid excluding a substantial  
173 fraction of preterm births. We modelled both the exposure-response and the lag-response  
174 relationship using natural cubic splines with equally spaced knots and three degrees of  
175 freedom (chosen by testing 3-6 degrees of freedom for the lowest value that minimized the  
176 Akaike information criterion).

177 We adjusted all models for possible confounders or predictors of the outcome selected *a*  
178 *priori* based on the literature and our reasoning: cohort area, season of conception, urbanicity,  
179 normalized difference vegetation index (NDVI), child sex, and maternal characteristics (age at  
180 conception, height, pre-pregnancy BMI, parity, education, and smoking during pregnancy).  
181 We did not adjust for gestational hypertension or preeclampsia as these may mediate the  
182 association between temperature and preterm birth. Urbanicity was based on data from the  
183 French National Institute of Statistics and Economics for the home address at birth. NDVI  
184 was the mean Landsat satellite NDVI<sup>37</sup> in a 500 m buffer around the home address at birth  
185 during June-August of the year of birth. We considered NDVI missing if it was unavailable  
186 over more than 25% of the buffer.

187 To better understand the associations with temperature and evaluate the robustness of our  
188 findings, we repeated our analyses 1) including the 309 participants (of which 16 preterm



189 births) that were missing covariates, which we imputed using the cohort area-specific median  
 190 or mode; and 2) using temperature estimated at a 1 km spatial resolution for all participants  
 191 (rather than using 200 m temperature for the 33% of participants that lived in large urban  
 192 areas).

193 We calculated the relative risk (RR) and 95% confidence interval (CI) of preterm birth  
 194 associated with moderate (10<sup>th</sup>, 90<sup>th</sup> percentiles), severe (5<sup>th</sup>, 95<sup>th</sup> percentiles), and extreme  
 195 (1<sup>st</sup>, 99<sup>th</sup> percentiles) exposure compared to the median exposure (50<sup>th</sup> percentile) during the  
 196 chronic and acute periods. We conducted all statistical analyses using R version 4.1.0<sup>38</sup> with  
 197 the packages survival v3.2-11<sup>39</sup> and dlnm v2.4.6.<sup>40</sup>

## 198 Results

199 Over half (58%) of the women lived in Brittany; 18% lived in Nancy, 16% in Poitiers, and  
 200 8% in Grenoble (Table 1). Almost half (45%) lived in a rural area. Most women (72%) were  
 201 25 to 34 years old at conception, had completed at least one year of post-secondary education  
 202 (63%), and were multiparous (56%). A quarter (25%) of women smoked during pregnancy.

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

|                                            | Consortium<br><i>n (%) or<br/>mean (sd)</i> | EDEN<br><i>n (%) or<br/>mean (sd)</i> | PELAGIE<br><i>n (%) or<br/>mean (sd)</i> | SEPAGES<br><i>n (%) or<br/>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)         | 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                            | 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%) |
| 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%)  |

204 Note: BMI, body mass index; NDVI, normalized difference vegetation index.

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

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

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

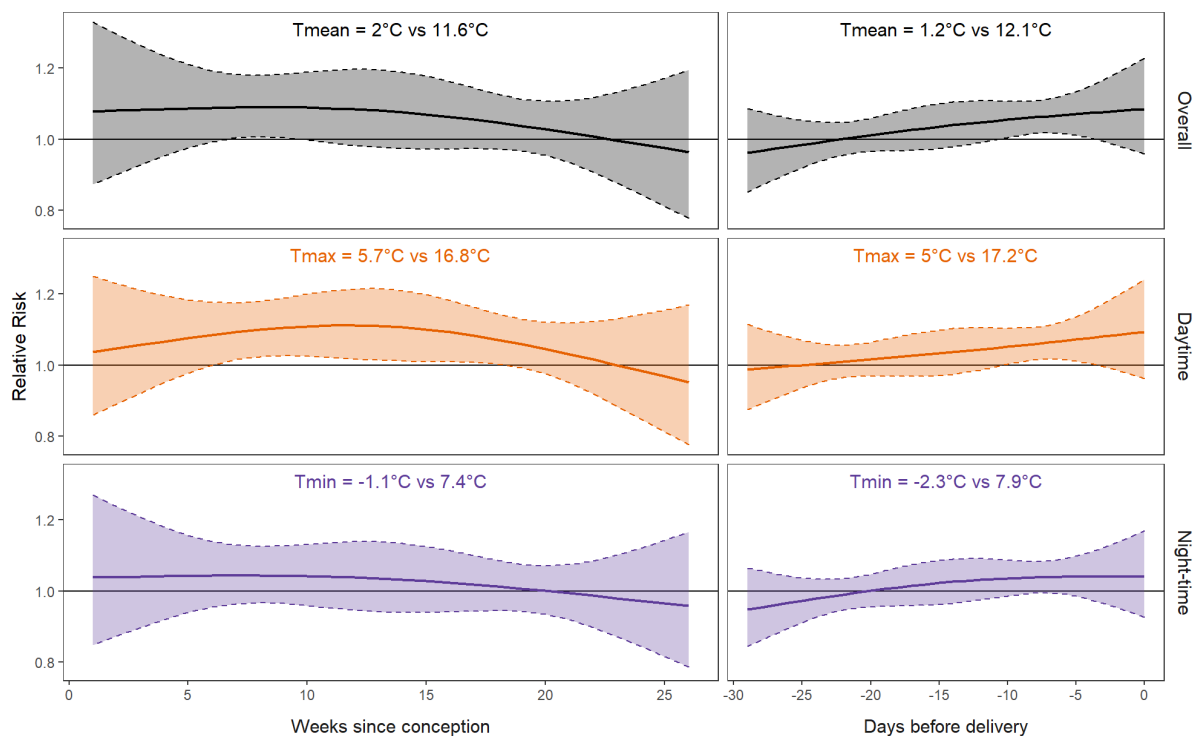
208 <sup>d</sup> Mean during days 30-181 after conception (up to 26 weeks following conception).

209 Mean duration of pregnancy (conception to delivery) was 37.9 weeks and 4.3% of births were  
210 preterm. Mean temperature  $\pm$  standard deviation during the 26 weeks following conception  
211 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  
212 EHF was  $0.7 \pm 1.1$  over days 30 to 181 since conception. Figure S2 shows the distribution of  
213 mean temperature and EHF over time for each cohort and Table S2 summarizes the  
214 distribution of the exposure indicators.

## 215 Cold

216 Severe cold (5<sup>th</sup> vs 50<sup>th</sup> percentile of Tmean) during weeks 7-9 after conception and days 10-4  
217 before delivery increased the risk of preterm birth (Figure 2). A mean temperature of  $2^\circ\text{C}$   
218 throughout weeks 7-9 after conception was associated with RR for preterm birth of 1.29 (95%  
219 CI: 1.02-1.64) compared to the reference temperature of  $11.6^\circ\text{C}$  (Figure 4). A mean  
220 temperature of  $1.2^\circ\text{C}$  throughout days 10-4 before delivery had RR of 1.55 (95% CI: 1.14-  
221 2.11) compared to  $12.1^\circ\text{C}$ . Considering a single week or day during each critical window, the  
222 mean RR for preterm birth was 1.09 (95% CI: 1.01-1.18) following severe cold on one of  
223 weeks 7-9 after conception; the mean RR for preterm birth was 1.06 (95% CI: 1.01-1.12)  
224 following severe cold on one of days 10-4 before delivery (Figure S3). For extreme cold (1<sup>st</sup>

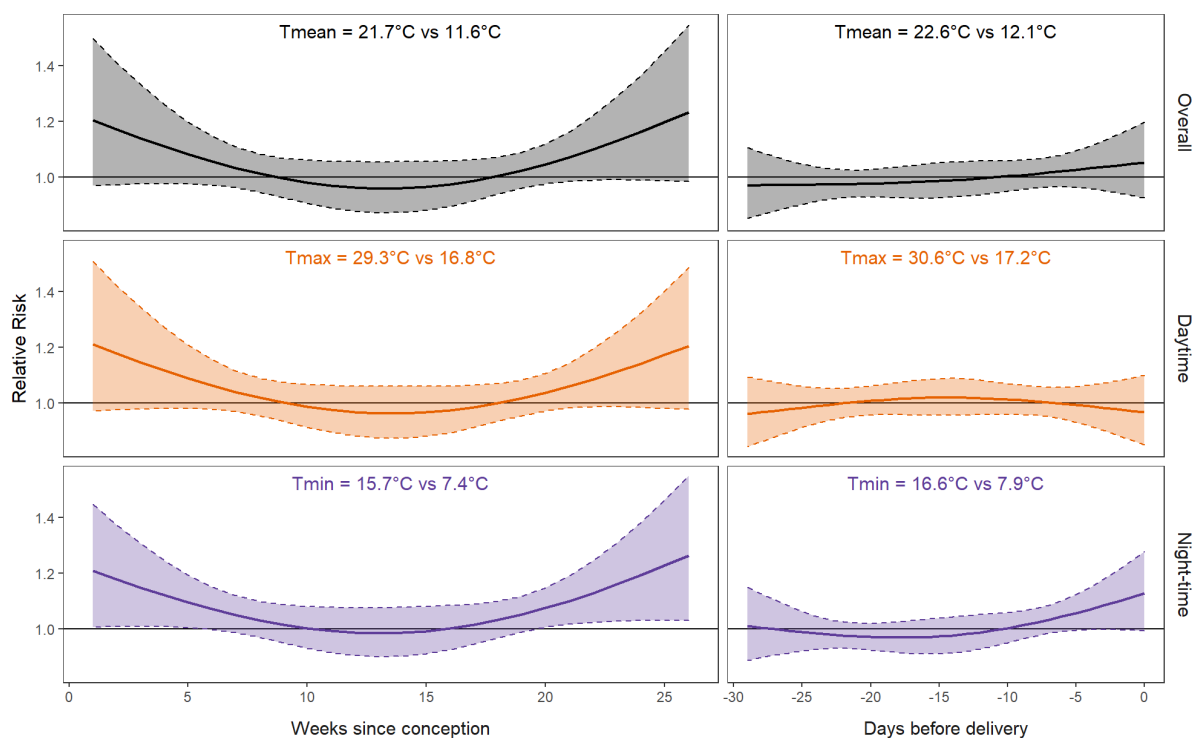
225 percentile of Tmean), the critical windows were 4-9 weeks after conception and 10-4 days  
 226 before delivery; the only critical window for moderate cold (10<sup>th</sup> percentile of Tmean) was  
 227 10-5 days before delivery (Figure 4). Chronic daytime cold (low Tmax) showed a longer  
 228 critical window than chronic overall cold (low Tmean) (Figure 2), while night-time cold (low  
 229 Tmin) was only significant when it was extreme (1<sup>st</sup> percentile) 7-6 days before delivery  
 230 (Figure 4). Imputing missing covariates did not substantially change the associations. Using  
 231 only 1 km temperature made the critical windows shorter or widened the confidence intervals.  
 232 Maternal education was the only variable that did not satisfy the proportional hazards  
 233 assumption; stratifying the Cox models on education did not substantially alter our results.



234  
 235 Figure 2. Adjusted relative risk (solid line) and 95% confidence interval (shaded area) for  
 236 preterm birth associated with severe cold during the 26 weeks following conception (left) and  
 237 the 30 days ending at delivery (right). Top: overall cold (5<sup>th</sup> percentile of Tmean); middle:  
 238 daytime cold (5<sup>th</sup> percentile of Tmax); bottom: night-time cold (5<sup>th</sup> percentile of Tmin).  
 239 Reference is 50<sup>th</sup> percentile of temperature. Models included exposure throughout pregnancy,  
 240 area, season of conception, urbanicity, NDVI, child sex, and maternal characteristics (age at  
 241 conception, height, pre-pregnancy BMI, parity, education, smoking during pregnancy).

242 Heat

243 Heat (high Tmean) during the first weeks following conception, the second half of the second  
 244 trimester, and the last days before delivery seemed to correspond with an increased risk of  
 245 preterm birth (Figure 3). We identified critical windows for severe night-time heat (95<sup>th</sup> vs  
 246 50<sup>th</sup> percentile of Tmin; 15.7°C vs 7.4°C) during weeks 1-5 after conception (RR: 2.00; 95%  
 247 CI:1.05-3.84) and 20-26 weeks after conception (RR: 2.87; 95% CI: 1.21-6.79) (Figure 3,  
 248 Figure 4). Focusing on a single week during each critical window, an average minimum  
 249 temperature of 15.7°C during any one of weeks 1-5 or weeks 21-26 after conception was  
 250 associated with mean RR of about 1.16 (95% CI: 1.02-1.34) (Figure S3). Moderate (90<sup>th</sup>  
 251 percentile) night-time heat showed a somewhat smaller effect during the same windows,  
 252 while extreme (99<sup>th</sup> percentile) night-time heat showed a larger effect but only 21-26 weeks  
 253 after conception (Figure 4). Sensitivity analyses did not substantially alter the results.



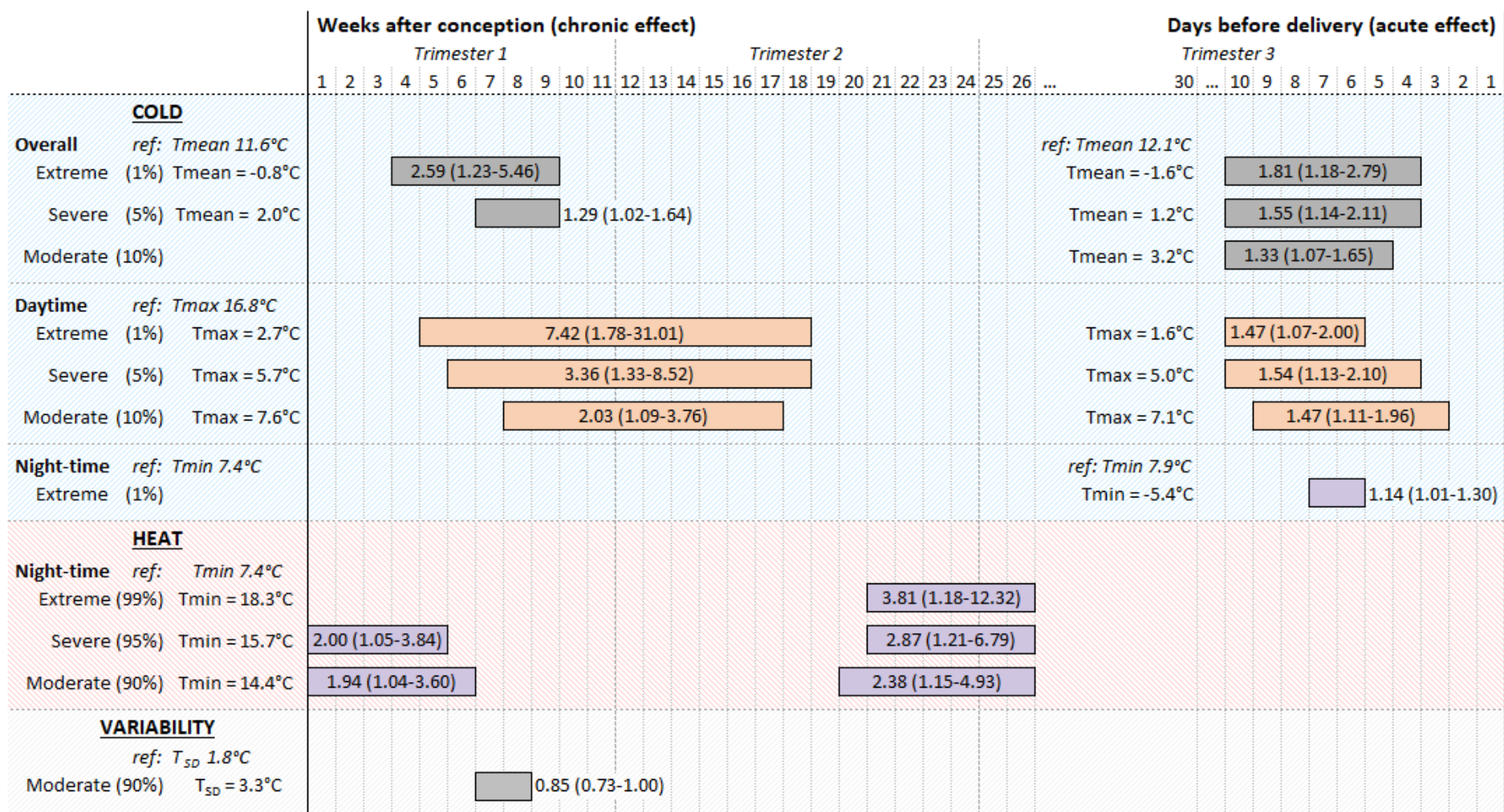
254 Figure 3. Adjusted relative risk (solid line) and 95% confidence interval (shaded area) for  
 255 preterm birth associated with severe heat during the 26 weeks following conception (left) and  
 256 the 30 days ending at delivery (right). Top: overall heat (95<sup>th</sup> percentile of Tmean); middle:  
 257 daytime heat (95<sup>th</sup> percentile of Tmax); bottom: night-time heat (95<sup>th</sup> percentile of Tmin).  
 258 Reference is 50<sup>th</sup> percentile of temperature. Models included exposure throughout pregnancy,  
 259 area, season of conception, urbanicity, NDVI, child sex, and maternal characteristics (age at  
 260 conception, height, pre-pregnancy BMI, parity, education, smoking during pregnancy).  
 261

262 Temperature variability and Excess Heat Factor

263 There was no clear association between temperature variability and risk of preterm birth.

264 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  
265 after conception may have had a protective effect (Figure S4), but the association did not  
266 clearly differ from null (RR: 0.85; 95% CI: 0.73-1.00). There were no critical windows for  
267 other exposure levels, and sensitivity analyses showed similar results.

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



1  
2 Figure 4. Cumulative adjusted relative risk (RR) for preterm birth associated with ambient temperature exposure throughout an entire critical  
3 window. Bars show timing of critical windows; bar labels show cumulative RR (95% confidence interval). Models included exposure throughout  
4 pregnancy, area, season of conception, urbanicity, NDVI, child sex, and maternal characteristics (age at conception, height, pre-pregnancy BMI,  
5 parity, education, smoking during pregnancy).

## 6 Discussion

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

### 16 Cold

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

21 Few previous studies examined cold early during pregnancy in temperate climates, with most  
22 finding protective effects.<sup>17,18,21,22</sup> Consistent with our results, a study in the USA found that  
23 cold during the two weeks before or five weeks after conception increased the risk of preterm  
24 birth, and studies in China reported increased risk from entire-pregnancy cold in temperate<sup>17</sup>  
25 and cold areas.<sup>18</sup> Compared to previous studies, we examined narrower windows (single  
26 weeks during the first two trimesters), estimated residence-based temperature (rather than  
27 using city-wide or regional temperature), and adjusted for temperature later in pregnancy,  
28 which may have improved our ability to detect critical windows.

29 We also found a critical window for acute cold 10-4 days before delivery. Previous studies of  
30 acute cold in temperate climates have reported conflicting results of no association with  
31 preterm birth,<sup>18,20,41,42</sup> a decreased risk,<sup>22</sup> or oscillating positive and negative associations.<sup>10,14</sup>  
32 Most of these studies considered only the last seven days or four weeks of pregnancy, which  
33 may have limited their ability to detect a critical window starting about 10 days before  
34 delivery, and most did not adjust for temperature earlier in pregnancy as we did. Click or tap  
35 here to enter text.

## 36 Heat

37 We found critical windows for chronic heat during the five weeks after conception and 20-26  
38 weeks after conception. The association was clearest for night-time heat, but the shape of the  
39 lag-response curve was similar for overall and daytime heat. Heatwave mortality studies have  
40 suggested that hot nights following hot days may be particularly dangerous because they limit  
41 the ability to recover from daytime exposure,<sup>43,44</sup> and recent studies in California and Belgium  
42 found a clearer association with preterm birth for night-time than daytime heat.<sup>14,27</sup> Our study  
43 may have been particularly suited to examining night-time heat because we estimated  
44 residence-based exposure using a model that captures the higher night-time temperatures of  
45 urban heat islands.<sup>34</sup> Taken together, these results suggest that future studies should consider  
46 night-time heat indicators in order to clarify the effects of heat during pregnancy, particularly  
47 in countries such as France where only about 13% of homes have air conditioning.<sup>45</sup>

48 Many studies have reported that heat in the last days of pregnancy may trigger preterm  
49 delivery,<sup>2,3</sup> although a few have reported no effect in cold or cool climates.<sup>10,18,20,41</sup> In our  
50 study, heat during the last five days of pregnancy may have increased risk of preterm birth,  
51 but the association was unclear. This might be because we adjusted for temperatures earlier in  
52 pregnancy whereas most previous studies did not. Our residence-based exposure estimates  
53 may also be less accurate during the final days of pregnancy for some women who may have  
54 been admitted to maternity units before the day of delivery.

## 55 Temperature variability and acclimation

56 Temperature variability and acclimation to location and season have been shown to affect the  
57 risk of mortality,<sup>29,30</sup> but few studies have examined them in relation to birth outcomes. A  
58 recent study in the Andes associated more variable temperature with lower birth weight,<sup>46</sup> and  
59 a study in France using a subset of our study population associated more variable temperature  
60 during weeks 4-18 after conception with lower term birth weight.<sup>47</sup>

61 We did not find an association between preterm birth and the variability of temperature. Nor  
62 did we find an association with EHF, a heatwave index that accounts for acclimation to both  
63 location and season. This might be related to the fact that we only found critical windows for  
64 night-time heat (high T<sub>min</sub>) whereas EHF is based on T<sub>mean</sub>. Our sample size may also have  
65 limited our ability to examine an infrequent acute exposure such as EHF. We also adjusted for  
66 EHF earlier in pregnancy, which may have reduced the effect of EHF shortly before delivery;



67 previous heatwave studies only examined exposure during the last week of pregnancy.<sup>28,48</sup>  
68 Overall, our findings suggest that daily mean, minimum, and maximum temperature may be  
69 more relevant for preterm birth than temperature variability or heatwaves.

## 70 Strengths and limitations

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

77 DLNM requires complete equal-length exposure histories, so we only considered exposure  
78 during the 26 weeks following conception and the 30 days ending at delivery. This could have  
79 led us to miss critical windows early in the third trimester (e.g. weeks 27-30 after conception).  
80 A recent study in Rome and Barcelona found that acute heat was more harmful earlier in the  
81 third trimester,<sup>15</sup> so future studies should investigate critical windows in the first half of the  
82 third trimester. We also did not account for humidity, which may modify the physiological  
83 effects of heat.<sup>49</sup> However, the evidence for humidity is mixed: some studies found it did not  
84 substantially modify the association between temperature and mortality<sup>50,51</sup> or birth  
85 outcomes<sup>28</sup> while others suggested a significant role<sup>47</sup> or that humidity's importance varies  
86 between locations.<sup>52</sup>

87 Despite these limitations, our study has several strengths. Pooling three cohorts from different  
88 regions of France allowed us to increase the study population and capture greater climatic  
89 variability while maintaining detailed health data and similar lifestyles across participants. We  
90 estimated exposure at participants' home address with a spatiotemporally resolved  
91 temperature model. This likely reduced exposure error for the 45% of women that lived in  
92 rural areas, which often have few weather monitors, and the 33% of women that lived in large  
93 urban areas, where we were able to use 200 m temperature estimates that better capture urban  
94 heat islands and fine-scale spatial patterns. One previous study of temperature and birth  
95 weight found that associations disappeared when using coarser monitor-based exposure rather  
96 than residence-based exposure.<sup>20</sup> Consistently, our sensitivity analyses using 1 km rather than

97 200 m temperature for urban women showed similar trends as the main analysis but the  
98 associations were weakened and critical windows shortened.

99 We performed a survival analysis with pregnancy duration as the time variable, which is the  
100 most effective method to study time-varying exposures in cohorts.<sup>53,54</sup> It also avoids possible  
101 confounding by temporal trends in conception rates and accounts for the fact that the risk of  
102 preterm birth increases exponentially later in pregnancy.<sup>55</sup> To avoid underestimating  
103 gestational age in the case that temperature affects foetal growth during the first trimester, we  
104 preferred gestational duration calculated from the last menstrual period rather than from  
105 measurements performed at the first ultrasound. We accounted for lags in the effect of  
106 exposure, examined narrow windows, and adjusted our estimates of chronic effects (during  
107 the 26 weeks following conception) for acute effects (during the 30 days preceding delivery)  
108 and vice versa. We further adjusted for potential confounders such as season of conception,  
109 maternal age, education, and smoking, but did not adjust for air pollution because it may be  
110 on the causal pathway from temperature to preterm birth.<sup>56</sup> Future research may investigate  
111 the possible synergistic effects of air pollution and temperature.<sup>48,57</sup>

## 112 Conclusion

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

## 121 Ethics approval

122 EDEN, PELAGIE and SEPAGES were approved by the relevant ethical committees: la  
123 Commission Nationale de l'Informatique et des Libertés, le Comité Consultatif pour la  
124 Protection des Personnes dans la Recherche Biomédicale du Kremlin Bicêtre, le Comité  
125 Consultatif sur le Traitement de l'Information en Matière de Recherche dans le Domaine de la  
126 Santé, le Comité de Protection des Personnes Sud-Est V, and le Comité d'Éthique de

127 l'Inserm. All participating women gave informed written consent for themselves and their  
128 children.

## 129 Author contributions

130 IH helped design the study, prepared data, performed analyses, interpreted the results, and  
131 wrote the manuscript. MR helped design the study, prepared data, performed analyses, helped  
132 interpret the results, and edited the manuscript. AG helped design the study, prepared data,  
133 helped interpret the results, and edited the manuscript. ES prepared data and edited the  
134 manuscript. BH prepared data and edited the manuscript. RS edited the manuscript. SLC  
135 prepared data and edited the manuscript. IP edited the manuscript. CC prepared data and  
136 edited the manuscript. IK helped direct the study and edited the manuscript. JL designed and  
137 directed the study, helped interpret the results, and edited the manuscript.

## 138 Data availability

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

## 141 Supplementary data

142 Supplementary data are available at *IJE* online.

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## 189 Conflict of interest

190 None declared.

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