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1 Early delivery following chronic and acute 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 distributed lags to evaluate
32 time-varying associations with preterm birth simultaneously controlling for exposure during
33 the first 26 weeks and last 30 days of pregnancy. We examined weekly mean, daytime, night-
34 time, and variability of temperature, and heatwaves accounting for adaptation to location and
35 season.

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

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

49 Keywords

50 preterm birth, heat, cold, exposure windows

51 Key Messages

- 52 • We examined chronic and acute windows of susceptibility to temperature during pregnancy
53 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 and
59 the frequency and intensity of extreme weather events will magnify morbidity and mortality
60 impacts.¹ A growing body of research suggests that extreme ambient temperatures can increase
61 the risk of adverse birth outcomes such as preterm birth.^{2,3} Preterm birth (delivery at <37 weeks
62 amenorrhea) is the leading cause of under-5 mortality worldwide⁴ and increases the risk of
63 adverse health outcomes throughout childhood and into adulthood.⁵ Globally, about 11% of
64 births are preterm, and the rate is increasing in many countries.⁶ In France, the rate of preterm
65 birth increased from 5.4% in 1995 to 7.5% in 2016.⁷ The drivers of these trends remain unclear,⁸
66 but exposure to extreme and variable temperatures may contribute and is expected to increase
67 as climate change progresses.⁹

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

81 Many previous studies of temperature and preterm birth focused only on the last days of
82 pregnancy (acute exposure), and most reported that high temperatures or heatwaves were
83 associated with decreased gestational duration or increased risk of preterm or early term
84 birth.^{12,15-17} Fewer studies have examined chronic exposure earlier in pregnancy, and results
85 have been less consistent: chronic heat and cold may increase the risk of preterm birth in some
86 populations,¹⁸⁻²² but may protect or have no effect in others.^{19,20,23,24} These mixed findings
87 could in part be due to misidentification of critical windows in studies that did not fully account
88 for correlation in exposure between trimesters.²⁵ Since windows of susceptibility may not align
89 with trimesters,²⁴ some recent studies have examined narrower exposure windows such as
90 months or weeks,^{20,24,26} but the timing of critical windows remains unclear. Previous studies
91 mostly estimated temperature exposure for all inhabitants of a city or region based on one or a
92 few monitoring stations. This can lead to exposure error that biases associations towards the
93 null,²⁷ particularly for rural populations, which may live far from monitors, and for urban
94 residents, who may be affected by urban heat islands. To address this, a few recent studies
95 estimated exposure with spatiotemporally resolved models coupled to home addresses.^{19,22,26,28}
96 Previous studies also considered various exposure indicators such as mean, minimum,
97 maximum, and apparent temperature. Some reported stronger associations for certain
98 indicators^{16,29} while others found that all indicators gave similar results.³⁰ Mortality studies
99 suggest that temperature variability may have health impacts³¹ and that acclimation to location
100 and season may modify associations,³² but few studies have examined these in relation to
101 preterm birth.

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

115 Methods

116 Study population

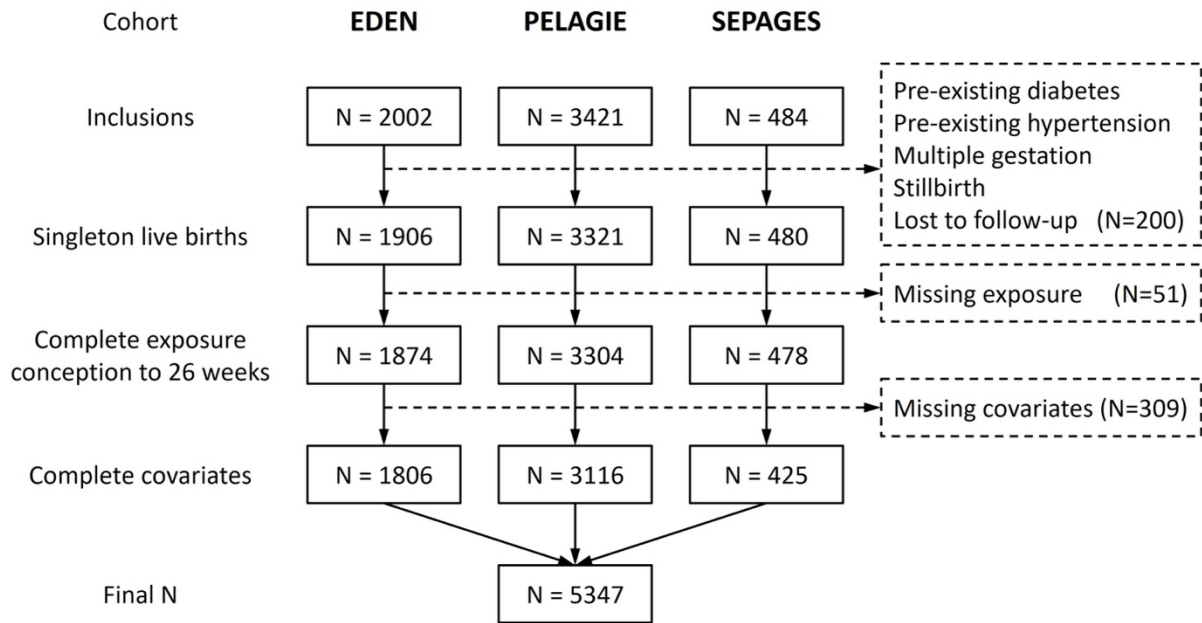
117 We obtained data from three French prospective mother-child cohorts that were designed to
118 study the effects of prenatal environmental exposures on child development and health: EDEN
119 (Étude des Déterminants pré et post natals du développement et de la santé de l'Enfant),³³
120 PELAGIE (Perturbateurs Endocriniens : étude Longitudinale sur les Anomalies de la
121 Grossesse, l'Infertilité, et l'Enfance),³⁴ and SEPAGES (Suivi de l'Exposition à la Pollution
122 Atmosphérique durant la Grossesse et Effets sur la Santé).³⁵ Briefly, EDEN included 2002
123 women recruited between 2003 and 2006 at <24 weeks amenorrhea in the metropolitan areas
124 of Poitiers and Nancy; PELAGIE included 3421 women recruited between 2002 and 2006 at
125 <19 weeks amenorrhea in the Brittany region; SEPAGES included 484 women recruited
126 between 2014 and 2017 at <19 weeks amenorrhea in the metropolitan area of Grenoble
127 (**Supplementary Figure S1**).

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

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

139 Outcome definition

140 Duration of pregnancy (conception to birth) was assessed in days using both the reported date
141 of the last menstrual period (LMP) and the estimate from the first trimester ultrasound (when
142 LMP was not reported or when the two differed by more than 30 days). When neither of these
143 were available ($n = 3$ in EDEN; $n = 84$ in PELAGIE), we used the obstetrician's estimate of
144 gestational age at delivery. We defined preterm birth as delivery at <37.0 weeks amenorrhea
145 (<35.0 weeks since conception).³⁶



146

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

148 [Exposure assessment](#)

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

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

168 Main analysis

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

181 We adjusted all models for possible confounders or predictors of the outcome selected *a priori*
182 based on the literature and our reasoning: cohort recruitment area (Nancy / Poitiers / Côtes-
183 d'Armor / Finistère / Ille-et-Vilaine / Grenoble), season of conception (Winter / Spring /
184 Summer / Fall), urbanicity (city centre / suburban / rural), normalized difference vegetation
185 index (NDVI; a measure of vegetation density), child sex, and maternal characteristics (age at
186 conception, height, pre-pregnancy body mass index [BMI], parity, education, and smoking
187 during pregnancy [none / active smoker]). **Table 1** lists the levels of the covariates. We did not
188 adjust for gestational hypertension or preeclampsia as these may mediate the association
189 between temperature and preterm birth. Nor did we adjust for air pollution, as it is on the causal
190 pathway between temperature and preterm birth.⁴⁰ Urbanicity was based on data from the
191 French National Institute of Statistics and Economics for the home address at birth. We
192 calculated mean NDVI from Landsat satellite data⁴¹ in a 500 m buffer around the home address
193 during summer (June-August) of the year of birth. Our intent was to capture total vegetated area
194 (rather than temporal changes in vegetation extent and greenness) and to minimize the influence
195 of missing data due to snow and cloud cover during colder seasons. Previous studies of preterm
196 birth estimated NDVI on a single summer day,⁴²⁻⁴⁷ reported very high correlation between
197 seasonal and annual NDVI,⁴⁸ or reported consistent effects for every month.⁴⁹ We considered
198 NDVI missing if it was unavailable over more than 25% of the buffer.

199

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 ^a (weeks) | 37.9 (1.7) | 37.7 (1.8) | 38.1 (1.6) | 37.7 (1.5) |
| Temperature ^b (°C) | 11.8 (3.6) | 11.3 (4.1) | 12.1 (3.2) | 12 (4.4) |
| Temperature variability ^c (°C) | 2.0 (0.3) | 2.2 (0.2) | 1.9 (0.3) | 2.1 (0.2) |
| Excess Heat Factor ^d | 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) ^e | 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 ² | 412 (7.7%) | 157 (8.7%) | 229 (7.3%) | 26 (6.1%) |
| 18.5 – 25 kg/m ² | 3844 (71.9%) | 1177 (65.2%) | 2346 (75.3%) | 321 (75.5%) |
| >25 kg/m ² | 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 ^e | 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%) |

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

202 ^a From conception to delivery.

203 ^b Mean during the 26 weeks following conception.

204 ^c Mean weekly standard deviation during the 26 weeks following conception.

205 ^d Mean during days 30-181 after conception (up to 26 weeks following conception).

206 ^e Coded as a continuous variable.

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

215 We used the fitted models to estimate the relative risk (RR) of preterm birth and 95% confidence
216 interval (CI) associated with moderate (10th, 90th percentiles), severe (5th, 95th percentiles), and
217 extreme (1st, 99th percentiles) exposure compared to the median exposure (50th percentile)
218 during the chronic and acute periods. We report both the cumulative risk associated with
219 exposure throughout the entire duration of a critical window and the mean risk associated with
220 exposure on only a single week or day during each window. We calculated mean risk by
221 averaging the risk of all individual weeks or days in each window. We conducted all statistical
222 analyses using R version 4.1.0⁵⁰ with the packages survival v3.2-11⁵¹ and dlnm v2.4.6.⁵²

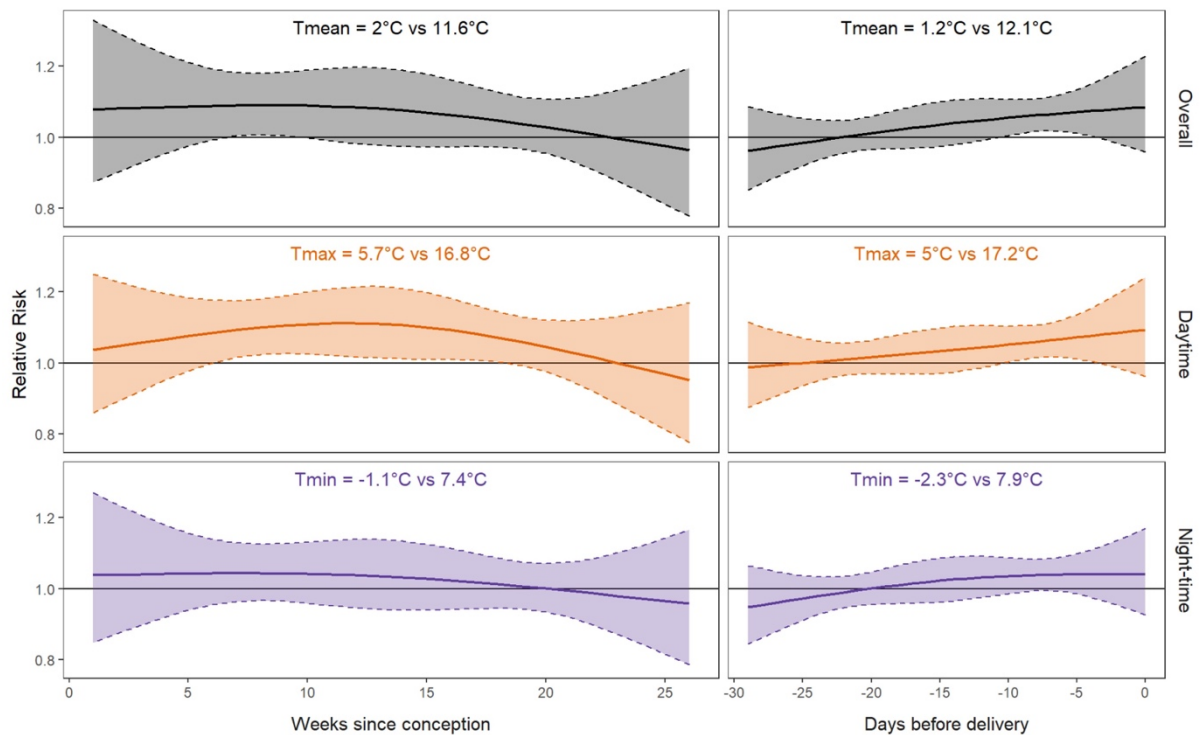
223 Results

224 Over half (58%) of the women lived in Brittany; 18% lived in Nancy, 16% in Poitiers, and 8%
225 in Grenoble (**Table 1**). Almost half (45%) lived in a rural area. Most women (72%) were 25 to
226 34 years old at conception, had completed at least one year of post-secondary education (63%),
227 and were multiparous (56%). A quarter (25%) of women smoked during pregnancy.

228 Mean duration of pregnancy (conception to delivery) was 37.9 weeks and 4.3% of births were
229 preterm. Mean temperature \pm standard deviation during the 26 weeks following conception was
230 $11.8 \pm 3.6^\circ\text{C}$; the standard deviation of weekly temperature averaged $2.0 \pm 0.3^\circ\text{C}$. Mean EHF
231 was 0.7 ± 1.1 over days 30 to 181 since conception. **Supplementary Figure S2** shows the
232 distribution of mean temperature and EHF over time for each cohort and **Supplementary Table**
233 **S1** summarizes the distribution of the exposure indicators.

234 Cold

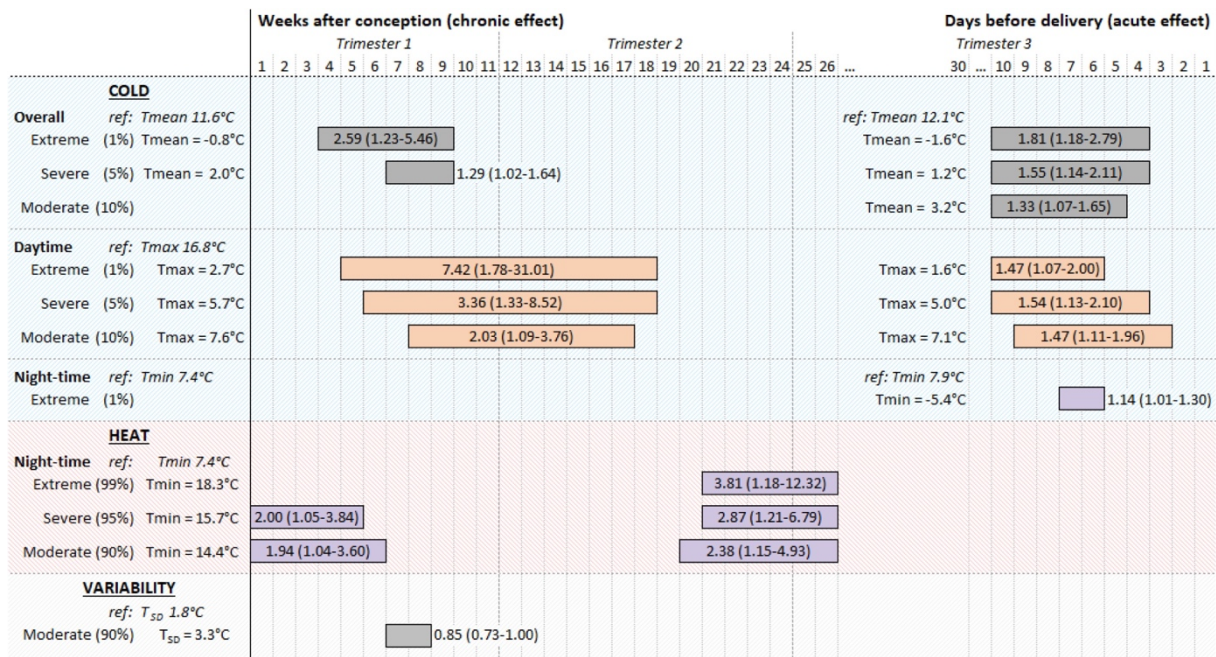
235 Severe cold (5th vs 50th percentile of T_{mean}) during weeks 7-9 after conception and days 10-4
236 before delivery increased the risk of preterm birth (**Figure 2**). A mean temperature of 2°C
237 throughout weeks 7-9 after conception was associated with RR for preterm birth of 1.29 (95%



238

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

247 CI: 1.02-1.64) compared to the reference temperature of 11.6°C (**Figure 3**). A mean
 248 temperature of 1.2°C throughout days 10-4 before delivery had RR of 1.55 (95% CI: 1.14-2.11)
 249 compared to 12.1°C. Considering a single week or day during each critical window, the mean
 250 RR for preterm birth was about 1.09 (95% CI: 1.01-1.18) following severe cold on one of weeks
 251 7-9 after conception; the mean RR for preterm birth was about 1.06 (95% CI: 1.01-1.12)
 252 following severe cold on one of days 10-4 before delivery (**Supplementary Figure S3**). For
 253 extreme cold (1st percentile of Tmean), the critical windows were 4-9 weeks after conception
 254 and 10-4 days before delivery; the only critical window for moderate cold (10th percentile of
 255 Tmean) was 10-5 days before delivery (**Figure 3**). Chronic daytime cold (low Tmax) showed
 256 a longer critical window than chronic overall cold (low Tmean) (**Figure 2**), while night-time
 257 cold (low Tmin) was only significant when it was extreme (1st percentile) 7-6 days before
 258 delivery (**Figure 3**).



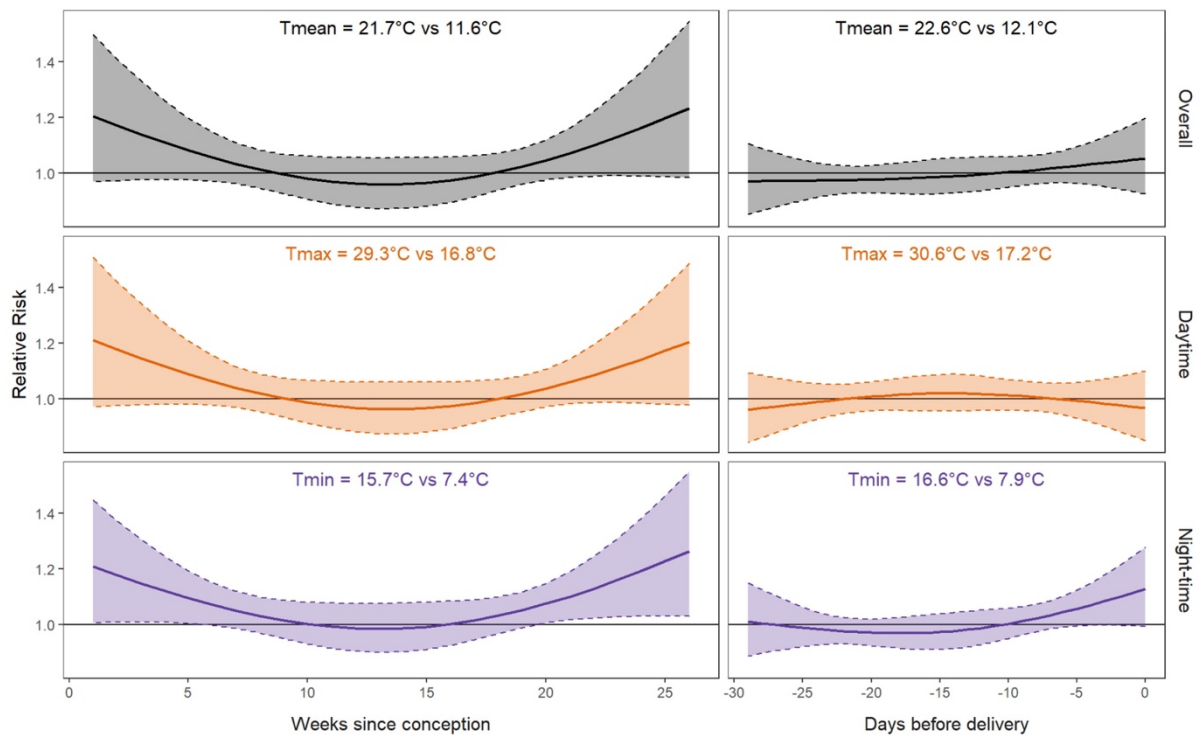
259

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

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

272 **Heat**

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



281
 282 **Figure 4.** Adjusted relative risk (solid line) and 95% confidence interval (shaded area) for preterm birth
 283 associated with severe heat during the 26 weeks following conception (left) and the 30 days ending at delivery
 284 (right). Top: overall heat (95th percentile of Tmean); middle: daytime heat (95th percentile of Tmax); bottom:
 285 night-time heat (95th percentile of Tmin). Reference is 50th percentile of temperature. Models included
 286 exposure throughout pregnancy, area, season of conception, urbanicity, NDVI, child sex, and maternal
 287 characteristics (age at conception, height, pre-pregnancy BMI, parity, education, smoking during pregnancy).
 288 BMI, body mass index; NDVI, normalized difference vegetation index; Tmax, daily maximum temperature;
 289 Tmean, daily mean temperature; Tmin, daily minimum temperature.

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

293 Temperature variability and Excess Heat Factor

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

299 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.^{19,20,23,24} 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 temperate¹⁹
319 and cold areas.²⁰ 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,^{20,22,53,54} a decreased risk,²⁴ or oscillating positive and negative associations.^{12,16} 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,^{55,56} and recent studies in California and Belgium
335 found a clearer association with preterm birth for night-time than daytime heat.^{16,29} 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.³⁷ 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.⁵⁷

341 Many studies have reported that heat in the last days of pregnancy may trigger preterm
342 delivery,^{2,3} although a few have reported no effect in cold or cool climates.^{12,20,22,53} 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,^{31,32} 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,⁵⁸ 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.⁵⁹

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_{min}) whereas EHF is based on T_{mean}. 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.^{30,60}

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

363 [Strengths and limitations](#)

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

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

378 Although we adjusted for major confounders including maternal smoking, age, parity, and pre-
379 pregnancy BMI, we were unable to adjust for some possible confounders such as household
380 income (although we used education as a proxy), noise, and light at night. We also did not
381 account for humidity, which may modify the physiological effects of heat.⁶² However, the
382 evidence for humidity is mixed: some studies found it did not substantially modify the
383 association between temperature and mortality^{63,64} or birth outcomes³⁰ while others suggested
384 a significant role⁵⁹ or that humidity's importance varies between locations.⁶⁵

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

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

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

410 Conclusion

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

419 Ethics approval

420 EDEN, PELAGIE and SEPAGES were approved by the relevant ethical committees: la
421 Commission Nationale de l'Informatique et des Libertés, le Comité Consultatif pour la
422 Protection des Personnes dans la Recherche Biomédicale du Kremlin Bicêtre, le Comité
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425 All participating women gave informed written consent for themselves and their children.

426 Data availability

427 The data underlying this article will be shared on reasonable request to the corresponding author
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429 Supplementary data

430 Supplementary data are available at *IJE* online.

431 Author contributions

432 IH helped design the study, prepared data, performed analyses, interpreted the results, and wrote
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434 interpret the results, and edited the manuscript. AG helped design the study, prepared data,
435 helped interpret the results, and edited the manuscript. ES prepared data and edited the
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487 Conflict of interest

488 None declared.

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