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Ambient temperature as trigger of preterm delivery in a temperate climate

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ABSTRACT

Background Recent evidence suggests that elevated ambient temperatures may trigger preterm delivery. Because results from studies in temperate climates are inconclusive, we investigated the association between temperature and the risk of preterm birth in Flanders (Belgium).

Methods We used data on 807,835 singleton deliveries (January 1998 – July 2011). We combined a quasi-Poisson model with distributed lag non-linear models to allow for delayed and non-linear temperature effects, accounting for the daily pregnancies at risk and their gestational age distribution.

Results For moderate heat (95th *vs.* 50th percentile) up to 1 day before delivery (lag 0–1), the risk of preterm birth increased by 8.5% (95% CI 2.4% to 15.0%) when minimum temperature increased from 8.3° to 16.3°C and by 9.6% (95% CI 1.1% to 18.7%) when maximum temperature increased from 14.7°C to 26.5°C. Corresponding estimates for extreme heat (99th *vs.* 50th percentile) were 15.6% (95% CI 4.8% to 27.6%) for minimum temperature (19.0°C *vs.* 8.3°C) and 14.5% (95% CI 0.5% to 30.6%) for maximum temperature (30.7°C *vs.* 14.7°C). Despite the increased risk of preterm birth associated with cold at lag 2 (and lag 1 for minimum temperature), cumulative cold effects were small. The percent change in preterm birth associated with moderate cold (5th *vs.* 50th percentile) up to 3 days before delivery (lag 0–3) was 2.1% (95% CI -4.1% to 8.7%) for minimum temperature (-2.0°C *vs.* 8.3°C) and 0.6% (95% CI -7.3% to 9.2%) for maximum temperature (2.5°C *vs.* 14.7°C).

Conclusions Even in a temperate climate, ambient temperature may trigger preterm delivery, suggesting that pregnant women should avoid temperature extremes.

BACKGROUND

Preterm delivery is the primary cause of perinatal morbidity and mortality in developed countries.[1] While adverse health outcomes are most obvious for lower gestational ages, even late preterm births (34-36 weeks) have higher morbidity and mortality rates than full-term births.[2] Because many of these effects continue into childhood and even adulthood,[2] preterm birth is a serious public health issue with major economic implications.[3]

Despite extensive research and clinical efforts designed toward the reduction of preterm delivery, rates continue to rise in most regions.[1, 4] In 2010, the mean preterm birth rate in developed regions was 8.6%, and in the US it has increased from 10.6% to 12.0% during the last two decades.[4] The underlying causes of preterm birth are poorly understood, although genetic, demographic, social-behavioural, and environmental factors are likely to play a role.[1, 5]

Recent evidence, mainly from studies in warm climates, suggests that elevated ambient temperatures may trigger preterm delivery.[6, 7] Among the few studies conducted in temperate climates,[8-12] an association between temperature and preterm birth has only been found in Sweden.[11, 12] Moreover, although studies on seasonality of birth outcomes have reported peaks of preterm birth not only in summer but also in winter,[13] only a limited number of studies investigated short-term effects of cold.[8, 9, 11, 12, 14-16]

We studied the association between ambient temperature and the risk of preterm birth in the temperate climate of Flanders (Belgium). We investigated the impact of both heat and cold and we considered the possibility of non-linear and lagged exposure effects.

METHODS

Data

The Study Centre for Perinatal Epidemiology (SPE) supplied information on births in Flanders during the period 1998-2011. Flanders is the Northern part of Belgium and is predominantly Dutch-speaking, with about six million inhabitants and 68 fully equipped maternity-obstetric units where 99.8% of all births occur.[17] For each newborn of at least 500 g, an official and coded perinatal form is completed (most often by the midwife) and sent to the SPE, where all data are controlled by an error detection programme.[18] An assessment of the quality of SPE data shows that there is less than 5% discrepancy between electronic data and data out of medical files.[19] Gestational age is based on the last menstrual period and is corrected according to the estimation from the first ultrasound.

We limited our study population to live-born singleton births with a gestational age between 22 and 42 weeks. Preterm births were classified as follows: <32 weeks (extremely to very preterm) and 32-36 weeks (moderate to late preterm) (World Health Organization, http://www.who.int/mediacentre/factsheets/fs363/en/). For births from 1999 to 2009, information on maternal education was available through linkage of the medical birth certificates of the SPE with official birth declarations.

Data on daily minimum and maximum air temperature and relative humidity, measured at the representative station in Uccle (Brussels), were provided by the Belgian Royal Meteorological Institute. As air pollution may confound the association between temperature and preterm birth,[20, 21] data on daily concentrations of particulate matter with diameter less than 10 μm ($PM_{10,}$ daily average) and ozone (O_3, 8-hour maximum) were obtained from the Belgian Interregional Environment Agency. Flanders has a dense network of automatic monitoring sites, collecting real-time data on a half-hourly basis. The average distance between the nearest

measuring stations is about 25 km. Data from monitoring stations are combined with land cover data obtained from satellite images in a spatial-temporal (Kriging) interpolation model, described by Janssen *et al*.[22] This provides air pollutant concentrations on a 4 x 4 km^2 grid, which are then used to calculate population-weighted average daily concentrations for Flanders.

Higher preterm birth rates in winter have been linked to a higher prevalence of influenza, as influenza infections may trigger preterm delivery, potentially through inflammation.[23] To adjust for the potential confounding effect of influenza episodes, we obtained data on weekly consultation rates for influenza-like illnesses from the representative Belgian Sentinel General Practitioner network, coordinated by the WIV-ISP (Scientific Institute of Public Health).[24] Influenza epidemics were defined as weeks (from Monday to Sunday) with an incidence above the threshold of 141 cases per 100,000 inhabitants.[24]

The research protocol was approved by the medical ethics committee of Hasselt University.

Statistical analysis

Daily counts of preterm births were modelled by combining quasi-Poisson regression with distributed lag non-linear models (DLNM).[25] This approach allows simultaneous estimation of the non-linear exposure-response association and the non-linear effects across lags, the latter termed lag-response association. We used the following model for minimum and maximum temperature:

$Y_t \sim \text{Poisson}(\mu_t)$,

$$Log\left(\frac{\mu_t}{Z_t}\right) = \alpha + \boldsymbol{\beta T_{t,l}} + S(RH, 3) + S(PM_{10}, 3) + S(O_3, 3) + S(time, 6/\text{year}) + \boldsymbol{\gamma}\text{DOW}_t + \delta\text{Holiday}_t + \lambda\text{Influenza}_t + S(Log(W_t), 4),$$

where Y_t is the observed number of preterm births and Z_t the number of pregnancies at risk on day t; α is the intercept; $\boldsymbol{T_{t,l}}$ is a matrix representing the two-dimensional DLNM cross-basis for temperature and lag days, $\boldsymbol{\beta}$ is vector of coefficients for $\boldsymbol{T_{t,l}}$, and l is the lag days. $S(RH, 3)$, $S(PM_{10}, 3)$, and $S(O_3, 3)$ are natural cubic splines with 3 degrees of freedom (df) for relative humidity, PM_{10}, and O_3, respectively, using the average exposure of the current day and the previous for each of these variables. Long-term trends[26] and seasonality were modelled using a natural cubic spline of time with 6 df per year. DOW_t is a categorical variable for day of the week, and $\boldsymbol{\gamma}$ is vector of coefficients. $Holiday_t$ is a binary variable that is "1" if day t was a public holiday, and δ is the coefficient. $Influenza_t$ is a binary variable that is "1" if day t was inside an epidemic influenza week, and λ is the coefficient. $S(Log(W_t), 4)$ is a natural cubic spline with 4 df with:

$$W_t = \frac{\sum_{j=22}^{36}(\boldsymbol{Z_{tj}} * W_j)}{Z_t}$$

where $\boldsymbol{Z_{tj}}$ is the number of pregnancies at risk during gestational week j (ranging from 22 through 36 weeks) on day t, and W_j is the conditional probability of birth during gestational week j, as proposed by Vicedo-Cabrera *et al*[27] to account for the temporal variation in the number of pregnancies at risk of preterm birth and their gestational age distribution. This approach was used because, as demonstrated by Darrow *et al*[28], seasonality in the underlying risk of preterm birth could confound time-series studies examining a seasonally-varying exposure. Induced deliveries and caesarean sections were excluded from μ_t because they are less likely to be related to external factors such as temperature, but they were included in the calculation of Z_t and W_t because they are at risk of preterm birth until the date of induction or caesarean section. As pregnancies with birth dates after the end of the study period do not appear in the at risk set, the denominator is decreasing at the end of the dataset. Therefore, the last 5 months of the study period (August–December 2011) were excluded from the analysis.

We used a DLNM that modelled both the nonlinear temperature effect and the lagged effect using a natural cubic spline. The maximum lag was set at 6 days. Lag 0 was defined as the 24-hour period from midnight to midnight, of the day of the birth, and lag 1 as the preceding 24-hour period, and so on. Spline knots were placed at equal spaces in the temperature range, whereas knots in the lag space were set at equally spaced values on the log scale of lags.[29] The df were selected according to the Akaike information criterion for quasi-Poisson models,[25] varying the df for the exposure-response from 2 to 6 and for the lag-response from 3 to 6. The final model for minimum temperature contained 3 df for temperature and 4 df for the lag structure, whereas the final model for maximum temperature contained 2 df for temperature and 5 df for the lag structure. The estimated dispersion parameter was 0.97 in the model for minimum temperature and 0.98 in the model for maximum temperature. The median values of the temperature indicators were used as reference. Relative risks of preterm birth were calculated for moderate heat (95th percentile), extreme heat (99th percentile), moderate cold (5th percentile), and extreme cold (1st percentile). Cumulative effects over lag 0–1, lag 0–3, and lag 0–6 days were computed by summing the log relative risks over the lags.

In addition to the analysis for all (non-induced vaginal) preterm births, we conducted stratified analyses by gestational age (<32 weeks, 32-36 weeks), gender, parity (first, higher), maternal age group (<25 years, 25-34 years, ≥35 years), maternal education (lower secondary or less, higher secondary, higher education) and the degree of urbanization of mother's residence (urban/semi-urban *vs.* rural).[30] Because temperature may also act as a trigger for labour among term births,[10] we additionally considered early-term (37-38 weeks) and full-term (>38 weeks) births in the stratified analysis. Z_t and W_t were recalculated for each of the subpopulations.

We did a sensitivity analysis to assess the impact of model choices. We increased the maximum lag to 8 and 10 days and we varied the df for temperature (2 to 6 df), for the lag structure (3 to

6 df), for the seasonal and long-term trend component (4 to 10 df per year), and for $Log(W_t)$ (1 to 6 df). We also explored the potential confounding by air pollution (PM_{10} and O_3) and by the pregnancies at risk (Z_t) and their gestational age distribution (W_t) by excluding these variables from the model one at a time. Results from subpopulation and sensitivity analyses are presented as the cumulative heat effect over lag 0–1 days and the cumulative cold effect over lag 0–3 days. All analyses were performed with the statistical software R, using the "dlnm" package.[29]

RESULTS

Data description

There were 807,835 live-born singleton births in Flanders from January 1998 until July 2011, including 467,502 (57.9%) non-induced vaginal births (table 1). A total of 27,076 (5.8%) from these non-induced vaginal births were preterm. The mean number of cases per day was 5.5 and the percentage of days without cases was less than 0.4%. The majority of preterm births (92.6%) had a gestational age from 32 to 36 weeks (moderate to late preterm).

Table 1 Descriptive characteristics of the study population, Flanders, Belgium, January 1998 – July 2011

	All births[a]		Non-induced vaginal births[b]			
	All		All		Preterm	
Characteristic	**No.**	**%**	**No.**	**%**	**No.**	**%**
Total	807,835	100	467,502	100	27,076	100
Season						
Spring (Mar-May)	211,101	26.1	122,494	26.2	7,086	26.2
Summer (Jun-Aug)	210,512	26.1	122,043	26.1	7,010	25.9
Autumn (Sep-Nov)	190,029	23.5	109,550	23.4	6,159	22.8
Winter (Dec-Feb)	196,193	24.3	113,415	24.3	6,821	25.2
Gestational age						
<32 weeks	5,099	0.6	2,005	0.4	2,005	7.4
32-36 weeks	43,166	5.3	25,071	5.4	25,071	92.6
37-38 weeks	201,222	24.9	106,091	22.7	/	/
>38 weeks	558,348	69.1	334,335	71.5	/	/
Gender						
Male	414,898	51.4	239,976	51.3	15,160	56.0
Female	392,937	48.6	227,526	48.7	11,916	44.0
Parity						
First	377,331	46.7	217,888	46.6	14,999	55.4
Higher	430,504	53.3	249,614	53.4	12,077	44.6
Maternal age						
<25 years	134,225	16.6	79,559	17.0	5,687	21.0
25-34 years	574,430	71.1	335,520	71.8	18,310	67.6
≥35 years	99,180	12.3	52,423	11.2	3,079	11.4
Maternal education[c]						
Low	82,350	12.7	46,611	12.5	3,339	15.2
Medium	251,334	38.8	137,427	36.8	9,145	41.7
High	274,075	42.3	164,519	44.1	7,978	36.4
Missing data	40,841	6.3	24,519	6.6	1,457	6.7
Urbanization						
Urban	609,440	75.4	352,857	75.5	20,486	75.7
Rural	198,395	24.6	114,645	24.5	6,590	24.3

[a]Used to calculate the daily number of pregnancies at risk (Z_t).

[b]Used to calculate the daily number of preterm births (μ_t).

[c]From 1999 to 2009.

Minimum temperature ranged from -12.3 to 23.9°C, with a median of 8.3°C. Maximum temperature ranged from -6.0 to 35.8°C, with a median of 14.7°C (table 2). Relative humidity had a median (range) of 79.5% (32.1 to 99.9%). The median (range) PM_{10} and O_3 concentrations were 25.9 μg/m^3 (5.2 to 150.5 μg/m^3) and 45.4 μg/m^3 (6.1 to 129.9 μg/m^3), respectively.

Table 2 Distribution of the meteorological and air pollution variables, Flanders, Belgium, January 1998 – July 2011

	Percentiles						
Exposure	**0th**	**1st**	**5th**	**50th**	**95th**	**99th**	**100th**
Minimum temperature, °C	-12.3	-5.6	-2.0	8.3	16.3	19.0	23.9
Maximum temperature, °C	-6.0	-1.0	2.5	14.7	26.5	30.7	35.8
Mean relative humidity, %	32.1	45.6	56.1	79.5	93.6	97.0	99.9
PM_{10}, μg/m^3	5.2	10.9	13.9	25.9	54.4	76.6	150.5
O_3, μg/m^3	6.1	7.5	11.6	45.4	77.9	95.5	129.9

PM_{10}, particulate matter with diameter less than 10 μm; O_3, ozone.

The Pearson correlation (r) between minimum and maximum temperature was 0.90 (supplementary table S1). Humidity was more strongly correlated with maximum temperature (r = -0.52) than with minimum temperature (r = -0.27), whereas PM_{10} showed a higher correlation with minimum temperature (r = -0.20) than with maximum temperature (r = -0.05). Correlations with O_3 were 0.52 for minimum temperature and 0.59 for maximum temperature.

Main analysis

For minimum temperature, the distributed non-linear lag surface showed a non-linear relationship with preterm birth at lags 0 to 2, whereas the response was relatively flat at longer lags (figure 1A). The heat effect was highest at lag 0 and relative risks increased with increasing

temperature. An effect of cold was observed at lags 1 and 2: relative risks were >1 for minimum temperatures roughly between the 50th percentile (8.3°C) and the 5th percentile (-2.0°C), but not for lower temperatures. Maximum temperature effects were delayed by one day compared to minimum temperature effects, i.e. the heat effect appeared at lag 1 and the cold effect at lag 2 (figure 1B). For the heat effect as well as the cold effect, relative risks were highest at the most extreme temperatures.

Figure 2 presents the lag-specific relative risks of preterm birth for moderate heat (95th *vs.* 50th percentile, figure 2A) and for moderate cold (5th *vs.* 50th percentile, figure 2B). For minimum temperature, the heat effect was highest at lag 0 (RR=1.072; 95% CI 1.015 to 1.133), and the cold effect was highest at lag 1 (RR=1.056; 95% CI 1.006 to 1.108). For maximum temperature, the heat effect was highest at lag 1 (RR=1.107; 95% CI 1.024 to 1.196) and the cold effect at lag 2 (RR=1.069; 95% CI 0.982 to 1.163). Note that relative risks for moderate cold at lag 0 were <1 for both temperature indicators (figure 2B).

Figure 3 presents the cumulative effect of temperature on preterm birth estimated over lag 0–1 days (A) and over lag 0–3 days (B). For minimum temperature, the cumulative heat effect over lag 0–3 days was larger than the heat effect over lag 0–1 days, whereas for maximum temperature, the lag 0–3 curve was relatively flat. Due to the seemingly protective effect of cold at lag 0, cumulative relative risks were <1 (or close to 1) at low minimum and maximum temperatures.

Table 3 presents the cumulative relative risks of preterm birth associated with moderate heat (95th percentile), extreme heat (99th percentile), moderate cold (5th percentile), and extreme cold (1st percentile), relative to the median of the temperature distribution. The risk of preterm birth increased by 8.5% (95% CI 2.4% to 15.0%) when minimum temperature up to 1 day before delivery (lag 0–1) increased from 8.3° to 16.3°C (moderate heat) and by 15.6% (95% CI

4.8% to 27.6%) when minimum temperature increased to 19.0°C (extreme heat). Corresponding estimates for maximum temperature were 9.6% (95% CI 1.1% to 18.7%) for an increase from 14.7°C to 26.5°C (moderate heat) and 14.5% (95% CI 0.5% to 30.6%) for an increase to 30.7°C (extreme heat). Despite the increased risk of preterm birth associated with cold at lag 2 (and lag 1 for minimum temperature), cumulative relative risks for moderate and extreme cold were close to one. For minimum temperature up to 3 days before delivery (lag 0–3), the percent change in preterm birth associated with moderate cold (-2.0°C *vs.* 8.3°C) was 2.1% (95% CI -4.1% to 8.7%). The corresponding estimate for maximum temperature (2.5°C *vs.* 14.7°C) was 0.6% (95% CI -7.3% to 9.2%).

Table 3 Cumulative heat and cold effects of minimum temperature (Tmin) and maximum temperature (Tmax) on preterm birth in Flanders, Belgium, January 1998 – July 2011

	Relative risk (95% CI)[a]							
	Moderate heat				**Extreme heat**			
Lag, day	**Tmin**		**Tmax**		**Tmin**		**Tmax**	
0–1	1.085	(1.024 to 1.150)	1.096	(1.011 to 1.187)	1.156	(1.048 to 1.276)	1.145	(1.005 to 1.306)
0–3	1.103	(1.034 to 1.176)	1.027	(0.947 to 1.113)	1.217	(1.091 to 1.358)	1.046	(0.915 to 1.194)
0–6	1.088	(1.007 to 1.175)	1.091	(0.997 to 1.192)	1.192	(1.045 to 1.359)	1.146	(0.990 to 1.328)
	Moderate cold				**Extreme cold**			
Lag, day	**Tmin**		**Tmax**		**Tmin**		**Tmax**	
0–1	0.973	(0.918 to 1.031)	0.921	(0.842 to 1.008)	0.930	(0.842 to 1.028)	0.906	(0.803 to 1.021)
0–3	1.021	(0.959 to 1.087)	1.006	(0.927 to 1.092)	0.961	(0.865 to 1.067)	1.011	(0.906 to 1.127)
0–6	0.998	(0.928 to 1.074)	0.965	(0.884 to 1.053)	0.910	(0.804 to 1.029)	0.963	(0.857 to 1.081)

Moderate heat, extreme heat, moderate cold, and extreme cold were defined as the 95th (Tmin: 16.3°C; Tmax: 26.5°C), 99th (Tmin: 19.0°C; Tmax: 30.7), 5th (Tmin: -2.0°C; Tmax: 2.5°C), and 1st (Tmin: -5.6°C; Tmax: -1.0°C) percentile temperatures over the study period, respectively.

[a]Estimates are relative to the median temperature (Tmin: 8.3°C; Tmax: 14.7°) and are adjusted for the pregnancies at risk and their gestational age distribution, long-term and seasonal trends, humidity, PM_{10}, O_3, day of the week, holidays, and influenza epidemics.

Effect modification

We explored potential effect modification by gestational age, gender, parity, maternal age, maternal education and degree of urbanization of maternal residence. Figure 4 presents the cumulative moderate heat effect over lag 0–1 days estimated for different subpopulations. In addition to the heat-related increases in preterm delivery among extremely to very preterm (<32 weeks) and moderate to late preterm (32-36 weeks) births, we also found heat effects among early-term (37-38 weeks) and full-term (>38 weeks) births (the two latter groups not being part of the main analysis). Although confidence intervals were overlapping, there was a trend of decreasing heat effects for increasing gestational age: for minimum temperature for example, relative risks were 1.133 (95% CI 0.920 to 1.395), 1.078 (95% CI 1.015 to 1.144), 1.050 (95% CI 1.019 to 1.081), and 1.035 (95% CI 1.019 to 1.051) for extremely to very preterm, moderate to late preterm, early-term, and full-term births, respectively. Except for a tendency of higher heat estimates for girls than for boys, there was no indication of effect modification by other variables, as confidence interval of subgroup estimates were large and the direction of differences between groups was not consistent for minimum and maximum temperature. Estimates of the cumulative moderate cold effect over lag 0–3 days did not reach significance in any of the subpopulations (figure 5).

Sensitivity analysis

Results for minimum temperature were fairly robust to changes in the maximum lag and the df for the lag-response function, the exposure-response function, the seasonal and long-term trend component, and $Log(W_t)$, as well as to the correction for the pregnancies at risk and their gestational age distribution: relative risk estimates ranged from 1.072 to 1.117 and from 0.992 to 1.046 for the moderate heat and cold effects, respectively (supplementary table S2). The

exclusion of O_3 from the model for minimum temperature resulted in a slight decrease of the heat effect estimate (RR=1.065, 95% CI 1.011 to 1.122). For maximum temperature (supplementary table S3), the heat effect decreased in models with fewer df for the lag-response function than in the main model, because the lag structure needs a lot of flexibility to capture the lag 1 effect. Other model changes gave similar results as the main analysis, with relative risks ranging from 1.071 to 1.100 for the heat effect and from 0.982 to 1.026 for the cold effect.

DISCUSSION

Based on data from 807,835 singleton births, we observed significant effects of recent minimum and maximum ambient temperature on the risk of preterm delivery in a temperate climate. We found an increased risk of preterm birth for high minimum temperature on the day of delivery and for low minimum temperature one to two days before delivery. Heat and cold effects of maximum temperature appeared to be delayed by one day compared to the effects of minimum temperature.

The absence of an association between maximum temperature and preterm birth on the day of delivery (lag 0) is plausible because for maximum temperature the birth precedes the exposure for a considerable number of cases. In summer, maximum temperatures can occur as late as 5 PM, whereas in winter they tend be closer to around 1 PM (Central European Time). Minimum temperatures, however, generally occur around or shortly after sunrise, so a much larger proportion of women actually experienced the lag 0 exposure before giving birth.

Although we found some indication for a cold-related increase in preterm birth few days after the exposure, cumulative cold effects were small and nonsignificant because of the seemingly protective effect of cold on the day of delivery observed for both temperature indicators. Moreover, minimum temperature showed an N-shaped association with preterm birth, as

increased relative risks were only observed for relatively mild low temperatures (between the 50th and the 5th percentile), but not for more extreme cold. These findings may be explained by the fact that, via clothing and heating, it is easier to adjust to low than to high temperatures. Although virtually all houses in Belgium have heating equipment, houses with air conditioning are limited.[31]

A review of the epidemiological literature on the influence of ambient temperature on birth outcomes concluded that findings for preterm delivery are inconclusive.[6] In temperate climates, a temperature-related increase in preterm birth has only been reported for Sweden,[11, 12] whereas studies on populations in Montreal, London and Germany did not find an association.[8-10] In warmer climates, effects of heat on preterm birth have been reported for Negev (Israel), California, Barcelona, Brisbane, Rome, Valencia, and China,[14-16, 27, 32-35] but not for New York and Chicago.[36, 37] Based on warm season data, Basu *et al*[33] found a 8.6% (95% CI 6.0% to 11.3%) increase in preterm birth risk for a 5.6°C increase in mean apparent temperature the week before delivery in California, whereas Schifano *et al*[15] reported an increase of 1.87% (95% CI 0.86% to 2.87%) for a 1°C increase in maximum apparent temperature (lag 0–2) in Rome. Different results for minimum and maximum temperature were reported for the warm season in Valencia[27]: compared with the median temperature, the risk of preterm birth increased up to 20% when maximum apparent temperature exceeded the 90th percentile two days before delivery and by 5% when minimum temperature rose to the 90th percentile during the 4th to 6th day before delivery. There was a trend for a negative association between preterm birth and heat exposure on the day of birth for maximum apparent temperature, but not for minimum temperature. An effect of cold on preterm birth has only been found for the historical study population (1915-1929) from Uppsala (Sweden)[11] and in a recent study from Guangzhou (China)[16]. Comparing the 1st (7.6°C) and 99th (31.9°C) percentile temperatures to the median value (24.4°C) in the mild climate of

Guangzhou, the effect of cold on preterm birth (17.9%, 95% CI 10.2% to 26.2%) was higher than the effect of heat (10.0%, 95% CI 2.9% to 17.6%).[16]

We observed a trend of higher heat effects for decreasing gestational age. This is consistent with results from the Chinese study, which found that extreme heat was more strongly associated with preterm births during 20-31 and 32-34 weeks of gestation than with preterm birth during weeks 35-36.[16] Other studies, however, have reported smaller or even negative estimates for low gestational ages.[14, 15, 33] Our study suggests that high temperatures may also trigger labour among term births, and the observation of a smaller but significant heat effect for term births compared to preterm births is consistent with previous studies.[14, 33] Auger *et al*[10] found an association between high temperatures and the risk of delivery among term pregnancies, with higher estimates for early-term than for full-term births, but not among preterm pregnancies.

By aggregating foetuses at risk across different gestational ages, some studies ignored potential confounding caused by seasonal variations in the gestational age distribution and increasing probabilities of preterm birth with higher gestational age.[6, 28] Recent studies accounted for this issue by using a pregnancy-at-risk approach correcting for the gestational age distribution,[9, 12, 27] or by using a time-to-event Cox proportional hazards model.[10, 11, 14, 16, 35] Studies using Cox regression estimated hazards of preterm birth associated with weekly average temperatures, which might be less appropriate to pick up very acute single-day effects as observed in our study. In the recent study from China,[16] associations based on quasi-Poisson regression with DLNM were strongest for recent exposures, whereas the average temperature in the week before delivery was not associated with preterm birth in the Cox proportional hazards model.

Temperatures for which heat-related increases in preterm birth are observed in our study are fairly mild (16.3° for minimum temperature and 26.5°C for maximum temperature), but such temperatures are rather exceptional in Belgium (representing only 5% of days). Multi-country studies on the association between temperature and mortality have shown that the unusualness of temperature rather than its absolute value determines the thresholds for health effects,[38-41] indicating some adaptation to local climate. In Belgium, excess mortality is not only observed during heat waves, but also on days with maximum and minimum temperatures below 30°C and 20°C, respectively.[42] In neighbouring countries (the Netherlands, Germany and the UK), estimated heat thresholds for mortality based on mean temperature range from 16.5°C to 22.3°C.[38, 43] A recent study[41] including a wide range of climates showed that minimum mortality in temperate regions occurs around the 80th–90th percentile of mean temperature, which is between 16.9°C and 19.2°C for our study period. Heat thresholds for non-fatal health outcomes have been studied less extensively. Significant increases in respiratory hospital admissions have been reported at fairly mild maximum apparent temperatures in North-Continental cities such as London (24.6°C) and Stockholm (22.8°C).[44] Estimated mean temperature thresholds for hospital admissions for respiratory and renal diseases in Greater London were 23°C and 18°, respectively.[45]

Relative extremes of temperature are known to affect human blood flow with excess cardiovascular deaths during heat waves and cold spells.[43, 46] Exposure to high temperatures and dehydration reduce maternal blood flow, which may affect foetal nutrition or induce uterine contractions.[47] In addition, high ambient temperatures are associated with preeclampsia, which is a major cause of preterm birth.[5] Also the release of heat-shock proteins is linked to preterm delivery through induction of proinflammatory cytokines.[48] Furthermore, heat stress may lead to preterm delivery through an increased secretion of corticotrophin-releasing hormone and cortisol.[49] Potential biological mechanisms for an effect of low temperatures

on preterm birth are cold-related increases in preeclampsia, pregnancy-induced hypertension, blood viscosity and vascular constriction.[11, 16]

Our study has some limitations. We used ambient temperature measurements from only one monitoring station, which may have led to exposure misclassification due to spatial variability in temperature. However, the region of Flanders is quite uniform for temperature, due to extremely small altitudinal and latitudinal gradients: elevations range from 0 to 200 m above sea level, and the distance between the northernmost and southernmost part is only 100 km. Nonetheless, pregnant women may spend a lot of time indoors, where temperatures may be different because of the use of air-conditioning and/or heating. As discussed above, this may explain the absence of significant cold effects at very low temperatures. On warm days, however, outdoor temperature may be a better reflection of the true exposure because the proportion of houses equipped with air conditioning in Belgium is relatively low.[31]

The effect of temperature may differ between women with different baseline risks of premature birth. We were able to study potential effect modification by gestational age, gender, parity, maternal age, maternal education and urbanization, but we had no information on some other important risk factors for preterm birth, such as maternal comorbidity,[1] nutrition,[50] drinking[51] and smoking[52]. Maternal underweight increases the risk of spontaneous preterm birth, whereas maternal obesity is more closely linked to elective preterm delivery through obesity-related disorders such as preeclampsia and diabetes.[1, 50] Schifano *et al*[15] found that mothers with an obstetric pathology, eclampsia, or a chronic condition during pregnancy were less vulnerable to the effect of heat on preterm birth, which might be explained by a greater medical attention received during pregnancy by these groups of women. On the other hand, hospitalization for chronic diseases during the 2 years preceding the delivery (with cardiac disease accounting for 60% of the cases) was found to confer a greater susceptibility to

temperature.[15] By excluding induced deliveries and caesarean sections from our study population, we limited the potential influence of pregnancy complications on our study findings. Moreover, a major strength of the time-series design is the inherent control for non-time-varying individual risk factors. Furthermore, the temporal variation and the gestational age distribution of the pregnancies at risk for preterm birth were properly accounted for in our study.

CONCLUSIONS

Our results suggest that pregnant women should protect themselves from temperature extremes. In the light of future climate projections including increases in the frequency and intensity of extreme weather events, our study may have important implications for public health, because even a mild reduction in gestational age has been linked to adverse health outcomes in early and later life.

What is already known on this subject?

Recent evidence suggests that high ambient temperatures increase the risk of preterm birth. Most of these studies were performed in warmer climates, whereas results for temperate climates are inconclusive. Moreover, only few studies have investigated the effect of cold.

What this study adds?

In a temperate European climate (Flanders, Belgium), we observed an increase in the risk of preterm birth associated with high minimum and maximum ambient temperatures. Despite the increased risk of preterm birth associated with low temperatures a few days before delivery, cumulative cold effects were small. Our results suggest that, even in a temperate climate,

pregnant women should avoid exposure to high temperatures. In the context of climate change, these findings may have important public health implications.

COMPETING INTERESTS

The authors declare no competing interests.

FUNDING

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CONTRIBUTORSHIP STATEMENT

TSN and BC designed the study. BC did, with help from AVC and AG, the statistical analysis and wrote, together with TSN, the first draft of the paper. EM collected the data. All authors have contributed to the discussion and interpretation of the data, the writing of the article and approved the final version of the manuscript.

FIGURES

Figure 1 Relative risks (RR) of preterm birth by temperature and lag days for: A) minimum temperature (Tmin); and B) maximum temperature (Tmax). Estimates are relative to the median temperature (bold lines: 8.3°C for Tmin and 14.7° for Tmax) and are adjusted for the pregnancies at risk and their gestational age distribution, long-term and seasonal trends, humidity, PM_{10}, O_3, day of the week, holidays, and influenza epidemics.

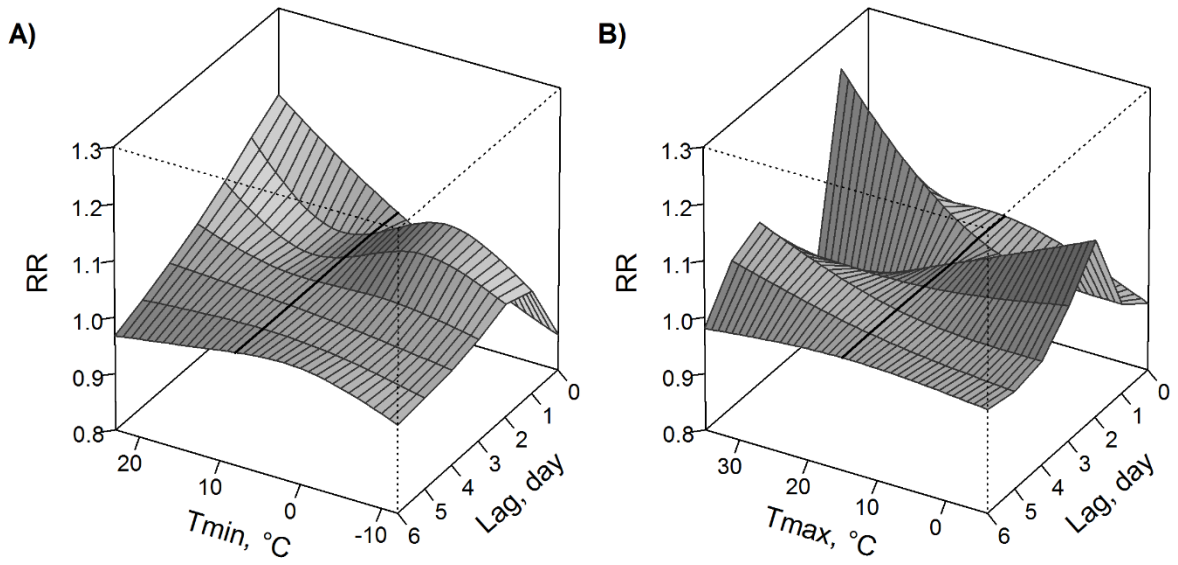


Figure 2 Lag-specific effects of minimum (Tmin) and maximum (Tmax) temperature on preterm birth estimated for: A) moderate heat; and B) moderate cold. Moderate heat and cold were defined as the 95th percentile (Tmin: 16.3°C; Tmax: 26.5°C) and the 5th percentile (Tmin: -2.0°C; Tmax: 2.5°C) temperatures, respectively. Estimates are relative to the median temperature (Tmin: 8.3°C; Tmax: 14.7°) and are adjusted for the pregnancies at risk and their gestational age distribution, long-term and seasonal trends, humidity, PM_{10}, O_3, day of the week, holidays, and influenza epidemics. Symbols represent relative risks (RR) and error bars are 95% CIs.

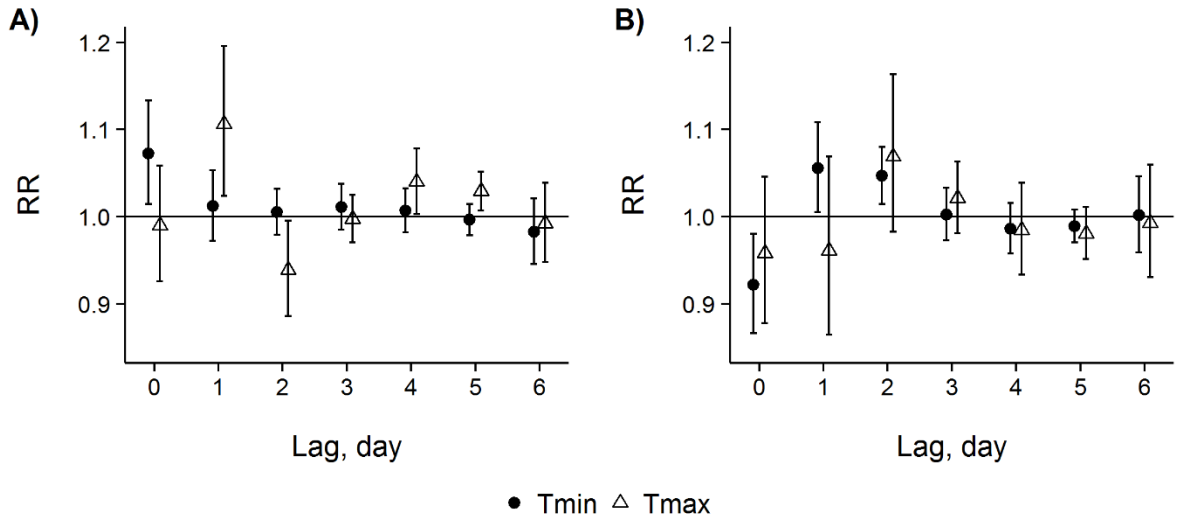


Figure 3 Cumulative effect of minimum (Tmin) and maximum (Tmax) temperature on preterm birth estimated over: A) lag 0–1 days; and B): lag 0–3 days. Estimates are relative to the median temperature (Tmin: 8.3°C; Tmax: 14.7°) and are adjusted for the pregnancies at risk and their gestational age distribution, long-term and seasonal trends, humidity, PM_{10}, O_3, day of the week, holidays, and influenza epidemics. Lines represent the relative risks (RR), and shaded regions are 95% CIs.

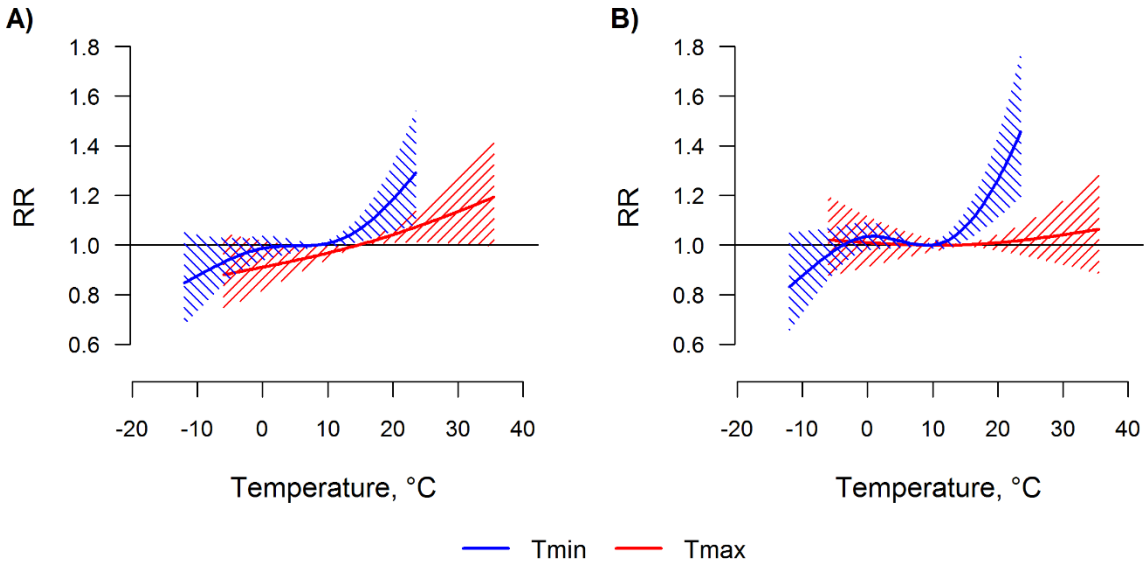


Figure 4 Cumulative moderate heat effect of minimum (Tmin) and maximum (Tmax) temperature on preterm birth over lag 0–1 days, overall and by subpopulations. Moderate heat was defined as the 95th percentile temperature (Tmin: 16.3°C; Tmax: 26.5°C). Estimates are relative to the median temperature (Tmin: 8.3°C; Tmax: 14.7°) and are adjusted for the pregnancies at risk and their gestational age distribution, long-term and seasonal trends, humidity, PM_{10}, O_3, day of the week, holidays, and influenza epidemics. *Term births (37–38 and >38 weeks) are not included in the main analyses (All).

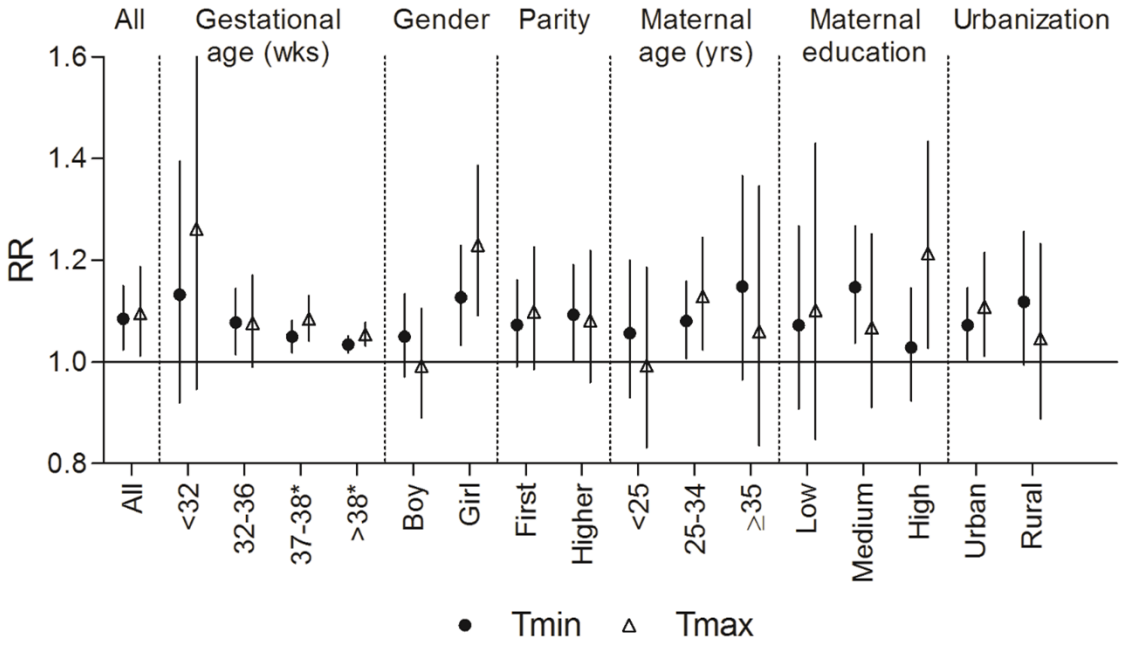
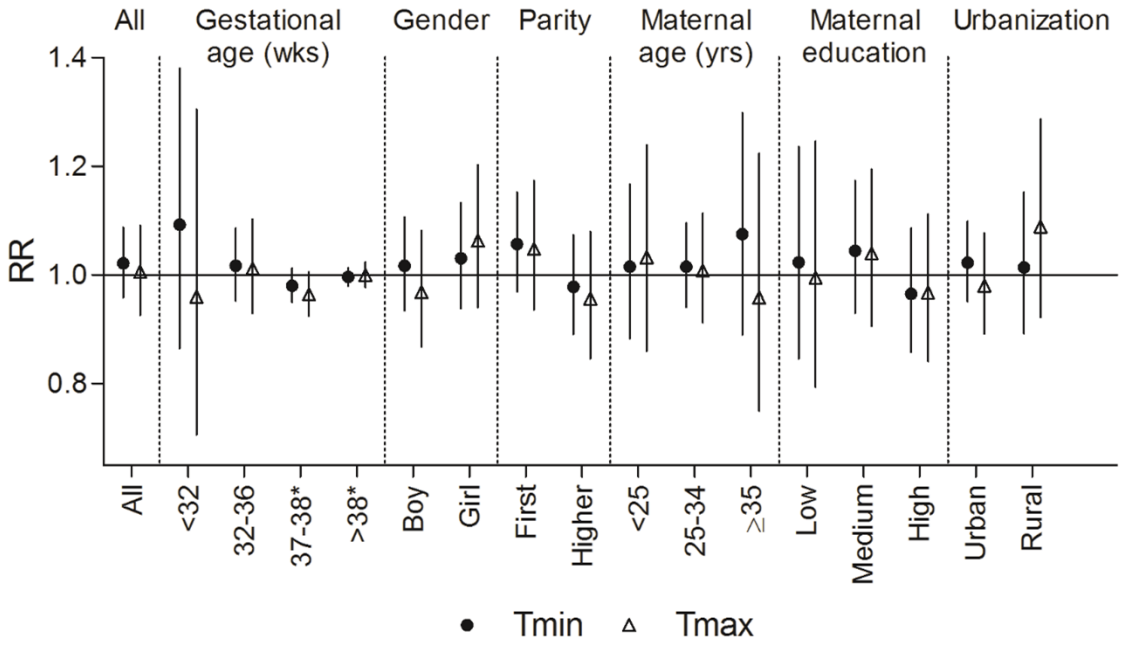


Figure 5 Cumulative moderate cold effect of minimum (Tmin) and maximum (Tmax) temperature on preterm birth over lag 0–3 days, overall and by subpopulations. Moderate cold was defined as the 5th percentile temperature (Tmin: -2.0°C; Tmax: 2.5°C). Estimates are relative to the median temperature (Tmin: 8.3°C; Tmax: 14.7°) and are adjusted for the pregnancies at risk and their gestational age distribution, long-term and seasonal trends, humidity, PM_{10}, O_3, day of the week, holidays, and influenza epidemics. *Term births (37–38 and >38 weeks) are not included in the main analyses (All).



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Supplementary material

Ambient temperature as trigger of preterm delivery in a temperate climate

Bianca Cox, Ana M Vicedo-Cabrera, Antonio Gasparrini, Harry A Roels, Evelyne Martens, Jaco Vangronsveld, Bertil Forsberg, Tim S Nawrot

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Table S1 Pearson correlation coefficients between meteorological variables and air pollutants, Flanders, Belgium, January 1998 – July 2011

Variable	**Tmin**	**Tmax**	**Humidity**	**PM_{10}**	**O_3**
Tmin	1.00				
Tmax	0.90	1.00			
Humidity	-0.27	-0.52	1.00		
PM_{10}	-0.20	-0.05	-0.10	1.00	
O_3	0.52	0.59	-0.58	-0.23	1.00

Tmin, minimum temperature; Tmax, maximum temperature; PM_{10}, particulate matter with diameter less than 10 μm; O_3, ozone.

Table S2 Sensitivity analysis estimates for the cumulative moderate heat and cold effects of minimum temperature on preterm birth in Flanders, Belgium, January 1998 – July 2011

Change in main model[b]	Relative risks (95% CI)[a]	
	Moderate heat (lag 0–1)	Moderate cold (lag 0–3)
/	1.085 (1.024 to 1.150)	1.021 (0.959 to 1.087)
Maximum lag (*l*), days [Df for lag-response function]		
8 [4]	1.090 (1.029 to 1.154)	1.029 (0.966 to 1.097)
8 [5]	1.092 (1.027 to 1.162)	1.028 (0.962 to 1.099)
10 [4]	1.090 (1.028 to 1.154)	1.027 (0.964 to 1.094)
10 [5]	1.089 (1.026 to 1.155)	1.020 (0.958 to 1.087)
Df for lag-response function		
3	1.085 (1.024 to 1.150)	1.014 (0.953 to 1.079)
5	1.108 (1.039 to 1.182)	1.024 (0.958 to 1.094)
6	1.117 (1.046 to 1.192)	1.046 (0.971 to 1.127)
Df for temperature-response function		
2	1.072 (1.013 to 1.134)	0.992 (0.934 to 1.053)
4	1.075 (1.013 to 1.141)	1.031 (0.960 to 1.106)
5	1.094 (1.024 to 1.169)	1.029 (0.958 to 1.105)
6	1.089 (1.020 to 1.163)	1.032 (0.962 to 1.108)
Df/year for long-term and seasonal trends (*time*)		
4	1.076 (1.017 to 1.138)	1.020 (0.959 to 1.084)
5	1.079 (1.019 to 1.143)	1.020 (0.959 to 1.086)
7	1.088 (1.026 to 1.153)	1.017 (0.954 to 1.083)
8	1.086 (1.025 to 1.151)	1.011 (0.948 to 1.078)
9	1.090 (1.028 to 1.156)	1.010 (0.947 to 1.078)
10	1.089 (1.026 to 1.155)	1.003 (0.940 to 1.071)
Df for correction gestational age distribution pregnancies at risk ($Log(W_t)$)		
1	1.087 (1.026 to 1.151)	1.022 (0.960 to 1.088)
2	1.086 (1.025 to 1.150)	1.021 (0.959 to 1.087)
3	1.085 (1.024 to 1.150)	1.022 (0.960 to 1.088)
5	1.086 (1.026 to 1.151)	1.021 (0.959 to 1.087)
6	1.087 (1.026 to 1.151)	1.022 (0.960 to 1.088)
Variable removed		
O_3	1.065 (1.011 to 1.122)	1.018 (0.958 to 1.081)
PM_{10}	1.085 (1.027 to 1.146)	1.017 (0.956 to 1.083)
Z_t	1.072 (1.015 to 1.133)	1.022 (0.960 to 1.088)
$Log(W_t)$	1.075 (1.015 to 1.139)	1.025 (0.962 to 1.091)

Moderate heat and cold were defined as the 95th (16.3°C) and 5th (-2.0°C) percentile temperatures over the study period, respectively.

[a]Estimates are relative to the median temperature (8.3°C).

[b]The main DLNM model for minimum temperature has a maximum lag (*l*) of 6 days, 4 df for the lag-response function, 3 df for the temperature-response function, and is adjusted for the pregnancies at risk (Z_t) and their gestational age distribution ($Log(W_t)$, 4 df), long-term and seasonal trends (*time*, 6 df per year), humidity (3 df), particulate matter (PM_{10}, 3 df), ozone (O_3, 3 df), day of the week, holidays, and influenza epidemics.

Table S3 Sensitivity analysis estimates for the cumulative moderate heat and cold effects of maximum temperature on preterm birth in Flanders, Belgium, January 1998 – July 2011

Change in main model[b]	Relative risk (95% CI)[a]	
	Moderate heat (lag 0–1)	**Moderate cold (lag 0–3)**
/	1.096 (1.011 to 1.187)	1.006 (0.927 to 1.092)
Maximum lag (*l*), days [Df for lag-response function]		
8 [4]	1.071 (0.993 to 1.156)	1.017 (0.937 to 1.105)
8 [5]	1.095 (1.010 to 1.188)	1.016 (0.936 to 1.102)
10 [4]	1.048 (0.974 to 1.126)	1.005 (0.931 to 1.086)
10 [5]	1.087 (1.002 to 1.180)	1.008 (0.913 to 1.112)
Df for lag-response function		
3	1.037 (0.967 to 1.113)	0.987 (0.915 to 1.065)
5	1.037 (0.967 to 1.112)	0.989 (0.916 to 1.068)
6	1.093 (1.008 to 1.186)	1.022 (0.931 to 1.122)
Df for temperature-response function		
2	1.094 (1.010 to 1.186)	1.007 (0.928 to 1.092)
4	1.100 (1.009 to 1.200)	1.024 (0.938 to 1.117)
5	1.098 (1.006 to 1.198)	1.021 (0.934 to 1.117)
6	1.100 (1.007 to 1.201)	1.026 (0.936 to 1.124)
Df/year for long-term and seasonal trends (*time*)		
4	1.093 (1.011 to 1.181)	1.013 (0.936 to 1.097)
5	1.093 (1.009 to 1.183)	1.009 (0.930 to 1.095)
7	1.094 (1.009 to 1.186)	0.998 (0.919 to 1.084)
8	1.094 (1.009 to 1.186)	0.989 (0.910 to 1.076)
9	1.100 (1.014 to 1.193)	0.991 (0.911 to 1.079)
10	1.099 (1.013 to 1.193)	0.982 (0.903 to 1.069)
Df for correction gestational age distribution pregnancies at risk ($Log(W_t)$)		
1	1.097 (1.013 to 1.188)	1.006 (0.927 to 1.092)
2	1.096 (1.011 to 1.187)	1.006 (0.927 to 1.092)
3	1.095 (1.011 to 1.187)	1.006 (0.927 to 1.092)
5	1.097 (1.012 to 1.188)	1.006 (0.927 to 1.092)
6	1.097 (1.013 to 1.189)	1.007 (0.928 to 1.093)
Variable removed		
O_3	1.079 (1.003 to 1.161)	0.996 (0.920 to 1.079)
PM_{10}	1.100 (1.021 to 1.186)	1.003 (0.924 to 1.089)
Z_t	1.096 (1.011 to 1.187)	1.006 (0.926 to 1.092)
$Log(W_t)$	1.078 (0.995 to 1.168)	1.013 (0.933 to 1.100)

Moderate heat and cold were defined as the 95th (26.5°C) and 5th (2.5°C) percentile temperatures over the study period, respectively.

[a]Estimates are relative to the median temperature (14.7°C).

[b]The main DLNM model for maximum temperature has a maximum lag (*l*) of 6 days, 5 df for the lag-response function, 2 df for the temperature-response function, and is adjusted for the pregnancies at risk (Z_t) and their gestational age distribution ($Log(W_t)$, 4 df), long-term and seasonal trends (*time*, 6 df per year), humidity (3 df), particulate matter (PM_{10}, 3 df), ozone (O_3, 3 df), day of the week, holidays, and influenza epidemics.