Ambient temperature as a 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. Since 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 centile) 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°C 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 centile) 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 per cent change in preterm birth associated with moderate cold (5th vs 50th centile) 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] Since 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 towards 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 USA it has increased from 10.6% to 12.0% during the past two decades.[4] The underlying causes of preterm birth are poorly understood, although genetic, demographic, socio-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 both in summer and in winter,[13] only a limited number of studies have investigated the 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 also 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 6 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 <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 (extreme to very preterm) and 32–36 weeks (moderate to late preterm) (WHO, 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. Since air pollution may confound the association between temperature and preterm

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birth,[20 21] data on daily concentrations of particulate matter with a diameter <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 4×4 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 the 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 the lag-response association. We used the following model for minimum and maximum temperature:

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

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

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; $\mathbf{T}_{t,l}$ is a matrix representing the two-dimensional DLNM cross-basis for temperature and lag days, $\boldsymbol{\beta}$ is vector of coefficients for $\mathbf{T}_{t,l}$, 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 (RH), PM_{10}, and O_3, respectively, using the average exposure of the current day and the previous day 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:

$$W_t = \frac{\sum_{j=22}^{36} (\mathbf{Z}_{tj} \times W_j)}{Z_t}$$

where $\mathbf{Z}_{tj}$ 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. Since 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 data set. 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 the reference. Relative risks (RR) of preterm birth were calculated for moderate heat (95th centile), extreme heat (99th centile), moderate cold (5th centile) and extreme cold (1st centile). Cumulative effects over lag 0–1, lag 0–3 and lag 0–6 days were computed by summing the log RR 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 urbanisation of mother's residence (urban/semiurban vs rural).[30] Since 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 (2–6 df), for the lag structure (3–6 df), for the seasonal and long-term trend component (4–10 df/year), and for Log(W_t) (1–6 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 <0.4%. The majority of preterm births (92.6%) had a gestational age from 32 to 36 weeks (moderate to late preterm).

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

The Pearson correlation (r) between minimum and maximum temperature was 0.90 (see online 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.

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

	Centiles						
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

O_3, ozone; PM_{10}, particulate matter with a diameter <10 μm.

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 RR increased with increasing temperature. An effect of cold was

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

	All births*		Non-induced vaginal births†			
	All		All		Preterm	
Characteristic	Number	Per cent	Number	Per cent	Number	Per cent
Total	807 835	100	467 502	100	27 076	100
Season						
Spring (March–May)	211 101	26.1	122 494	26.2	7086	26.2
Summer (June–August)	210 512	26.1	122 043	26.1	7010	25.9
Autumn (September–November)	190 029	23.5	109 550	23.4	6159	22.8
Winter (December–February)	196 193	24.3	113 415	24.3	6821	25.2
Gestational age (weeks)						
<32	5099	0.6	2005	0.4	2005	7.4
32–36	43 166	5.3	25 071	5.4	25 071	92.6
37–38	201 222	24.9	106 091	22.7	–	–
>38	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 (years)						
<25	134 225	16.6	79 559	17.0	5687	21.0
25–34	574 430	71.1	335 520	71.8	18 310	67.6
≥35	99 180	12.3	52 423	11.2	3079	11.4
Maternal education‡						
Low	82 350	12.7	46 611	12.5	3339	15.2
Medium	251 334	38.8	137 427	36.8	9145	41.7
High	274 075	42.3	164 519	44.1	7978	36.4
Missing data	40 841	6.3	24 519	6.6	1457	6.7
Urbanisation						
Urban	609 440	75.4	352 857	75.5	20 486	75.7
Rural	198 395	24.6	114 645	24.5	6590	24.3

*Used to calculate the daily number of pregnancies at risk (Z_t).
†Used to calculate the daily number of preterm births (Y_t).
‡From 1999 to 2009.

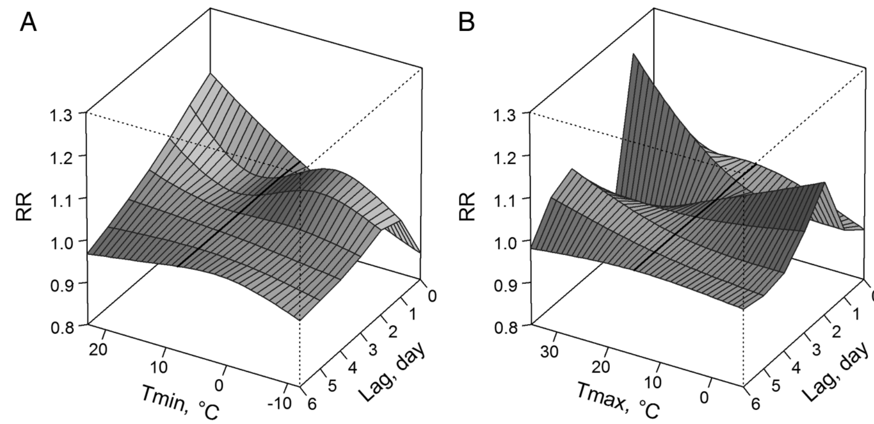

Figure 1 Relative risks (RR) of preterm birth by temperature and lag days for: (A) minimum temperature (Tmin); and (B) maximum temperature (Tmax). Estimates are relative to the median temperature (bold lines: 8.3°C for Tmin and 14.7°C for Tmax) and are adjusted for the pregnancies at risk and their gestational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

observed at lags 1 and 2: RR were >1 for minimum temperatures roughly between the 50th centile (8.3°C) and the 5th centile (−2.0°C), but not for lower temperatures. Maximum temperature effects were delayed by 1 day compared with minimum temperature effects, that is, 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, RR were highest at the most extreme temperatures.

Figure 2 presents the lag-specific RR of preterm birth for moderate heat (95th vs 50th centile, figure 2A) and for moderate cold (5th vs 50th centile, 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 RR 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 (Figure 3A) and over lag 0–3 days (Figure 3B). 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. Owing to the seemingly protective effect of cold at lag 0, cumulative RR were <1 (or close to 1) at low minimum and maximum temperatures.

Table 3 presents the cumulative RR of preterm birth associated with moderate heat (95th centile), extreme heat (99th centile), moderate cold (5th centile) and extreme cold (1st centile), 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°C 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 RR for moderate and extreme cold were close to one. For minimum temperature up to 3 days before delivery (lag 0–3), the per cent 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%).

Effect modification

We explored potential effect modification by gestational age, gender, parity, maternal age, maternal education and degree of urbanisation of maternal residence. Figure 4 presents the cumulative moderate heat effect over lag 0–1 days estimated for

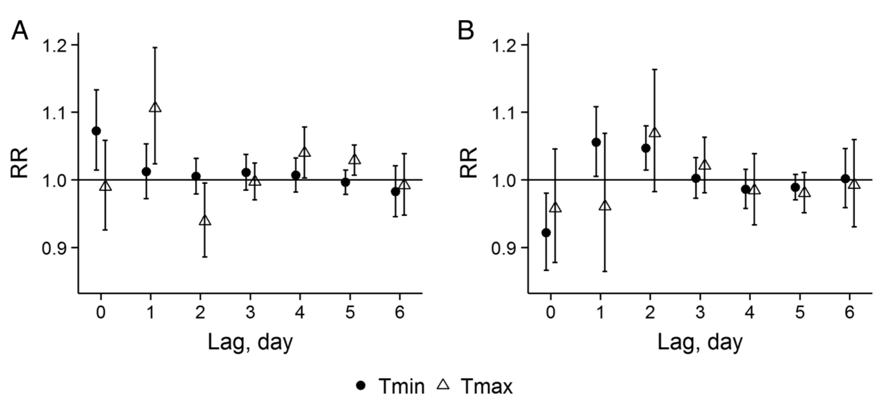

Figure 2 Lag-specific effects of minimum temperature (Tmin) and maximum temperature (Tmax) on preterm birth estimated for: (A) moderate heat; and (B) moderate cold. Moderate heat and cold were defined as the 95th centile (Tmin: 16.3°C; Tmax: 26.5°C) and the 5th centile (Tmin: −2.0°C; Tmax: 2.5°C) temperatures,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

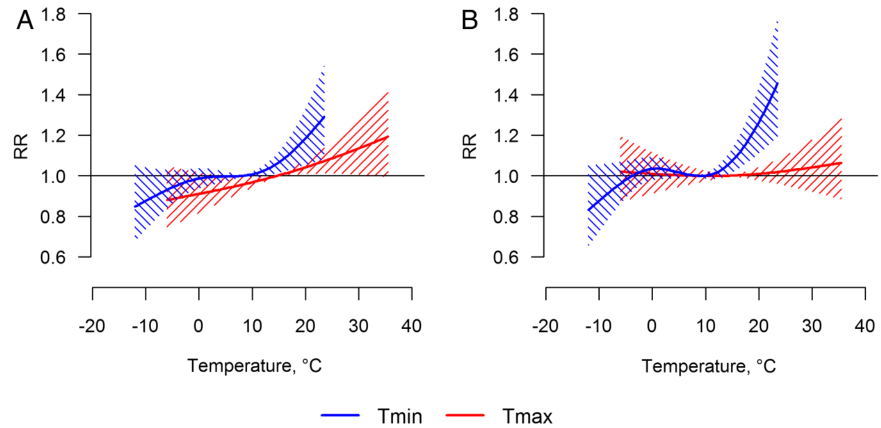

Figure 3 Cumulative effect of minimum temperature (Tmin) and maximum temperature (Tmax) on preterm birth estimated over: (A) lag 0–1 days; and (B): lag 0–3 days. Estimates are relative to the median temperature (Tmin: 8.3°C; Tmax: 14.7°C) and are adjusted for the pregnancies at risk and their gestational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

different subpopulations. In addition to the heat-related increases in preterm delivery among extreme 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 latter two groups not being part of the main analysis). Although CIs were overlapping, there was a trend of decreasing heat effects for increasing gestational age: for minimum temperature, for example, RR 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 extreme 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 CIs 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 $\mathrm{Log}(W_t)$, as well as to the correction for the pregnancies at risk and their gestational age distribution: RR estimates ranged from 1.072 to 1.117 and from 0.992 to 1.046 for the moderate heat and cold effects, respectively (see online supplementary table S2). The exclusion of O_3 from the model for minimum temperature resulted in a slight decrease in the heat effect estimate (RR=1.065, 95% CI 1.011 to 1.122). For maximum temperature (see online 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 RR ranging from 1.071 to 1.100 for the heat effect and from 0.982 to 1.026 for the cold effect.

DISCUSSION

On the basis of 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 1–2 days before delivery. Heat and cold effects of maximum temperature appeared to be delayed by 1 day compared with 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

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

	Relative risk (95% CI)*							
Lag, day	Tmin		Tmax		Tmin		Tmax	
	Moderate heat				Extreme heat			
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			
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) centile temperatures over the study period, respectively.
*Estimates are relative to the median temperature (Tmin: 8.3°C; Tmax: 14.7°C) 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.
O_3, ozone; PM_{10}, particulate matter with a diameter <10 μm; Tmax, maximum temperature; Tmin, minimum temperature.

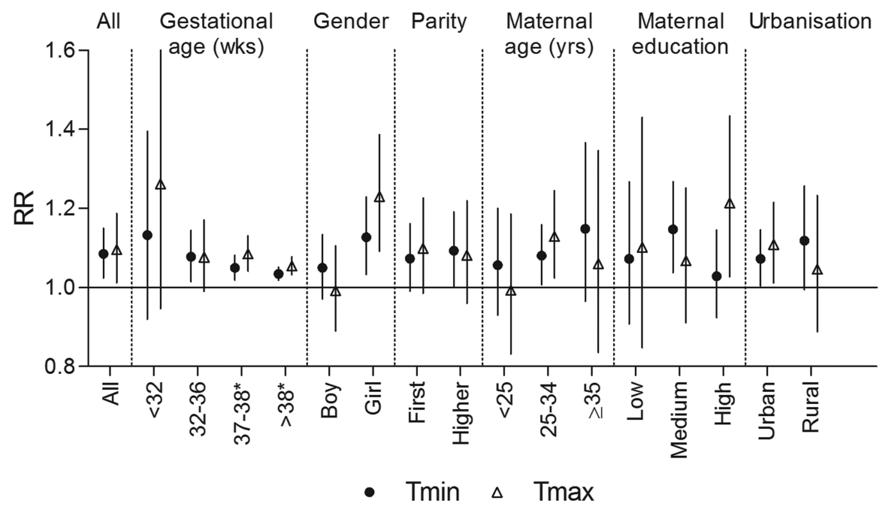

Figure 4 Cumulative moderate heat effect of Tmin and Tmax on preterm birth over lag 0–1 days, overall and by subpopulations. Moderate heat was defined as the 95th centile temperature (Tmin: 16.3°C; Tmax: 26.5°C). Estimates are relative to the median temperature (Tmin: 8.3°C; Tmax: 14.7°C) and are adjusted 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). O_3, ozone; PM_{10}, particulate matter with a diameter <10 μm; RR, relative risks; Tmax, maximum temperature; Tmin, minimum temperature; wks, weeks; yrs, years.

temperatures can occur as late as 17:00, whereas in winter they tend to be closer to around 13:00 (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 a few days after the exposure, the cumulative cold effects were small and non-significant because of the seemingly protective effect of cold (RR<1) on the day of delivery observed for both temperature indicators. Moreover, minimum temperature showed an N-shaped association with preterm birth, as increased RR were only observed for relatively mild low temperatures (between the 50th and the 5th centile), 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] On the basis of warm season data, Basu *et al*[33] found an 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 centile 2 days before delivery, and by 5% when minimum temperature rose to the 90th centile during the 4th–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

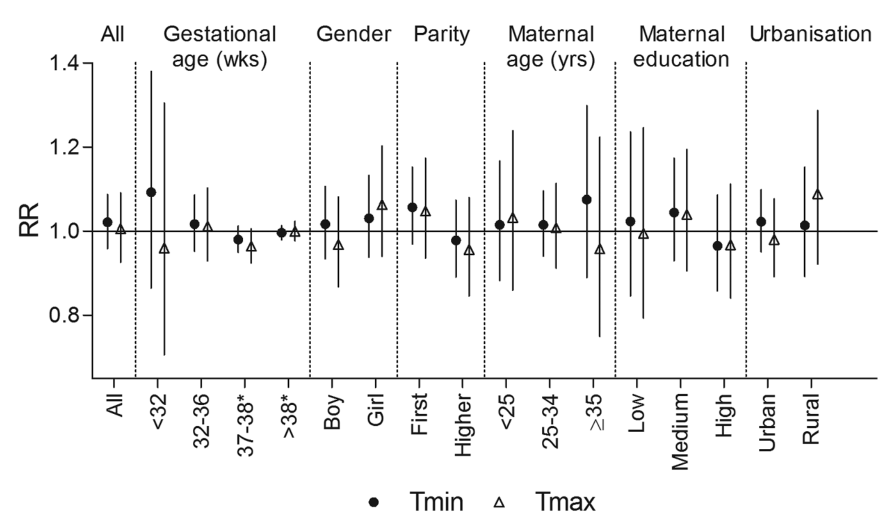

Figure 5 Cumulative moderate cold effect of Tmin and Tmax on preterm birth over lag 0–3 days, overall and by subpopulations. Moderate cold was defined as the 5th centile temperature (Tmin: −2.0°C; Tmax: 2.5°C). Estimates are relative to the median temperature (Tmin: 8.3°C; Tmax: 14.7°C) and are adjusted 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). O_3, ozone; PM_{10}, particulate matter with a diameter <10 μm; RR, relative risks; Tmax, maximum temperature; Tmin, minimum temperature; wks, weeks; yrs, years.

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) centile 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 with 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 fetuses 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 the 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°C for minimum temperature and 26.5°C for maximum temperature), but such temperatures are rather exceptional in Belgium (representing only 5% of days). Multicountry 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 observed during heat waves, as well as 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 80–90th centile 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°C, 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 fetal nutrition or induce uterine contractions.[47] In addition, high ambient temperatures are associated with pre-eclampsia, 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 pre-eclampsia, 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 parts 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 urbanisation, 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 pre-eclampsia 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 greater medical attention received during pregnancy by these groups of women. On the other hand, hospitalisation 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 a 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.

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

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