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Associations between ambient temperature and risk of preterm birth in Sweden: A comparison of analytical approaches

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ABSTRACT

Background: Evidence indicates that high temperatures are a risk factor for preterm birth. Increasing heat exposures due to climate change are therefore a concern for pregnant women. However, the large heterogeneity of study designs and statistical methods across previous studies complicate interpretation and comparisons. We investigated associations of short-term exposure to high ambient temperature with preterm birth in Sweden, applying three complementary analytical approaches.

Methods: We included 560,615 singleton live births between 2014 and 2019, identified in the Swedish Pregnancy Register. We estimated weekly mean temperatures at 1-km^2 spatial resolution using a spatiotemporal machine learning methodology, and assigned them at the residential addresses of the study participants. The main outcomes of the study were gestational age in weeks and subcategories of preterm birth (<37 weeks): extremely preterm birth (<28 weeks), very preterm birth (from week 28 to <32), and moderately preterm birth (from week 32 to<37). Case-crossover, quantile regression and time-to-event analyses were applied to estimate the effects of short-term exposure to increased ambient temperature during the week before birth on preterm births. Furthermore, distributed lag nonlinear models (DLNM) were applied to identify susceptibility windows of exposures throughout pregnancy in relation to preterm birth.

Results: A total of 1924 births were extremely preterm (0.4%), 2636 very preterm (0.5%), and 23,664 moderately preterm (4.2%). Consistent across all three analytical approaches (case-crossover, quantile regression and time-to-event analyses), higher ambient temperature (95th vs 50th percentile) demonstrated increased risk of extremely preterm birth, but associations did not reach statistical significance. In DLNM models, we observed no evidence to suggest an increased effect of high temperature on preterm birth risk. Even so, a suggested trend was observed in both the quantile regression and time-to-event analyses of a higher risk of extremely preterm birth with higher temperature during the last week before birth.

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Conclusions: In Sweden, with high quality data on exposure and outcome, a temperate climate and good quality ante-natal health care, we did not find an association between high ambient temperatures and preterm births. Results were consistent across three complementary analytical approaches.

1. Introduction

Climate change is a serious threat to humanity (Rocque et al., 2021; Woodward et al., 2014). Increased temperatures and extreme weather events around the globe, have a significant and long-term impacts on human health (Rocque et al., 2021; Woodward et al., 2014). The frequency and severity of health impacts from high temperatures are expected to increase in high-risk populations such as pregnant women, the developing foetus, and the neonate (Watts et al., 2019). Emerging epidemiological evidence indicates that increased temperatures may be associated with multiple birth outcomes such as increased risk of low birthweight, stillbirth and preterm birth (Chersich et al., 2020). Preterm births (before 37th gestation week) account for around 5% of all births in high-income countries and have major short-and long-term health consequences for the child. Preterm birth is the leading cause of neonatal death, comprising 35% of neonatal mortality globally, which corresponds to about 900,000 deaths every year (Liu et al., 2015; Vogel et al., 2018). The health consequences of preterm birth are especially important among extremely preterm (born before 28 weeks of gestation) and very preterm infants (before 32 weeks) (Barfield, 2018). The aetiology of preterm birth is multifactorial and heterogenous, involving sociodemographic, nutritional, medical, obstetric, and environmental factors including air pollution (Vogel et al., 2018). Better understanding of possible causes of preterm birth will advance the development of solutions to prevent preterm birth, especially within the context of increasing risks of heat as a result of climate change.

Systematic reviews indicate that high ambient temperatures could be a risk factor for preterm birth (Chersich et al., 2020; Zhang et al., 2017), however, the large heterogeneity of study designs and statistical methods across studies makes interpretation and comparisons difficult. Most studies relied on time-series designs (Liang et al., 2016; Schifano et al., 2013a; Vicedo-Cabrera et al., 2014), case-crossover designs (Auger et al., 2015; Basu et al., 2010) and time-to-event analyses (Kloog et al., 2015; Spolter et al., 2020; Wang et al., 2020). New approaches such as quantile regression have been employed in analogous studies of air pollution and preterm birth (Qiu et al., 2020). These various study designs offer slightly different approaches to the relevant research questions and bring different strengths and limitations. Nevertheless, to our knowledge, we lack a head-to-head comparison of analytical approaches that might help future studies to select the most appropriate methodology regarding the effects of ambient air temperature on gestational age.

Previous studies shared several methodological limitations. With a few recent exceptions (Kloog et al., 2015; Spolter et al., 2020), the exposure assessment of ambient air temperature was based on the nearest meteorological station. This approach might adequately capture temporal variation in exposure but not spatial variation, inducing potential exposure error and therefore bias in effect estimates (Kloog, 2019). Using accurate spatiotemporal exposure assessment is an important step forward in reducing exposure error (Kloog, 2019). A second limitation of previous studies is the focus on urban areas only. In fact, previous studies have been restricted to specific cities and/or regions with smaller sample sizes, sharing similar climate zones within the same country and reducing external validity. Nation-wide prospectively collected birth registries such as the Swedish Pregnancy Register (SPR), by contrast, can provide high statistical power, accurate measurement of outcomes (e.g. gestational age), and information on individual adjustment factors (Stephansson et al., 2018). Combining a national birth registry such as this with a national spatiotemporal exposure model may help overcome previous limitations. Finally, previous investigations were only partially able to assess the stage of pregnancy at which ambient air temperature might have the largest impact on preterm birth. Studies have focused on heat exposure in the last week or month preceding birth, or during specific pregnancy trimesters (Zhang et al., 2017), and the current evidence indicates that the final week of pregnancy is the most important for preterm birth (Chersich et al., 2020). The mechanisms underlying the effects extreme heat and preterm births are still poorly understood (Samuels et al., 2022). Recent studies indicate that in a sudden extreme heat event, a series of biological mechanisms may occur including reduction in placental blood flow, dehydration, and an inflammatory response may trigger preterm birth. However, more sophisticated studies are needed to identify potential windows of vulnerability during the entire pregnancy. Overall, nation-wide studies combined with spatiotemporal models are needed to provide robust estimates and identify windows of vulnerability.

The overall aim of this study is to evaluate the effect of short-term (week before pregnancy) exposure to ambient temperature on preterm birth in Sweden, and to identify windows of susceptibility, applying three complementary statistical approaches using a national high-quality birth registry and a national spatiotemporal ambient temperature model.

2. Methods

2.1. Data source and study population

We obtained data from the SPR. This population-based cohort covers more than 92% of births in Sweden and provides high quality data for research in pregnancy and early childhood as well as quality of care improvement (Stephansson et al., 2018). For this study, we included all pregnant women with live singleton births identified in the SPR between January 1, 2014 and December 31, 2019. Each individual in Sweden has a unique identifier assigned at birth or immigration, and is used to link the pregnant woman in the SPR with the National Patient Register (for maternal and neonatal health outcomes) (Ludvigsson et al., 2011), and Statistics Sweden for socioeconomic and residential address information. Lack of a maternal unique identifier and non-residence in Sweden within 1 year before conception were reasons for exclusion from this analysis. The study was approved by the Regional Ethical Review Board in Stockholm, Sweden (2020/00390).

2.2. Outcome assessment: gestational age and preterm births

The main outcomes of the study are “continuous” gestational age (completed weeks) at birth and “binary” subcategories of preterm birth. Gestational age was captured from the Swedish SPR using a hierarchical definition for gestational age dating using date for embryo transfer, ultrasonography and/or date of last menstrual period. Early second-trimester ultrasonography for determining gestational age is performed in about 95% of all pregnant women in Sweden. Gestational age values $\leq$ 22 gestational weeks and $>$44 gestational weeks were excluded. Preterm birth was defined as birth before 37 completed weeks (WHO, 2018). Preterm births were categorized into extremely preterm birth ($<$28 weeks), very preterm birth (from 28 to 32 weeks), and moderately preterm birth (from 32 to 37 weeks) (WHO, 2020).

2.3. Exposure assessment: temperature

Daily mean air temperature with a spatial resolution 1-km^2 was derived using satellite land surface temperature (LST), observed temperature data and spatiotemporal land use and land cover predictors. Briefly, a three-stage approach based on machine learning models was developed. In the first stage, missing data in LST retrievals were imputed using collocated estimates of air temperature from atmospheric models; in the second stage, calibration between monitored air temperature and imputed LST data for each year in was performed; in the third stage, this model was used to predict temperature in all grid cells without monitors. Ultimately, we obtained estimates of daily mean air temperature for each 1-km^2 of Sweden (years 2014–2019). In the second stage, we have used spatial parameters (land use, climatic zones, population density, elevation, NDVI) as well as spatiotemporal parameters (imputed LST, meteorological variables) to do the calibration. The procedure was cross-validated on the monitors: we used one tenth of the monitors as training set, and the remaining 90% as testing, and we reiterated the procedure for each 10% of the monitors, in order to obtain daily predictions in all left-out monitors. Finally, we compared observations and cross-validated predictions and estimated R^2 (proportion of variability captured by the predictions), RMSE (root mean squared error), intercept and slope (from a univariate linear regression between observations and predictions, as measures of bias). Model performance was excellent: on average across the year, we estimated a CV-R^2 = 0.94, with RMSE = 1.6 °C, intercept = −0.04 and slope = 1.008, showing almost perfect agreement between observed temperature and estimated temperature at left-out monitors. Hence, we assigned daily air temperature exposure to each woman in the registry based on residential address and childbirth date. Our initial hypothesis was that the pregnant women would be at higher risk to large changes of ambient temperature relative to their own geographical area, as humans tend to be more adaptive to their local climate (Basagaña et al., 2021; Hondula et al., 2015). In addition, in Sweden the temperatures vary substantially between North and South regions (Fig. 2). For this, we estimated the percentiles of daily temperatures among women living in the same municipality across Sweden (N° of municipalities = 290) and used them as individual exposures rather than absolute temperature values. Then, we used the daily percentile data to estimate average weekly percentiles from date of birth until 39 weeks (approximately close to conception).

2.4. Covariates

We retrieved clinical variables from the SPR, National Patient Register and Statistics Sweden. These variables included infant sex (male, female), type of birth (caesarean section, induced or spontaneous birth), period of birth (December–February, March–May, June–August, September–November), geographic location across Sweden (North, Central, South), maternal age in years (≤24, 25–29, 30–34, ≥35), maternal educational level (1–9 years, 10–12 years, 13 or more years), body mass index (BMI) categories of the mother at first antenatal care visit [(underweight (<18.5 kg/m^2), normal (18.5–24.9 kg/m^2), overweight (25.0–29.9 kg/m^2), obese (≥30.0 kg/m^2)], maternal smoking during pregnancy (yes, no), and hypertension and diabetes mellitus status (yes, no).

2.5. Statistical analyses

We estimated the association between ambient air temperature and preterm birth using three complementary analytical approaches: case-crossover design, quantile regression, and time-to-event analysis (Supplement Table S1 and Fig. S1). In all three approaches, we considered ambient temperature during the week before birth (lag 0–6 days) as our referent exposure. We modelled the shape of the relationship between ambient temperatures and preterm birth with natural splines with two inner knots. From the curves, risks were extrapolated comparing temperatures above the 90th, 95th or 99th percentiles versus the 50th percentile of municipality-specific exposure distribution. For quantile regression and time-to-event analysis only, we selected the covariates using directed acyclic graph (DAG; Supplement Fig. S2). This included month and year of conception, region, BMI, maternal education, and maternal age. In the quantile regression and time-to-event analysis, we also applied a distributed lag nonlinear model (DLNM) to identify potential windows of vulnerability during the entire pregnancy (Gasparrini, 2011). We evaluated different weekly exposures preceding birth for each preterm outcome: 28 weeks for extremely preterm births, 32 weeks for very preterm births, and 37 weeks for moderately and all preterm births. The effect estimates were expressed comparing the 95th vs the 50th percentile of lag-specific and municipality-specific exposure distributions. We further evaluated whether the association between short-term exposure of ambient air temperature (lag 0–6 days) and preterm birth varied by some key effect modifiers including sex, period of birth, geographic location, maternal age, maternal education, BMI categories, and smoking during pregnancy. Here, we stratified the analyses by these effect modifiers. All analyses were conducted in R software (version 3.5.1; by R Development Core Team). Details of the individual models are described below and in the supplement Table S1, and an overview of the analyses plan in supplement Fig. S1.

2.5.1. Case-crossover design

Case-crossover design has been extensively applied in the literature to investigate associations between short-term exposures to environmental determinants and health outcomes, including temperature and preterm birth (Auger et al., 2015; Basu et al., 2010). The key strength of the design is that each case serves as its own control, which implies perfect adjustment for observed or unobserved individual-level confounders that do not vary, or vary slowly, over time, such as age, smoking habits and socio-economic deprivation (Maclure and Mittleman, 2000). In our approach, control days were selected following the time-stratified strategy, according to which, controls are defined, for each case, as the same days of the week within the same month of childbirth. This strategy allows strict control for day of the week and other short-term time trends, as cases and controls are very close in time. At the same time, since cases and controls are separated by seven days, serial autocorrelation in exposures and outcomes is also substantially reduced (Maclure and Mittleman, 2000). The main limitation of the case-crossover, and the time-stratified approach for control selection, is that only short lags are allowed in the analyses, preventing applying DLNM models to investigate longer-term windows of susceptibility to ambient temperature. Longer lags should be used cautiously as cases and control windows could overlap leading to a form of overmatching. This would lead to drop of power and increase selection bias as the control exposure will not be conditionally independent of the matched case exposure. We used conditional logistic regressions to estimate odds ratios (ORs) and 95% confidence intervals (CI) of preterm birth comparing the 95th vs the 50th percentile of individual-level exposures up to six days before birth.

2.5.2. Quantile regression

The main feature of quantile regression is that it allows modelling the full gestational age as a continuous outcome, rather than using categorized measures of preterm birth based on predefined cut-off points of gestational age (Bind et al., 2016; Qiu et al., 2020). With this model, we estimated the effect of ambient temperature on specific quantiles of the gestational age distribution. We selected the quantiles of the gestational age based on the preterm birth categories (at 28, 32 and 37 weeks of gestation). The main strength of this model is that it can evaluate associations at the tails of the gestational age distribution (a relevant feature in our study), still including the total population in the analysis, thus increasing the sample size and the statistical power. Also, it does not require normality of the outcome variable (Bind et al., 2016; Qiu et al., 2020). Finally, it allows for investigation of temporal windows of susceptibility during pregnancy because inclusion of longer-lags of exposure are not precluded in the statistical model.

2.5.3. Time-to-event

In the time-to-event approach, we modelled the hazard of preterm births in relation to ambient temperature exposure and considered gestational age as the time axis. The analysis was repeated for each preterm category and the time of follow-up was estimated as follows: for extremely preterm birth, from gestational week 22 until week 28; for very preterm birth, from week 28 until week 32; moderately preterm births from week 32 until 37; and all preterm births from week 22 until week 37. We left-censored all the observations at the lower bound of each time interval, and right-censored the non-cases at the end of each time-period. In each analysis, we only included the population at risk and the relevant lags of exposure. For instance, for the very preterm births, we only included the populations with births above 28 weeks (excluding the extremely preterm births), and for the DLNM we included 32 weekly lags. Then, we applied Cox proportional hazard regressions to estimate the associations between temperature and each preterm birth category. The main strengths of this design are: 1) the high statistical power, as all foetuses at risk are included in the analyses, not only the cases; 2) the strict control of temporal trends of the study outcomes during pregnancy, since the use of gestational age as time axis accounts for the increasing likelihood of giving birth with increasing gestational age (Zhang et al., 2017). Applying this model, it avoids potential confounding by gestational age as the comparison takes place among foetuses with the same gestational age.; and 3) the possibility to investigate temporal windows of susceptibility via time-varying models because the design does not require short-term lags of exposures.

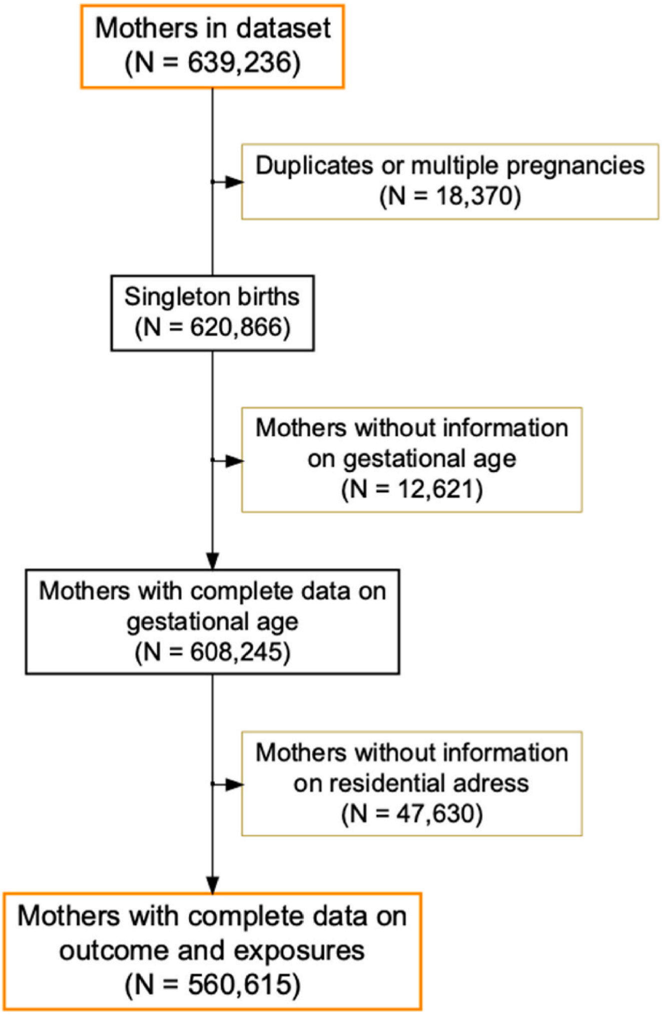

Fig. 1. Flowchart of the included study population.

3. Results

Our study population included 560,615 singleton births between 2014 and 2019 (Fig. 1). Of these, a total of 0.4%, 0.5%, and 4.2% were born extremely, very, and moderately preterm, respectively (Table 1). In total 28,221 (5.1%) were born preterm. Compared to term births, preterm births were more likely to occur in male infants (53.9% vs 51.4%), and in mothers above 35 years of age (23.9% vs 22.1%), with lower attained education level (39.5% vs 43.8%) and with obesity (15.7% vs 13.1%). These differences were pronounced among extremely preterm births, especially in male infants (53.5%), mothers above 35 years of age (27.9%), and with lower education level (30.7%). Differences in smoking during pregnancy, hypertensive status and diabetes mellitus were more difficult to compare as higher missing values were observed, especially among the extremely and very preterm infants.

In Fig. 2 we present the ambient temperature values corresponding to the 50th and 95th percentiles of municipality-specific distributions across Sweden. The ambient temperature varied between −1 °C and 10 °C in the 50th percentile whereas in the 95th percentile it varied between 13 °C and 20 °C. In addition, in the highest percentile, we could observe a heat island effect (red colour >19 °C) in the central east part which corresponds to Stockholm municipality, the largest city in Sweden.

We observed no statistically significant associations between short-term exposure of ambient temperature and preterm birth, but there were similar trends in all the three analytical approaches (Table 2). No effects were observed among the moderately preterm and all preterm births, but there was an indication of a possible association between heat exposure in the week before birth and extremely preterm birth in all three analytical approaches. In particular, when comparing the 95th vs the 50th percentile, we estimated an OR = 1.21 (95% CI, 0.82; 1.78) in the case-crossover design, a reduction of −0.65 (95% CI, −9.67; 8.36) days in gestational age at birth in the quantile regression, and a hazard ratio (HR) = 1.25 (95% CI, 0.92; 1.70) in the time-to-event analysis. The shape of the relationship between ambient temperature and the different preterm subcategories was mostly linear and almost identical in each of the three analytical approaches (supplement Figs S3–S5). Again, the extremely preterm births showed the strongest effects but with wider confidence intervals. The infant's sex, period of birth, geographic location, maternal age, education, and BMI did not modify any of the associations between air temperature and extremely or all preterm births (supplement Table S2). However, in the case-crossover design we observed lower risks of extreme preterm births (OR = 0.10 (95% CI, 0.01; 0.66) as well as total preterm births (OR = 0.62 (95% CI, 0.41; 1.84) comparing 95th to 50th percentile temperature among smokers.

In the DLNM models, we did not observe associations between ambient temperature during pregnancy and preterm births that reached statistical significance (Figs. 3 and 4 and supplement Table S3 and S4). Even so, consistently across both the quantile regression and time-to-event analyses, we observed associations indicative of an increased risk of extremely preterm birth by high temperature exposure during the last week before birth. We observed a reduction of −2.77 (95% CI, −7.04, 1.51) days in gestational age at birth using the quantile regression and a HR = 1.14 (0.97, 1.34) in the time-to-event analyses. For moderately preterm and all preterm births, null associations during pregnancy were found. Finally, we observed a small protective effect of heat temperature on extremely preterm births around week 10 in both the quantile regression and time-to-event analyses.

4. Discussion

In our study of >560,000 singleton births using a nation-wide registry in Sweden, we estimated the association between weekly exposure to ambient temperature and preterm birth applying three analytical approaches: a case-crossover design, a quantile regression, and a time-to-event analysis. Consistently across the three analytical approaches,

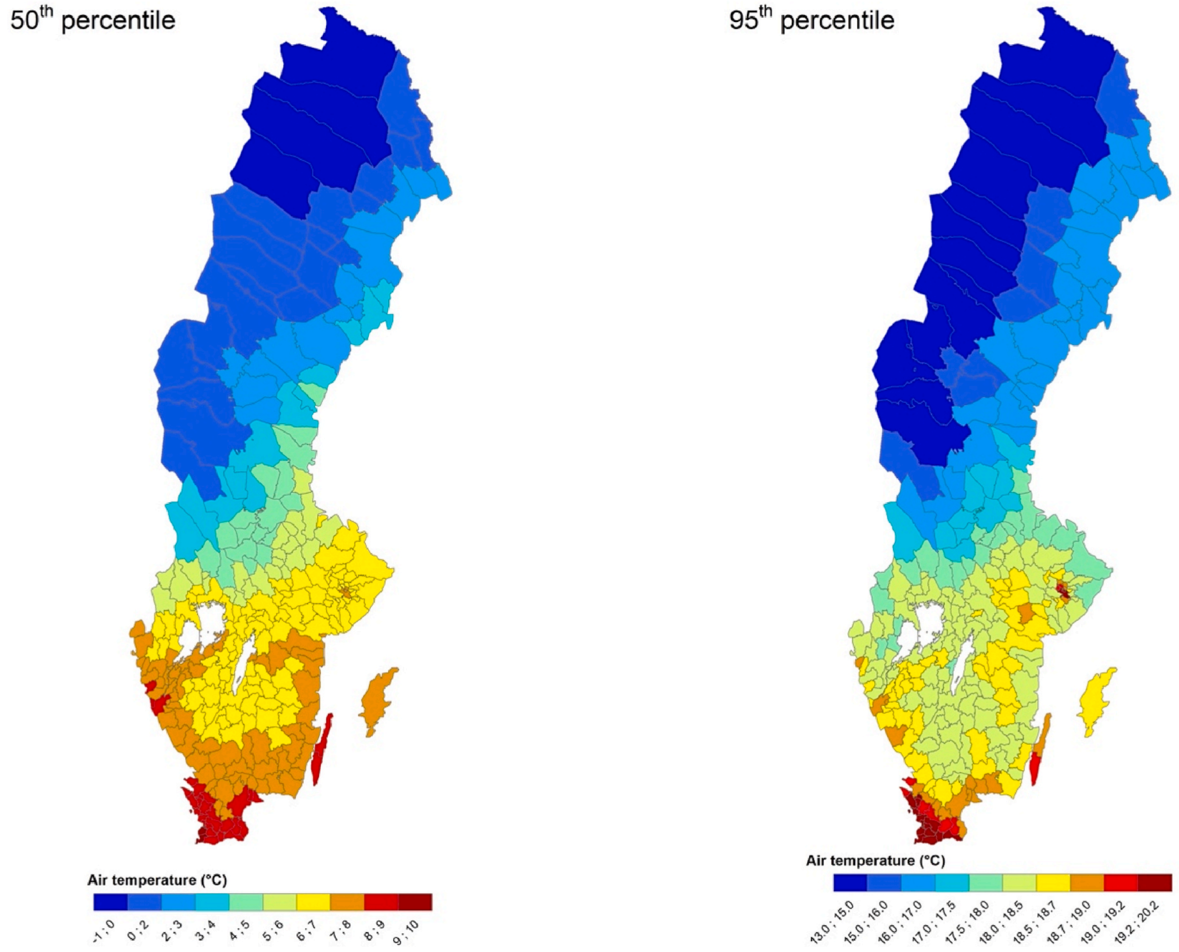

Fig. 2. Map of Sweden showing the distribution of temperatures (°C) by the 50th and 95th percentiles by municipalities.

we did not find an association between high ambient air temperatures and preterm birth. However, in both the short-term and the DLNM models, all three analytical approaches suggested non-significant associations for increased risk of extremely preterm birth with higher temperature during the last week before birth.

There are several possible explanations for the lack of statistically significant findings. Housing conditions are universally good in Sweden, irrespective of socioeconomic situation, with good insulation as well as access to cooling systems (fans, air conditioning). Additionally, overall health in the population is good with high access to primary healthcare services (Graviditetsregistrets, 2020). Women generally enter pregnancy in good health and have good access to antenatal care services as well as high adherence to appointments and, consequently, timely detection of complications, which can be carefully monitored. There are no fees for antenatal care, potentially raising clinic attendance to antenatal care services. The non-significant increased risk of extreme preterm birth during the last week before birth, was higher among women with high BMI, potentially due to the increased insulation of body fat in pregnant women with high BMI (Wells, 2002). High maternal age is also an independent risk factor for preterm birth and when exposed to heat, there may be an increased risk of preterm birth through effect modification (Strand et al., 2011). In the DLNM models, we observed a positive association between heat and preterm births around week 10 and would implicate a reduction in the risk of pre-term with higher air temperatures during early pregnancy. However, these results should be interpreted with caution and are possibly an artefact of the cubic constraint of DLNM model. One finding of interest was the non-significant association of lower risk of extremely preterm birth among smoking women who are exposed to higher ambient temperatures. We cannot explain the apparently protective effect of smoking and this finding needs to be corroborated in future studies. Being born preterm carries health risks for later in life, such as pulmonary problems and also neuropsychiatric disorders (Liu et al., 2015; Vogel et al., 2018). Therefore, our findings provide some evidence that we need to give special attention to further understanding the risk that higher ambient temperatures might have on the developing foetus.

Currently increasing evidence indicates that high ambient temperatures may increase the risk of preterm birth, however discrepancies remain across studies (Chersich et al., 2020; Zhang et al., 2017). The heterogeneity of the results might be related to the different climate zones or geographic regions across the globe, exposure assessment methods, windows of exposure explored, different population characteristics, and/or the different study designs and statistical methods (Zhang et al., 2017). Two previous studies available in Sweden modelled long-term or seasonal exposure to temperature in relation to preterm births and reported positive associations (Bruckner et al., 2014; Vicedo-Cabrera et al., 2015). Focussing on short-term exposure comparable with our results, a similar study in Sweden and other studies in mild and cold climate zones such as Canada, England and Germany did not find an association between high temperature and preterm birth (Auger et al., 2015; Lee et al., 2008; Vicedo-Cabrera et al., 2015; Wolf and Armstrong, 2012). However, studies in the United States (US) and in China have found stronger associations between heat and preterm birth in colder and drier climates (Guo et al., 2018; Sun et al., 2019). As mentioned before, the varying results between climate zones could be related to adaptation to the climate, different building standards and their

Table 1
Descriptive of the population by subcategories of preterm births.

	Extremely preterm N = 1924 (0.34%)	Very preterm N = 2636 (0.47%)	Moderately preterm N = 23,664 (4.22%)	No preterm N = 532,519 (94.97%)	P.trend
Sex					<0.001
Male	53.5%	55.6%	53.9%	51.4%	
Female	46.5%	44.4%	46.1%	48.6%	
Birth type					<0.001
Caesarean	0.8%	2.4%	4.9%	7.6%	
Induced	18.2%	8.4%	18.5%	18.2%	
Spontaneous	81.0%	89.2%	76.6%	74.2%	
Period of birth					<0.001
December–February	23.9%	25.9%	24.5%	22.6%	
March–May	27.2%	25.4%	25.4%	26.1%	
June–August	24.4%	25.2%	26.4%	26.9%	
September–November	24.5%	23.5%	23.8%	24.4%	
Geographic location					0.010
North	11.1%	8.8%	9.9%	9.5%	
Central	34.7%	37.4%	37.6%	39.0%	
South	54.2%	53.8%	52.5%	51.5%	
Maternal age (years old)					0.516
≤24	13.4%	14.1%	13.4%	11.7%	
25–29	28.6%	29.5%	31.0%	31.6%	
30–34	30.1%	30.8%	31.7%	34.5%	
≥35	27.9%	25.5%	23.9%	22.1%	
Missing	0.1%	0.0%	<0.1%	<0.1%	
Maternal education					<0.001
1–9 years	8.4%	8.5%	7.3%	7.2%	
10–12 years	30.8%	33.0%	34.0%	31.8%	
>12 years	30.7%	36.0%	39.5%	43.8%	
Missing	30.1%	22.5%	19.2%	17.3%	
BMI categories					<0.001
Underweight	1.7%	2.4%	3.1%	2.4%	
Normalweight	35.1%	44.6%	48.1%	53.4%	
Overweight	20.6%	22.7%	24.3%	24.3%	
Obesity	16.1%	15.4%	15.7%	13.1%	
Missing	26.6%	14.9%	8.8%	6.8%	
Smoking pregnancy					<0.001
Yes	5.6%	6.1%	6.3%	4.2%	
No	64.4%	75.5%	80.5%	84.5%	
Missing	30.0%	18.5%	13.2%	11.3%	
Hypertension					<0.001
Yes	1.7%	1.9%	1.2%	0.4%	
No	78.5%	88.4%	93.8%	96.4%	
Missing	19.8%	9.7%	5.0%	3.1%	
Diabetes mellitus					<0.001
Yes	1.4%	2.4%	3.8%	0.7%	
No	79.4%	88.1%	91.4%	96.3%	
Missing	19.2%	9.6%	4.8%	3.0%	

Values are mean (SD) for continuous normal distributed variables, median (interquartile range) for continuous non-normal distributed variables, and percentage for categorical variables. Pearson chi^2 was used to calculate p-value.

capacity to provide thermal comfort, and access to health care (Sun et al., 2019). Overall, compared to our results from Sweden, ambient temperature was more consistently associated with preterm birth in warmer climate zones such as those in Australia, China (warmer regions), Italy, and Spain (Arroyo et al., 2016; Mathew et al., 2017; Schifano et al., 2013b; Wang et al., 2020). This might indicate that pregnant women residing in geographic regions with warmer temperatures or warmer climates will be more vulnerable to the effects of high temperatures. Whether this may be due to lower building standards with fewer opportunities to even out changes in ambient temperatures, or lower access to antenatal care services, lower adherence to regular pregnancy check-ups, needs to be elucidated in future studies using high quality data collected during pregnancy.

Previously, most studies have used meteorological stations for exposure assessment of ambient temperature, which primarily capture temporal changes in temperature exposure and largely ignores spatial gradients. However, our study, similar to two studies in the US and in Israel (Kloog et al., 2015; Spolter et al., 2020), improves upon exposure assessment by using a spatiotemporal model. Both the studies in the US and Israel found associations between high ambient temperature during pregnancy and preterm birth. In contrast to our study, the US study averaged temperature over the entire pregnancy whereas the Israeli study modelled weekly means throughout gestation (Kloog et al., 2015; Spolter et al., 2020). Understanding when in pregnancy to expect the highest vulnerability to heat is important both for understanding the physiological effects and for suggesting mitigation strategies. Studies have variably focused on exploring associations with exposure during the last day, week or month preceding birth, specific pregnancy trimesters, or the entire pregnancy (Zhang et al., 2017). We focused on short-term exposure to high ambient temperature within the last week of pregnancy based on current evidence indicating that the final week of pregnancy is the most important for preterm birth (Chersich et al., 2020). However, we also explored other time windows of ambient temperature exposure by assigning weekly averages across pregnancy without finding clear indications of other vulnerable periods of exposure in our dataset.

We observed consistent results in the three different analytical approaches: the case-crossover design, quantile regression and time-to-event analyses. Most studies found positive associations between elevated temperature and preterm births using mainly time-series designs (Liang et al., 2016; Schifano et al., 2013a; Vicedo-Cabrera et al., 2014), case-crossover designs (Auger et al., 2015; Basu et al., 2010) and

Table 2

Associations between short-term exposure (lag0-6) to high levels of ambient air temperature and shortening pregnancy.

Heat	Extremely preterm [N = 1924 or percentile = 0.35%]	Very preterm [N = 2636 or percentile = 0.5%]	Moderately preterm [N = 23,661 or percentile = 4.3%]	Pre-term birth [N = 28,224 or percentile = 5.1%]
Case crossover design, OR (95% CI)				
90th vs 50th	1.11 (0.74, 1.66)	0.85 (0.61, 1.19)	1.08 (0.96, 1.21)	1.01 (0.98, 1.03)
95th vs 50th	1.21 (0.82, 1.78)	0.88 (0.63, 1.23)	1.07 (0.96, 1.20)	1.01 (0.99, 1.04)
99th vs 50th	1.34 (0.85, 2.12)	0.91 (0.62, 1.35)	1.06 (0.93, 1.21)	1.02 (0.99, 1.05)
Quantile regression, days (95% CI)				
90th vs 50th	−0.57 (−9.05, 7.91)	0.50 (−3.80, 4.81)	0.00 (−0.73, 0.72)	−0.30 (−1.05, 0.45)
95th vs 50th	−0.65 (−9.67, 8.36)	1.23 (−3.20, 5.67)	0.17 (−0.60, 0.94)	−0.13 (−0.93, 0.67)
99th vs 50th	−0.75 (−10.77, 9.26)	2.13 (−2.67, 6.94)	0.38 (−0.49, 1.25)	0.09 (−0.81, 0.99)
Time-to-event, HR (95% CI)				
90th vs 50th	1.22 (0.92, 1.63)	1.08 (0.85, 1.39)	0.98 (0.91, 1.07)	1.01 (0.93, 1.09)
95th vs 50th	1.25 (0.92, 1.70)	1.07 (0.82, 1.39)	0.97 (0.89, 1.06)	1.00 (0.92, 1.08)
99th vs 50th	1.29 (0.91, 1.81)	1.05 (0.78, 1.40)	0.96 (0.87, 1.06)	0.99 (0.90, 1.08)

Estimates were derived using a conditional logistic regression for the case-crossover design, a quantile regression, and a Cox proportional hazard regression for the time-to-event analyses. The quantile regression and time-to-event analyses were adjusted for year of conception, region, BMI, maternal education, and maternal age. The reference temperature was the 50th percentile level.

time-to-event analyses (Kloog et al., 2015; Spolter et al., 2020; Wang et al., 2020). These study designs are complementary on several aspects, including the exposure contrasts of inference (spatiotemporal for quantile regression and time-to-event, vs temporal only in case-crossover, within versus between individuals), the trade-off between confounding adjustment and statistical power, and the ability to investigate susceptibility windows of exposure. The main strength of the case-crossover design is that it achieves perfect adjustment for known and unknown time-fixed confounders, whereas quantile regression and time-to-event analysis might be prone to residual confounding from omitted covariates. This, however, comes with a cost: case-crossover only uses within-individual contrasts in exposure among cases, therefore severely reducing population size and statistical power. On the other side, as we have observed similar trends in the results and in the linearity of the associations across the three methods, it seems that the adjustment for relevant confounders in the quantile regression and time-to event was sufficient. Another limitation of the case-crossover design, also shared by the quantile regression, is that they do not account for foetuses at risk and are therefore prone to seasonal conception patterns. To overcome this problem, we selected control periods remarkably close in time in the case-crossover design, and we adjusted for season in quantile regression. In contrast, time-to-event analysis adjusts for seasonal conception patterns by design, because the Cox model with gestational age as time axis implies comparison of foetuses at the same gestational age (Auger et al., 2015). A nice feature of the quantile regression (Qiu et al., 2020) is the ease of clinical interpretability because the effect estimates are expressed in days of gestational age. Furthermore, both quantile regression and time-to-event analysis use the total population, increasing the sample size compared with the case-crossover design, and allow investigation of longer exposure windows. As consistent results were observed across the three analytical approaches, we recommend the use of at least one analytical approach according to the data available of each study. If full data on foetuses at risk and confounders are available, we would recommend the use of time-to-event analyses as it accounts for all foetuses at risk and for season patterns, whereas when the risk of residual confounding is high, the use of the case-crossover design is recommended. Furthermore, the choice should also be motivated by the main research question: if one seeks to identify susceptibility windows of exposure during pregnancy, methods allowing for longer lags should be prioritized. We highlight the inclusion of multiple approaches to assess the robustness of the results.

The main strength of our study is the high-quality data on exposure and outcome. We applied a spatially fine resolution spatiotemporal model to estimate daily ambient air temperature exposure levels at a 1 km^2 grid across the whole country of Sweden. Previous studies have used meteorological stations that are not able to account for between-subject variability in exposure, and lack rural coverage, thus limiting the generalizability of the results to the general population (Kloog, 2019). In our spatiotemporal models, we were able to assign daily exposure at the residential address of each individual, and to convert absolute temperature values in municipality-specific percentiles (Fig. 2). Another strength is the large sample size (over 560,000 pregnant women) with a high representativeness as the SPR covered more than 90% of all deliveries in the entire country of Sweden between 2014 and 2019. Besides a high-quality assessment of the study outcome (preterm birth), the SPR also provides a large amount of relevant individual confounders such as socioeconomic status and BMI status.

Our study faced some limitations. Our exposures were estimated at residential address, which could increase exposure misclassification as we did not account for residential mobility and time-activity patterns of the woman. We further did not account for humidity or other climatological variables in our spatiotemporal models. We cannot clearly rule out residual confounding resulting from area-level socioeconomic status or individual behaviour to whatever degree these characteristics might both be associated with preterm birth and ambient levels of temperature. However, we had information on individual socioeconomic status which is a good proxy of area SES, and behaviour data are more likely to be mediators rather than confounders in the association between ambient temperature and preterm births. As mentioned before, as the quantile regression and time-to-event showed comparable results as the unconfounded case-crossover design, our results seem unlikely to be affected by residual confounding.

5. Conclusion

In Sweden, with high quality data on exposure and outcome, we did not find an association between high ambient air temperatures and preterm birth in more than 560,000 singleton births, applying three analytical approaches: a case-crossover design, a quantile regression, and a time-to-event analysis. However, we observed non-significant

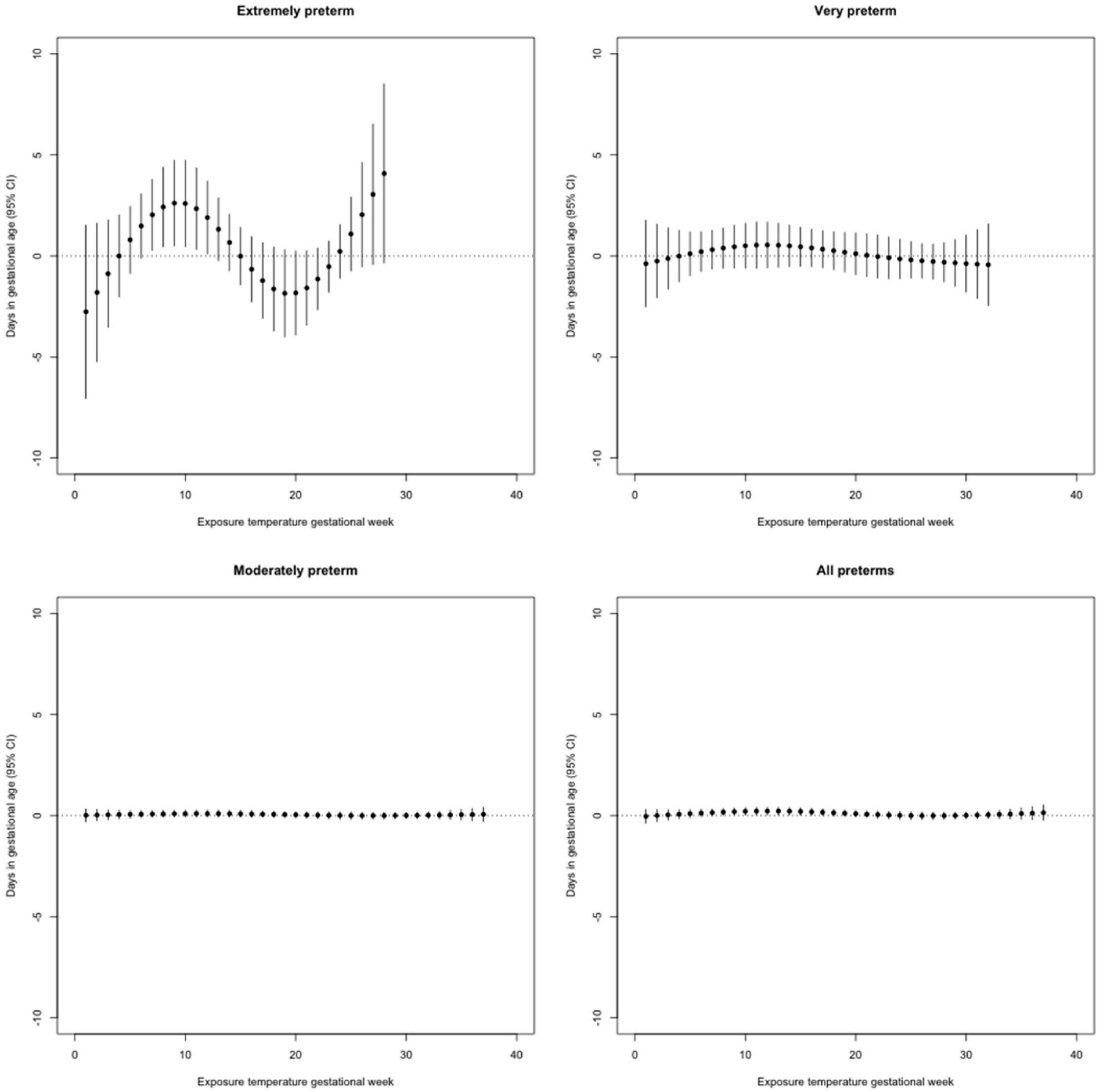

Fig. 3. Associations between warm temperatures (95th vs 50th percentile) during pregnancy and days in gestational age using the quantile regression. We applied a distributed lag nonlinear model to identify potential windows of vulnerability during the entire pregnancy. The effect estimates were expressed comparing the 95th vs the 50th percentile of lag-specific and municipality-specific exposure distributions. The models were adjusted for year of conception, region, BMI, maternal education, and maternal age. This figure corresponds to supplement Table S2.

associations in all three analytical approaches suggesting a higher risk of extremely preterm births with higher temperature during the last week before birth. The implementation of three complementary analytical designs and observing consistency across methods strengthens confidence in findings and may be a useful model for future studies regarding the effects of ambient air temperature on pregnancy outcomes.

Ethical committee

This study was approved by the Regional Ethical Review Board in Stockholm, Sweden (2020/00390).

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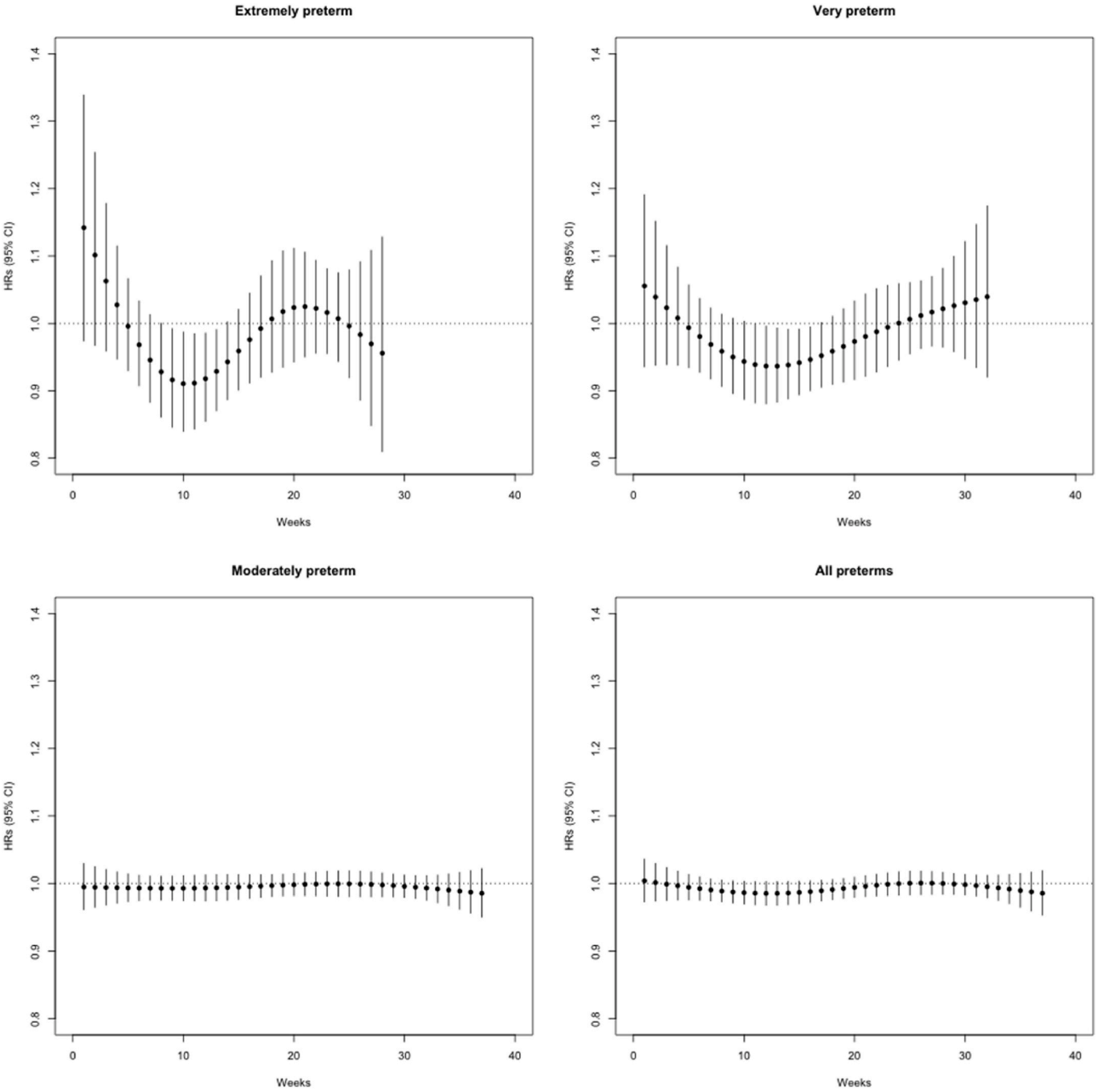

Fig. 4. Associations between warm temperatures (95th vs 50th percentile) during pregnancy and risk of preterm births using the time-to-event analyses.
We applied a distributed lag nonlinear model to identify potential windows of vulnerability during the entire pregnancy. The effect estimates were expressed comparing the 95th vs the 50th percentile of lag-specific and municipality-specific exposure distributions. The models were adjusted for year of conception, region, BMI, maternal education, and maternal age. This figure corresponds to supplement Table S3.

Credit author statement

Jeroen de Bont: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Massimo Stafoggia**: Conceptualization, Investigation, Methodology, Data curation, Formal analysis, Validation, Writing - original draft, Writing - review & editing. **Britt Nakstad:** Conceptualization, Writing - review & editing. **Shakoor Hajat:** Conceptualization, Writing - review & editing. **Sari Kovats:** Conceptualization, Project administration, Funding acquisition, Writing - review & editing. **Chérie Part:** Conceptualization, Writing - review & editing. **Matthew Chersich:** Conceptualization, Writing - review & editing. **Stanley Luchters:** Conceptualization, Writing - review & editing. **Veronique Filippi:** Conceptualization, Writing - review & editing. **Olof Stephansson:** Conceptualization, Data Curation, Writing - review & editing. **Petter Ljungman:** Conceptualization, Methodology, Supervision, Resources, Writing - original draft, Writing - review & editing. **Nathalie Roos:** Conceptualization, Methodology, Supervision, Project administration, Funding acquisition, Resources, Writing - original draft, Writing - review & editing.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jeroen de Bont reports financial support was provided by Swedish Research Council for Sustainable Development (FORMAS). Petter Ljungman reports financial support was provided by Strategic Research Area Epidemiology (Karolinska Institutet). Nathalie Rooos reports financial support was provided by Forskningsrådet för hälsa, arbetsliv och välfärd (FORTE). Nathalie Rooos reports financial support was provided by Belmont Forum (ID 2019-01570). Matthew Chersich holds investments in the fossil fuel industry through his pension fund.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.envres.2022.113586.

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