Author's response to reviews

Title: Methodological challenges when estimating the effects of season and seasonal exposures on birth outcomes

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Response to reviewers

Reviewer: Rupa Basu

This paper is interesting, as it covers the topic of a potential fixed cohort bias in studies considering season/seasonal exposures on adverse birth outcomes. However, I am unsure of whether this study is enough to warrant an entire paper, and there are some flaws in the authors’ assumptions that need to be addressed.

The fixed cohort bias will become a greater potential problem as more people use survival methods with time-dependent exposures. Recent studies have demonstrated how these models are far better than time series methods for examining the effects of environmental exposure on pregnancy outcomes, and how they are able to estimate key exposure periods during the pregnancy (Suh et al 2009, Meister & Schaefer 2008). Therefore our paper is important as it shows a simple way to avoid the bias.

Figure 5 in our paper shows how ignoring the fixed cohort bias gives a quite different picture of risk. Before adjusting for the fixed cohort bias, the biggest changes in risk are at the extremes of temperature, but after adjusting for the bias, the biggest changes in risk are observed for moderate temperatures. These results have very different public health implications about what temperatures are dangerous for pregnant women. We have now highlighted this important difference in the discussion.

References:


On P. 3, the authors state that “if there was unusually hot month in the first trimester…high temperature could be wrongly associated with longer gestations.” In epidemiologic studies, it is important to include more than one year of data, so that extreme events are not heavily weighted, but the results are instead based primarily on average exposures. Therefore, one hot month should not influence or bias the results of the overall distribution. Often, that hot month/heat wave is studied in a separate analysis.

We agree that a small number of influential observations should not affect the overall results, and indeed the fixed cohort bias is a reminder to look for influential observations (for example using the dfbeta statistic). The language we used on page 3 (concerning the unusually hot month) was as an example of how the fixed cohort bias could cause biased results, and it is certainly not the only way. We have added a clause to the start of the sentence.

On P. 4-5, the authors excluded conception dates prior to 19 weeks and post 43 weeks. However, these exposures should have a minor impact on the overall results, as the bias should almost balance out. Even the results of this study suggest that the bias only influences the extreme temperatures,
but since effect estimates are often depicted for the entire distribution, the bias, if any, would be minimal. This should be stated in the discussion section (which is missing—see specific comment below) in detail.

The simulation results in Figure 3 were based on four years of data, and show significant biases when ignoring the fixed cohort bias. After excluding conception dates 19 weeks before the cohort started and 43 weeks before the cohort ended the bias disappeared. These were around 13% of all pregnancies, and so represent a relatively large proportion of the sample which explains the relatively large bias.

In a new simulation we looked at longer cohorts from 4 to 14 years in length and examined the effect of month of exposure (see below). The y-axis shows the estimated hazard ratio, the true hazard ratio for all years is one. The fixed cohort bias still existed for a long cohort of 14 years. The bias decreases with increasing cohort length because the percentage of the sample that needs to be excluded to avoid the bias decreases.

![Diagram showing hazard ratio vs cohort length](image)

On P. 6 (top), the estimates for the conceptions in July and January are essentially the same. Was there a statistically significant difference? Please include that.

Did you mean the hazard ratios for July (HR = 1.043) and May (HR = 1.051)? An unpaired t-test of the 100 simulations gives $t = -4.0075$ and p-value < 0.001. This shows that the peak bias in the hazard ratio is not the same in every month.

On P. 4, please list and cite the statistical program that was used to simulate the data.

We have added the software used.

On P. 5, are the variables listed in the model all confounders? Infant sex, for example?

They may not all be confounders, but some are important sources of variance. For example, male sex has been shown to increase the risk of preterm birth (Zeitlin et al. Fetal sex and preterm birth: are males at greater risk? Hum. Reprod. (2002) 17(10): 2762-2768).

Was it possible to get information on education and socioeconomic status?

Unfortunately it was not possible to get information on mother’s education. We did control for smoking, which has been shown to correlate strongly with socio-economic status (Reid et al 2010). We also controlled for Indigenous status which is—sadly—a strong predictor of low socio-economic status in Australia.
On P. 5 (bottom), it is not clear whether Figure 3 refers to the entire data set or to the simulated data set. Please clarify.

The figure legend states “simulated cohorts”.

On P. 6, the Brisbane results would be better depicted a figure to show gestational weeks by month. Unfortunately using a Cox proportional hazards model with time-dependent exposures means the results cannot be presented in terms of time (gestation length - on an absolute scale), but instead are shown as the hazard ratio (on a relative scale). Using an accelerated failure time model or pooled logistic regression model (D’Agostino et al) would overcome this issue, and we have mentioned this in the discussion.


There should be a discussion of the strengths and limitations of the study, biological mechanisms, etc. That entire section is missing.

Our initial focus was on the methods, rather than the substantive results (which we mostly used to demonstrate the bias). We have added a paragraph to the discussion on the possible biological mechanisms, and a paragraph on limitations.

The Figures in this study are generally not very informative and difficult to interpret. I suggest deleting most of them, or making some major alterations.

We think that the fixed cohort bias involves some reasonably complex ideas, and that the pictures help communicate these ideas.

Figure 3 needs a label on the X axis titled, “Month of conception.” Also, J, F, M, etc. needs to be added to the top and bottom of the X axis.

Agreed and changed.

Reviewer: Johan Fellman

Many previous studies have presented seasonal models in birth outcomes, but with little agreement about the seasonality pattern. The initial attempt was to introduce sinusoidal models. However, empirical data have often had too complicated pattern for the simple sinusoidal model, which presupposes one peak, one trough and that the distance between these should be six months. A review of different models is given in Fellman and Eriksson (2000). Alternative more advanced models can be found in Fellman and Eriksson (2002). In addition, Eriksson and Fellman (2000) have, in connection with twinning studies, discussed the effect of different gestation lengths. Walter and Elwwod (1975) considered the variations in the population at risk. These problems are central in the manuscript.
We agree that Walter and Elwood’s test accounts for the population at risk and have referenced it, although we note that its power is relatively low compared with other tests (Barnett and Dobson, Chapter 3). We have also referenced the review paper by Fellman and Eriksson (2002). As pointed out in that paper, a difference in the statistical methods used could partly explain the different seasonal patterns in the literature.


Reviewer: Emily DeFranco

Two of the most influential factors in birth timing are race (black) and prior preterm birth. Neither of these was included in the adjusted model. Please comment on the reason for this and how this could influence the results.

Our model included Indigenous status, which is the most important racial group in terms of health in Australia. For example, in 2007, babies born to Indigenous women were twice as likely to be of low birthweight (less than 2,500 grams) than those born to non-Indigenous women (Laws & Sullivan 2009). Women of African or Asian origin would have been grouped with women of a European origin as simply non-Indigenous. In 2006, 2.2% of the entire Brisbane population were born in Africa or the Middle East, and 7.9% were born in Asia. There may be effects due to not controlling for these racial groups. Darrow et al (2009) found that there were seasonal patterns in birth numbers by racial groups, which could then cause seasonal patterns in birth outcomes (such as gestation length) if they are not controlled for. We have added this as a caveat to the discussion.

Our model included the number of previous pregnancies, which included previous live birth, stillbirths and abortions, but we had no information on prior preterm birth or the time since the previous birth. The potential effect of missing these variables is (we believe) less serious than missing race. This is because we are interested in temperature exposure, which depends upon the timing of conception. So temperature exposure is unlikely to be correlated with prior pregnancy history. Of course, previous prior preterm birth is a strong predictor of future preterm birth (Kashanian et al 2006), but one that we believe is independent of temperature (season).

References:


Editorial Requests:
Competing interests - Please include a 'Competing interests' section between the Conclusions and Authors' contributions

Done

In the abstract of your manuscript, please state the objective of your research study.

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