Author's response to reviews

Title: Autism, Circumcision and Analgesia: an Ecologic Link

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Author's response to reviews: see over
Response to Reviewers

First, thank you to the editorial staff for your persistence and patience and to all the reviewers for the thoughtful and constructive critique of this manuscript. An ecological study, such as this, is never definitive. The intended purpose of this paper is hypothesis generation, to share interesting observations and biologic similarities that may suggest the plausibility of a relationship between prenatal and neonatal exposure to paracetamol and autism. The hope is that this will be sufficiently persuasive and suggestive to generate interest in the further exploration of this relatively unstudied, yet prevalent, exposure and the possible association with the development of autism. In response to Reviewers Two and Three, we have included the statement “correlation in not causation” in the discussion section. We are aware that there are numerous and significant limitations to this study, not the least of which is the reliability of circumcision rates as a proxy for perinatal paracetamol exposure. As such, we have been particularly careful to avoid statements that may appear to imply a causal association.

In response to the comments of Reviewer One, normality was checked by standard graphical and statistical methods and seemed reasonable given the small sample size, so we assumed normality. As Reviewer One acknowledged, we found essentially the same results using the non-parametric test, leading to the same interpretation. The manuscript has been revised with a single data point for the United States being utilized in the Pearson’s correlation coefficient calculations for the country analysis, responding to a concern of Reviewer One. We are no longer including data on the US ethnic groups. For the post -1995 cohort we included newly identified U.S. state data which are shown on the same graph as the country level data. The graph does not include a data point for the U.S. overall. Because of the lack of state stratified circumcision data no state data are presented for the pre-1995 cohort. When the pre and post -1995 cohorts are compared for trend, only the country level data are compared.

In response to the comments of Reviewers Three and Four, the discussion of biologic plausibility and the subsequent sections have been considerably condensed.
In response to the additional constructive comments of Reviewer Three:

1) We have revised the conclusions to reflect your concerns of overstatement of the findings.
2) The title has been changed to reflect prenatal and perinatal exposure.
3) The abstract has been changed to reflect that both antenatal and perinatal exposure is being examined.
4) We added that this was an ecological analysis in the abstract.
5) The conclusion in the abstract has also been restated to more accurately reflect the level of evidence this study provides.
6) The background has been condensed.
7) Acknowledging the importance of reproducibility, an attempt has been made to clarify the methods.
8) Clarification of date ranges for studies - The year of publication and the youngest and oldest birth years for the autism prevalence studies are included in Additional File 1. The birth years were extrapolated from The CDC Summary of Autism Spectrum Disorder (ASD) Prevalence Studies which included the time period studied and the age range studies. We elected not to include these because of space constraints and they can be ascertained from the reported range of birth years. The year of publication and the youngest and oldest birth years for the paracetamol prevalence studies are included in Additional File 2. The year of study for the global circumcision rates are admittedly less clear. We have now identified all of the individual studies of circumcision rates instead of relying on the rates on the Circs.org website. This has allowed us to utilize the best rates available. Whenever possible the infant circumcision rate was utilized with the procedure date closest to the birth years of the autism prevalence cohorts. The available data still has limitation including the change of rates over time. This has been mentioned in the limitations section.
9) On the topic of other reasons for maternal paracetamol use: maternal use of paracetamol for fever is now mentioned in the introduction. The prenatal paracetamol studies generally did not provide indication for use, so this could not be included.
10) On the suggestion that we should pursue this study using a single country - An additional analysis was done using the US state data available. We identified circumcision data by state and year for eight years between 1997 and 2006 from the Health Care Utilization Project (HCUP) of the Agency for Health Care Research and Quality (AHRQ) of the United States Department of Health and Human Services. This allowed us to do a state level analysis only for the post-1995 cohort. We found a linear trend similar to the global data.

In addition to modifications made in response to all of the reviewers’ comments, we made some additional changes which we hope further improve this manuscript. First, the analysis was updated to include two new studies presented in the recent CDC autism prevalence tables. As mentioned above, we extracted the primary sources for the circumcision rates instead of relying on the findings from the Circs.org website, as was done previously. We used a 1/variance
weighted regression model in this paper revision instead of the previously presented unweighted model.

Once again, we thank you all for the time, effort and wisdom. We hope that we have adequately addressed your concerns.