Reviewer's report

Title: A comparison of temporal trends in United States autism prevalence to trends in suspected environmental causes.

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Reviewer: Sophie St-Hilaire

Reviewer's report:

I thought the manuscript titled “A comparison of temporal trends in United States autism prevalence to trends in suspected environmental causes” was well written and highlights important trends that should be published. The author uses a clever way to assess whether the increase in prevalence of autism in the last 20+ years is due to a change in the diagnostic criteria and assistance program or to a real increase in the disease. The author also examines trends of individual environmental pollutants and other factors over time to assess whether these followed a similar pattern to autism. Of particular interest to me was the trend for glyphosate use, which closely resembles the autism trend. This type of study (conducted at an aggregated data level) is meant to develop hypotheses. Based on the findings in this study there are several ideas are interesting and that should be followed up with further research. I think the problem with this manuscript in the past has been that the author over interprets the results. She presents aggregated trends and sometimes is tempted to apply the relationships to the individual level. If the author only interprets the results as trends that need to be further evaluated then this paper is very interesting and should be published. The following are my comments and suggested revisions:

Major issues to address

1) The author evaluates trends in autism but never uses the proper statistical change point analysis techniques. This was suggested by one of the previous reviewers. There are several software packages that do this. If the author is not familiar with this type of analysis she could consult (collaborate with) a statistician. A change point analysis may also detect other more subtle changes in the prevalence of autism.

2) The author needs to explain the logic for using the ratio of the snapshot slope to the tracking slope to estimate the level of increase in autism attributed to changes in diagnostic criterion. This is found in the discussion (section 4.1 1st paragraph) and it would be helpful to have earlier in the manuscript (i.e. in the methods or introduction).

3) I believe the bottom line is that autism is increasing even after the author adjusts or takes into account the change in diagnostic criteria. This is lost in the paper because of the amount of time the author spends on comparing the different data sources. I suggest at least adding it to the abstract (see suggested text).
4) The trends observed with the environmental pollutants are very interesting. The one I was most interested in was the use of glyphosate. I would move the figure comparing the trends for autism and glyphosphate to the main paper instead of the supplemental material because many people may not read the supplemental sections! I disagree with the last part of the last paragraph in section 4.5. The author is over interpreting her results and dismissing glyphosphate. This type of study does not lend itself to conclusions about cause and effect. Just because the first case of autism was in 1930’s doesn’t mean that this chemical is not associated with autism. There are most likely more than one trigger for autism and even the pathway for glyphosphate suggests a number of factors could be involved. I would simply make that suggestion that the two trends are very similar and this warrants further research using more robust type of study designs.

5) Many of the pollutants evaluated bioaccumulate in the environment and may act synergistically so it is difficult to make strong statements between autism trends and the trends in emissions of pollutants. For example, several of the pollutants appear to be endocrine mimicking compounds which could act on the developing brain in a similar manner. Of the 80,000 compounds that could have been evaluated several would be considered endocrine disruptors. It is possible that while the specific compounds examined are declining they are replaced with others that act in a very similar manner biologically. There was mention of this once but it should be stated very clearly.

6) It is also possible and likely that autism spectrum disorders are induced by more than one mechanism. So in addition to synergistic activity between pollutants it may also be that exposure to multiple types of pollutants results in an additive effect. This concept is only briefly mentioned in the last section of the discussion. The author should not make the statement that pollutants with decreasing trends are unlikely to account for the increasing trend in autism collectively because she only looked at 10 groups of compounds. I would limit such statements to individually these pollutants are less likely to account for the sharp increase in autism (see text for specific examples).

7) It is impossible to determine the exposure to individuals from these aggregated data. In several instances in the discussion the author implies that the correlation observed at the group level applies to the individuals (see comments in text). This should be corrected as it is incorrect. Ecological studies, where data are aggregated at the group level such as is the case in this study are only good for developing hypotheses. In some cases the author makes strong statements between the trends she observes that could be erroneously taken to mean that this trend occurs at the individual level. It is possible it does but she did not test this specifically. This is perhaps why other reviewers have been critical of the study in the past. I hope that the author clarifies this so that the findings of her paper are published as I think the trends are very interesting and insightful, and warrant publication.

8) There is no mention of how the vaccine data were obtained in the method section. The trend on AI administration is also very interesting and important.
9) The Swedish information in the paper is interesting but it doesn’t seem to add to the paper. What correlates with the decline in autism in Sweden? Why correlate the PBDE levels in Sweden to autism in California?

10) It seems that the abstract conclusions are missing some of the study’s findings. Add the statement in the summary section that suggests certain pollutants and vaccines have increasing trends and that this suggests hypotheses for drivers of autism that should be further investigated.

Minor revisions are outlined in the text.

**Level of interest:** An article of importance in its field

**Quality of written English:** Acceptable

**Statistical review:** Yes, but I do not feel adequately qualified to assess the statistics.

**Declaration of competing interests:**

'I declare that I have no competing interests'