Author's response to reviews

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

Authors:

Cynthia D Nevison (cynthia.nevison@colorado.edu)

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Author's response to reviews: see over
Response to Reviewer 1: Jennie Kline

I thank reviewer 1 for her comments. Please see my responses in blue below after each comment.

The purpose of this paper is to identify whether exposure levels for selected environmental agents increase over time as do the prevalence rates of diagnosed autism. The author concludes that the agents without increases in levels over time are unlikely to be “driving” the temporal increase in autism. This conclusion rests on the assumption that the increase in diagnosed autism over time is due to one (or perhaps a couple) of environmental exposures. The conclusion is not equivalent to saying that the agent is unlikely to be a cause of autism. The utility of an ecologic analysis of this type is limited.

With 1 in 42 boys in the U.S. now diagnosed with an autism spectrum disorder and no clear prevention strategies on the horizon, I would counter by arguing that it is important to encourage input from scientists who have diverse backgrounds, perspectives, and approaches to identifying the causes of autism.

That said, I’ve added some new text to Section 4.5 acknowledging some of the limitations of my study, such as its ecological nature.

It is best suited to identifying suspect agents for further study, rather than excluding agents.

I have made this point in my Abstract and in Section 4.5.

I appreciate the scholarly effort it took to describe temporal trends in selected environmental agents. While the main conclusion of the manuscript is clear (i.e., some exposures increase over time, others do not), I find the description of the analysis and interpretation unclear.

1. The terminology is unclear. What is an age-resolved snapshot? The closest I can come to a definition is on page 7 where it says Report year is held constant while age was varied from 5-17. Is this the same as the prevalence of autism at ages 5-17? In the tracking approach, “Age was held constant while Report year was varied from 1991-2010”. In Figure 1, for example, 8- and 11-year old “tracks” are provided. Are these the prevalence of autism among 8 and 11 year olds, respectively? Did the author consider using cumulative incidence to age x? I am not sure what age x should be, since there is a trade-off between the completeness of diagnosis in the birth cohort and the latest birth cohort that could be included.

I explain in the Introduction why I have done the analysis using age-resolved data rather than cumulative incidence: “The trend is defined and visualized by plotting autism prevalence vs. birth year, which permits direct comparison with trends in toxins, given assumption 1 above.” Assumption 1 is that “toxic exposures around the time of birth (± ~1 year) are the most important, since autism by definition is either present from birth or develops within the first few years of life.”
2. The author states that comparison of the age-resolved snapshot with estimated changes in prevalence over time from regression analysis identifies the proportion of the change over time in autism prevalence that is “real” (e.g., page 9, 15), rather than due to “better or expanded diagnosis”. I do not understand how this comparison yields the proportion of cases that are “real”. In response to both 1 and 2, I have clarified my analysis of the real fraction of the trend in the IDEA data in four ways: 1) I have added three paragraphs to the Introduction describing the terminology and motivation behind the approach. 2) I have overhauled the description of the Methodology in Section 2.1. 3) I have rewritten the Results Section 3.1. 4) I have rewritten the Discussion Section 4.1 to recap the introductory paragraphs before discussing the results.

I will also mention here that my assumptions about the age-resolved snapshot trends being relatively immune to changing diagnostic criteria and greater awareness are consistent with and partly based on my own experience in Colorado with the publicly funded Imagine program. This program serves all children with suspected developmental delays up until age 5, but then parents are required to provide a medical diagnosis with a neurological component (e.g., autism or ADHD) to continue services. My son, who has a speech articulation delay but not a neurological diagnosis, recently was terminated from Imagine when he turned 5. However, the staff reiterated multiple times that I could always self-refer him and start the evaluation process all over again if I had any new concerns about a neurological disorder in the future. They told me that it is not uncommon, for example, for new concerns to arise during a child’s teenage years.

3. It is unclear whether this paper is looking at time trends in autistic disorder (narrowly defined) or ASD. The CDDS primarily measures autistic disorder, whereas the IDEA includes ASDs. It is in fact not clear which ASDs are included in IDEA, so I was deliberately vague. I now acknowledge and discuss the ambiguity in IDEA data more clearly in Section 4.1. The inclusion of milder ASDs in IDEA is an important finding that I describe in both Section 3.1 and 4.1. My comparison of CDDS and IDEA data clearly shows that the IDEA data do not rigorously distinguish between AD and ASD in California, despite the fact that California in principle is ASD exclusive, according to MacFarlane and Kanaya (citation, #40). Conversely, my new comparison of ADDM and IDEA data for 8 year-olds in 2010 (see new Supplementary Figure S2) suggests that IDEA data generally underestimate prevalence compared to ADDM data (which include all ASDs).

The bottom line is that we need better autism data. However, as I was told in graduate school, “there are two kinds of data: imperfect data and no data.” Given the alternative, I’ve chosen to use imperfect data. Most importantly for my study, the IDEA data at least have the advantage of being self consistent and thus appropriate for use in my age-resolved snapshot v. tracking calculations.
4. I concur that the prevalence of diagnosed AD or of ASD has increased over time. This change does not mean, however, that either the true prevalence or incidence has changed. A major limitation of the analysis is the assumption that temporal trends reflect real changes rather than changes in diagnosis or the likelihood of ascertaining an affected child. For example, the Hertz-Picciotto and Delwiche paper (California data) suggests that 56% of the increase in rates in recent years may be due to providing services to milder cases (as compared with a 20% estimate in the current manuscript). The author considers the 56% estimate “wrong” (page 16), but I do not follow her argument. My intent here is to compare my estimate of 75-80% “real” to the 44% “real” fraction estimated by Hertz-Picciotto and Delwiche. In that paper, only one of the three factors, the earlier age of diagnosis, was actually derived from analysis of CDDS data. The remaining factors were little more than guestimates pulled from the literature. The expanding diagnosis factor was, in their own words, a “worst case” estimate that could well be much smaller. Rather than arguing that their estimate is “wrong” I have argued that our results are not inconsistent if they make other reasonable and defensible choices for those two factors. I have also added discussion explaining that my estimate is probably an upper limit of the “real” fraction, depending on whether some of the older children in the age-resolved snapshot are autistic but were never reevaluated even with the increased awareness of recent years.

The author refers to the “diagnosed prevalence of autism”. She means the “prevalence of diagnosed autism”.

I’ve changed the phrasing to “prevalence of diagnosed autism.”

5. The manuscript is not organized in the usual manner, making it difficult to follow. Thus, the author includes interpretation under Results (e.g., page 11 “the results indicate that the IDEA definition of ....”) and then again under Discussion (e.g., page 15 repeats the point on page 11). The discussion of the Hertz-Picciotto and Delwiche paper (page 16) is difficult to follow without reading the previous report.

I have moved this interpretation to the Discussion in Section 4.1.

6. The discussion of reasons for temporal changes in the selected environmental exposures, while interesting, detracts from the central points of the paper. What is the rationale for including obesity (which is not on the list of 10 agents set out by Landrigan et al 2012)?

I agree with the reviewer that obesity departs from the top 10 focus and have therefore removed it from the abstract. I still retain a paragraph discussing autoimmunity and obesity, because I feel, based on years of studying this topic, that these issues are relevant to autism and worthy of mention. I also now cite my obesity data source in Section 2.2, but acknowledge that it strays from the Landrigan list focus.

7. Throughout the discussion, the author provides references to both individual level and ecologic studies that implicate agents that do not show increases in
exposure levels over time (i.e., were not similar in direction to autism time trends in the current analysis). These examples illustrate that the approach taken in this paper cannot be used to identify agents that are not causally related to autism. Conversely, other exposures which increased in frequency or level over time (e.g., folic acid, ultrasound) are not positively associated with autism; indeed, folic acid exhibits an inverse association.

My paper investigates the temporal trends in the top ten suspected compounds and reports whether they are increasing, decreasing, flat, or mixed. In the reviewer’s opinion, this information is not important. Simply put, I disagree.

To respond to the second point, I think that trends in beneficial influences that can mitigate or help prevent autism are not directly relevant to my paper, since causal agents and mitigating factors are two separate issues. (For example, would anyone argue that deaths due to texting while driving cannot have increased since the 1980s because seat belt use has also increased?) Using the reviewer’s own example, folic acid metabolism is closely related to oxidative stress [see excellent review by Frye and James, 2014, ref.#8] and it’s possible that folate supplementation early in pregnancy or prior to conception can help reduce autism risk. However, unless folate deficiency per se is the main cause of autism, increasing folate supplementation may not be sufficient to override other increasing toxic exposures that are driving the rise in autism. Further, the reviewer does not provide evidence that folic acid exposure actually is increasing, so it’s hard to say what that trend is.

8. I find the terminology “drivers of the temporal trend” confusing. Does this terminology mean the same thing as “possible causes of autism”? Page 14 states that the premise of this paper is that the 20-fold increase in autism prevalence over 35 years is due to a single exposure or “collective influence of multiple environmental exposures”. The paper does not deal with collective multiple exposures, nor can I see how it could. As far as single exposures go, if the increase in autism prevalence were really 20-fold, it seems unlikely to me that a single cause would have gone undetected for the last two decades.

My view, which I’ve tried to express in this paper, is that autism is the result of a wide variety of risk factors, which include both genetics and toxic exposures, but that somewhere in the mix, there has to be one or more environmental influences with an increasing temporal trend to drive the strong rise in autism we’ve seen over the past few decades (which my paper concludes is mainly real). In my opinion, it would be valuable for the public health community to think more logically and quantitatively about what those temporal drivers could be. I now say this explicitly in Section 4.1.

It is common knowledge that some of the exposures studied (e.g., lead, air pollution) have decreased over time. I do not see a reason for carrying out a time trend analysis on these exposures.
I disagree with this opinion and present an example below demonstrating that 1) some of the leading U.S. experts on autism are claiming (without any apparent supporting data) that some components of air pollution are increasing and, more importantly, that 2) they are not thinking about the issue in a quantitative or evidence-based manner. My example involves excerpts from the recent NIH/NIEHS-sponsored expert panel discussion on Autism and the Environment, which took place on 4/22/14 in North Carolina (see transcript in red below). Air pollution featured prominently in the NIH/NIEHS discussion and was described by the director of the NIEHS as a probable “real agent involved in the increasing prevalence of ASD” (emphasis mine). Since NIH and NIEHS are major U.S. funding agencies, it seems likely that a significant portion of the money earmarked for autism-environment research will be spent investigating relationships between air pollution and autism.

But is this the best use of scarce resources if the specific goal of the research money is to prevent autism? Certainly air pollution is an ongoing concern and a serious public health threat, but can we realistically expect that if we further reduce air pollution in the U.S., the upward trend in autism is somehow going to be reversed, given that autism prevalence has increased dramatically over the past 25 years during the same time that substantial reductions in ozone, PM2.5 and vehicular emissions have already been achieved (see my Figure 4 and Figures S16-18)? This is a valid question that deserves serious consideration, but it was essentially brushed aside by the NIH/NIEHS expert panel.

When the panel was confronted with the conundrum of the opposing trends in autism and air pollution in the U.S. and the lower rates of diagnosed autism in China, a country with severe air pollution and PM2.5 levels about 10 times higher than those in the U.S. (a question submitted by me and chosen by moderator Dr. Cindy Lawler), the experts responded with assertions that were based on conjecture rather than scientific evidence and seemed to discredit the achievements that have been made by atmospheric scientists, engineers and regulatory agencies over the past few decades in understanding and reducing U.S. air pollution. As an atmospheric scientist myself, I was surprised by their suggestion that the chemical composition of air pollution is not well characterized and that there actually may be a countertrend in some components of air pollution, such as nanoparticles, even though air quality in general is improving in the United States. I’m also concerned they may be neglecting the concept of nuclei, accumulation and coagulation modes and the fact that very small particles tend to coagulate rapidly in the atmosphere.

I investigated the increasing nanoparticle allegation in response to an earlier reviewer and found no published articles on the topic (I discuss the issue briefly in Section 4.2 of my current manuscript). I also asked several colleagues who are aerosol experts and none knew of any basis for it. Furthermore, the earlier reviewer neither pursued the matter in his second review nor responded to my statement that I would be interested to see any documentation he had for an
increase over time in nanoparticles, which suggests he found no evidence either.

Below, I have appended a few excerpts from the transcript of the NIH/NIEHS expert panel, which I think speak for themselves in illustrating why it is important to carry out a time trend analysis of toxins like air pollution.

NIH/NIEHS Panel on Autism and The Environment 4/22/14
Response to my question about the conundrum of contemporaneously increasing autism and improving U.S. air quality.

Expert 1.
“Sure. There is several aspects tied up in that question, I think. So, one really is that the air pollution studies that were published haven’t been trying to explain the new cases that are occurring. We have been looking at associations in reoccurring cases. So, we can look for environmental factors that help explain rates that are current rates that have always been here. It’s likely not all one factor. So I think that is important to think about. And do you need to have a specific genetic background as we talked about earlier? And be exposed to pollution to then have that increased risk? That is two ways to think about it and then the last way is the pollutant mix keeps changing. So overall, what we measure and what we monitor has gotten better across the U.S. but there are particles smaller than the ones we monitor now that are not routinely monitored and animal studies show that can affect the brain and possibly effect the placenta developing. So there isn't necessarily the fact that because pollution and air quality overall is getting better and autism is going up, that it doesn't make sense. It is, the question is a little more nuanced than that, unfortunately. It’s understanding what we are exposed to now and how that changed over time as well.”

Well, I think there is also – I think people have a rosier impression about time trends in air pollution. Certainly our legislation dating back to the 70s when we began to see air pollution levels definitely going down, but the number of vehicles on the road has been going up rapidly, and young people driving bigger cars pollute more. So, I don’t think it is totally clear that in this last 10-15 years the autism rates have been really – at least the number of diagnosed cases has been going up steeply that that necessarily –that there is not some increase going on with air pollution.
I thank Reviewer 2 for her helpful review, including the annotated version of the manuscript.

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 overinterprets 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.

I think the changepoint analysis is an excellent suggestion and I hope my paper will inspire others to pursue it. However, statistical changepoint analysis is not my field of expertise. I used the best approach I know (based on the covariance matrix of each linear regression) to determine whether the trend could be estimated as a linear increase. Furthermore, McDonald and Paul (Ref#3) have already conducted a changepoint analysis on the CDDS 2002 snapshot data and identified 1988-1989 as the inflection point. My analysis supports their finding that there is an inflection in the IDEA autism data around that time, both in the tracking data and, probably more importantly, also in the snapshot data. I state, “…proving the 1988-1989 change point is beyond the scope of the current study,” but also try to encourage further research into this important topic. My paper is already long and I have worked on it for years, so I do feel that the proposed changepoint analysis is beyond the scope of what I realistically can do at this point.

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 first paragraph) and it would be helpful to have earlier in the manuscript (i.e. in the methods or introduction).

I have clarified my analysis of the real fraction of the trend in the IDEA data in four ways: 1) I have added three paragraphs to the Introduction describing the terminology and motivation behind the approach. 2) I have overhauled the description of the Methodology in Section 2.1. 3) I have rewritten the Results Section 3.1. 4) I have rewritten the Discussion Section 4.1 to recap the introductory paragraphs in Section 1 before discussing the results.

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).

I have made 2 changes to the abstract based on the reviewer’s suggestions.

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 glyphosate 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 glyphosate. 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 glyphosate 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.

I have moved the glyphosate figure from the Supplementary Materials to a more prominent place in the main text, as Figure 6. I have also rewritten the paragraph to emphasize that glyphosate is a plausible contributor to the ongoing increase in autism. I fully agree that this is one of the toxins most deserving of further study. At the same time I still feel it is appropriate to mention that glyphosate trends are lagged from the original identification of autism in the 1930s and the likely inflection point in the late 1980s.

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. I now make this point explicitly in Section 4.1, and also discuss it again in Section 4.2 and 4.5.

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). I have followed this advice and modified Sections 4.5 and 5 to say only that the individual compounds are “less likely” to be driving the increase in autism.

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.

I have modified Section 4.5 to acknowledge that my study is ecologically based and more useful for generating hypotheses than proving causation.

8) There is no mention of how the vaccine data were obtained in the method section. The trend on Al administration is also very interesting and important. I have added references to the aluminum content data in Section 2.2 in the main text and given the website reference for the CDC immunization schedules. I have also added a new graph, Supplementary Figure S7b, illustrating that the increase in aluminum adjuvant exposure has been greatest for very young U.S. infants.

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? I have deleted the section on Swedish PBDEs, since the attempt at international analysis was confusing to previous reviewers as well and probably beyond the scope of my current paper.

(In response to a question in the reviewer’s annotated manuscript, autism rates were historically high in Japan (a country with very high maternal blood Hg) in the
1970s and 1980s, but there are no new available data to my knowledge since birth year 1995. ASD prevalence in South Korea was recently reported at 2.6%, and ASD prevalence in Sweden has actually declined over the past 10 years, concurrent with a >50% decrease in mean blood Hg. All this information is interesting and possibly suggestive, but unfortunately beyond the scope of my current study.)

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. I’ve added such a statement to the end of my abstract. (I had taken this out because a previous reviewer objected to it.)