Reviewer's report

Title: Rate of first recorded diagnosis of autism and other pervasive developmental disorders in United Kingdom general practice, 1988 to 2001

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Reviewer: Craig Newschaffer

Reviewer's report:

*Is the question posed by the authors new and well-defined?

The question of whether autism spectrum disorders prevalence has been on the rise, while not new, is well-defined. However, most now accept the notion that prevalence of autism spectrum disorders has increased dramatically over the last two decades. The higher priority question, as the authors acknowledge, is whether the increase is due to changes in real risk or changes in diagnostic practice and, as they admit, their analysis cannot address that issue. That said, the data on prevalence trends this paper provides does come from a large and perhaps more representative source than that used in other published papers. This is not to say that the data used here are immune to diagnostic bias, that is very much NOT the case, but I still feel that it is a contribution to the literature to have prevalence trends seen in other sources confirmed by this data source.

*Are the methods appropriate and well-described? Are sufficient details provided to replicate the work?

The methods are described with sufficient detail. However, in my view, there are some problems. I do not think that addressing these methodologic issues will necessarily have a great impact on the paper’s findings and conclusions but, nonetheless, I feel the paper would be stronger if they were attended to.

DISCRETIONARY REVISION: As the authors acknowledge, the authors do not exclude person-time for individuals post-diagnosis. In a person-time analysis of new events time after event is not counted because the individual is no longer at risk. Although they state that the impact of this approach will be minimal because there are relatively few person-years post diagnosis, it is hard to understand, given how simple it is in the PC-age to calculate exact person-years data on start date and diagnosis date are entered into a database, why the correct analysis could not be performed.

COMPULSORY REVISION: I don’t think indirect is more appropriate than direct standardization for this analysis. It is true that indirect standardization can be more precise with sparse data but the real advantage of indirect standardization is when denominator data are absent in a given strata, not numerator data (“Because of low numbers of cases in some years, indirect standardization was used…”). I expect that person-year denominators are sufficient for direct standardization even when stratifying by year, gender or region. I would recommend shifting to direct standardization because the comparison of two indirectly standardized rates (or SIRs) has the potential to lead to biased inference since the adjusted estimates are based on standardized using different bases. An SIR comparison is always valid for to make two-group (observed-to-expected) comparison but using SIRs to compare multiple groups can be problematic. Although, the frequency with which biased inference results from comparing multiple SIRs may be low but, given that it appears that direct standardization can be done with these data, I would recommend going that route or using a Poisson regression model to adjust.
COMPULSORY REVISION: The main assumption to a person-time analysis like this is independence of censoring and event. I would like the authors to comment on the nature of the practices that join the GPRD late or who drop out early, as it is these practices that will contribute a disproportionate number of censored observations. Is there any reason to suspect that these would be more or less likely to diagnose children with ASDs?

DISCRETIONARY REVISION: Observations here are not completely independent – there is clustering by participating practice. Do the authors have a rationale for ignoring this clustering in the analyses?

*Are the data sound and well-controlled?

The GPRD autism data have some inherent limitations. However, the authors are well aware of these and have made reasonable efforts to assess the influence data quality concerns might have on their analyses.

*Does the manuscript adhere to the relevant standards for reporting and data deposition?

I believe so – although I admit that I might not understanding completely what needs to be considered when addressing this question.

*Are the discussions and conclusions well balanced and accurately supported by the data?

I have a number of comments regarding the Discussion and Conclusion. These follow…

The authors, in their discussion, mention a previously published analysis using the General Practitioner Database, Kaye et al., 2001 [reference 21], and remark on limitations of that earlier paper. I agree with the authors’ assessment of the differences between the approach used in the earlier paper and that used in their manuscript but, at the same time, I am not at all shocked that the author’s analysis essentially confirmed that seen in the earlier paper. In other words, although the two papers differ in nontrivial ways, given these, a priori, I would still not expect findings to differ. That said, I think it is still a contribution to have the findings from this larger sample published.

One smaller point with regard to the discussion of Kaye et al., 2001…. When comparing their work to that of Kaye et al., 2001, the authors note that the two papers were motivated differently, with Kaye et al. looking at secular trends in autism prevalence in the context of the vaccine controversy. However, I think it is a bit misleading to say that these papers “asked different questions” (page 12). Kaye et al., 2001, basically asked the same question (Is prevalence rising?) but then added a follow-up question (Is the rise in prevalence correlated to secular trends in the proportion of birth cohort members receiving MMR?) and went on to make broader interpretations of findings. DISCRETIONARY REVISION: I think the authors should revise their statement about the two papers “asking different questions.”

Although the authors cite the Kaye et al., 2001, paper they do not cite two later publications by that same group that added to this earlier work with the GPRD data to look at autism prevalence. These are:


COMPULSORY REVISION: I think the authors should cite and discuss this work. Adding these other papers is important because in the Jick and Kaye, 2003 paper diagnostic substitution bias is suggested. In that paper Jick and Kaye report that trends in prevalence of other new occurrences of other developmental delay diagnoses without autism decreased markedly over the same period of time that new occurrences of autism diagnoses were increasing. Given the familiarity of the authors of the manuscript now under review with the GPRD, I think it would be a valuable contribution to have them comment on Jick and Kaye’s findings.

DISCRETIONARY REVISION: Depending on what the authors’ feel about the value of Jick and Kaye’s, 2001 approach, it might be informative for the analysis with regard to other diagnoses to be replicated in the sample at hand.

I feel that the discussion section underemphasizes the potential role of the shift in database diagnostic coding systems in the mid-1990s. Not only was there no code for Aspergers in the earlier system it appears as if there was no code for PDDNOS. Further, the new system includes 23 separate codes the authors considered “autism” while the earlier coding system included just two (“autism” and “autistic child”). It seems possible that the shift in coding systems could contribute not only to the growth of other PDD, but also the growth of numbers of cases in the autism category. COMPULSORY REVISION: These impact of the coding system shift should be discussed in more detail.

COMPULSORY REVISION: As no real evidence is presented in this analysis to support the hypothesis that the observed prevalence increase is attributable to ascertainment, the authors should refrain from including in their conclusion unqualified statements like “However, much of the increase is likely due to better ascertainment…” Including this might suggest that the analysis is actually providing evidence supporting this. While many in the field, including myself, suspect that ascertainment issues account for a substantial portion of observed prevalence increases; we still need to be careful in scientific manuscripts to not to let opinion statements appear as if they are summary statements about evidence.

*Do the title and abstract accurately convey what was found?

Yes.

*Is the writing acceptable?

Yes. The paper is nicely written and well-organized.

*Other miscellaneous comments

DISCRETIONARY REVISION: I suggest replacing the last phrase of the last sentence of the first paragraph on page 10 with the following “…unable to assess how often true cases of PDD did not receive a PDD diagnosis recorded (sensitivity).”

DISCRETIONARY REVISION: I found the title to Table 2 slightly confusing, although I understand the authors’ intent. The children in the diagonals are not “the same age in different years” since the diagonals capture the birth cohorts. I would recommend changing the label and the sentence in the text to “…rates among children born in a given birth cohort in different years.”
MINOR ESSENTIAL REVISION: Word choice – page 12 first paragraph – “…patients who emigrate may fail to inform their…”

Which journal?: Appropriate or potentially appropriate for BMC Medicine: an article of importance in its field

What next?: Unable to decide on acceptance or rejection until the authors have responded to the major compulsory revisions

Quality of written English: Acceptable

Statistical review: No

Declaration of competing interests:

None.