Reviewer’s report

Title: A Cross-Sectional Study of Well Water Arsenic and Child IQ in Maine Schoolchildren

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Reviewer: Robert O Wright

Reviewer’s report:

Please number your comments and divide them into:

Overall assessment: This is a large, rigorously conducted study on water As and IQ in school age children in the US. The authors fill a major gap in the literature which is dominated by studies in developing and middle income countries and should be commended. The study is very well conducted. There is only one moderate weakness. A lot of time is spent making arguments for not adjusting for particular variables. To supplement these arguments the authors should show the models adjusted for these variable. This was done for maternal IQ but not for school district. This will strengthen the paper no matter the results. Adjusted and unadjusted models can be shown. Let the reader decide which is most valid.

- Major Compulsory Revisions

1. Authors should explain better why they feel adjusting for several of the covariates leads to “spurious” results rather than being a valid confounding variable. This is repeated in the manuscript for several variables such as mom’s education/intelligence, and school district. On page 11 an example is given that states that because HOME scores are not associated with water As, they are good covariates. But for any confounding variable, association with both the outcome and exposure of interest is the whole reason to adjust. IF you exclude all variables associated with water As, you exclude all potential confounders. The rationale for not adjusting for these variables needs to be better explained.

Did the authors use DAGs to assess the temporal relationship and feel that these were intermediate variables or downstream effects? While you may be right that it is inappropriate to adjust for some of these, the paper would be stronger with a more formal assessment of whether a particular variable is a confounder or not.

The issue gets confusing because model 3 does adjust for maternal IQ and the water As association while mitigated, is still there. It’s not clear why the argument to not adjust for Maternal IQ is being made? On the other hand, no such model with/without school district is presented. Why show one but not the other?

Water As is geospatially distributed and from the data it appears that water As is a marker of school district. What if a better school district does a better job teaching its students, wouldn’t school district be a confounder then? Why would it
be inappropriate to adjust for school district? It is also possible that the relationship is not due to confounding but something else, but the reader should have the option of deciding.

A full presentation with/without school district in the analysis will strengthen the paper and does not mitigate its many strengths or detract from the main findings that water As may be neurotoxic. It would show how rigorous the study is.

2. There is a great deal of interest in nonlinear dose response curves for As. A spline or a lowess function would give the reader a better sense of the shape of the dose response curve than the use of categorical cutpoints.

-Minor Essential Revisions

regarding this section: “Since the 1980’s [38], the field of developmental neurotoxicology has relied upon descriptive models that adjust for other possible contributors to child intelligence, such as maternal intelligence and education. The underlying assumption in that approach is that these known predictors of child intelligence are not associated with exposure.

The underlying assumption for any confounder is that there is an association between the confounder and exposure. The problem with adjusting for maternal IQ is not that there is no association with exposure, but rather that the association with exposure is part of a causal pathway to lower IQ. I think that is a stronger argument for not adjusting than what is written.

I do agree that it may be inappropriate to adjust for maternal intelligence however as it may be part of the overall exposure pathway. In that case there is a pathway relationship between maternal intelligence, arsenic exposure and child intelligence and the model is over fit. I think that argument is valid.

I am not so sure that the same sort of pathway relationship exists for school district however. But if a strong argument can be made for why it is part of a pathway or a downstream consequence the authors would be correct in not adjusting.

Level of interest: An article of outstanding merit and interest in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests