Author's response to reviews

Title: Prenatal Mercury Exposure, Autism, and Developmental Delay, Using Pharmacokinetic Combination of Newborn Blood Concentrations and Questionnaire Data: A Case Control Study

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Version: 6 Date: 25 April 2015

Author's response to reviews: see over
Dr Dr. Grandjean,

We would like to thank the reviewer for his additional comments. The reviewer primarily concerned that the model is not accurately predicting fish mercury concentrations due to imperfect dietary recall. The authors agree that imperfect recall is a source of measurement error and have clearly called this out as a limitation in the manuscript (pages 22 and 25). The authors also agree that the predicted concentrations from our initial model using separate fish types are implausible, which is highlighted in the manuscript (page 21). However, we maintain that the predicted concentration from the final model using combined fish types falls within the plausible range. We have added language clarifying how the estimated fish concentration from the final model compares to other popular fish species, as shown in Table 6 (page 21). We also point out in the manuscript that our estimates are consistent with seafood species lower in mercury, which would be expected in a population advised to consume low mercury seafood (page 22). The reviewer points out this is only hypothesis (and the language in the manuscript reflects this), but it is a hypothesis based on well-publicized clinical guidelines. To provide additional support, we added a sentence summarizing a finding from a recent study that tuna consumption declined during pregnancy relative to the pre-pregnancy period (page 22).

The reviewer also raised concerns regarding the reliability of dietary recall of fish consumption, and references several papers to suggest reliability could be low. The authors are aware that the seafood questionnaire data used in our model is prone to error resulting from imperfect dietary recall and have clearly identified this as a limitation (pages 22 and 25). The most relevant study referenced was by Lucas et al, which showed correlations of 0.3-0.4 between marine food intake and biomarkers for mercury and omega-3 fatty acids. The reviewer argues that these correlations are too low to use dietary recall data in our exposure models; however, we argue these correlations are acceptable, not only because there are other types of errors other than imperfect dietary recall that can reduce the correlations (e.g., pharmacokinetic differences among participants, and temporal variability in exposures), but also because the study was limited to women with relatively low seafood intake.

Finally, the reviewer points out that blood mercury levels vary throughout pregnancy and are not well-represented by a single blood biomarker. The authors agree entirely, and this is one of the motivating factors for combining both the single biomarker and the questionnaire data regarding fish consumption. Maternal blood mercury concentrations have modest correlations across trimesters (0.19-0.63 in the Tsuchiya et al. 2012 study), similar to the correlations for dietary recall, and indicating that the usual approach of assigning prenatal exposure based on a single biomarker measurement is also imperfect. Ideally studies of prenatal exposures would collect repeated biomarker measurements throughout pregnancy, but in the absence of such data epidemiologists...
believe it is best to move forward with the imperfect (yet informative) data at hand. Using a single biomarker alone would have serious limitations, as would using dietary questionnaire data alone. By the combining both the biomarker and questionnaire data, the exposure estimates should be improved if the dietary recall estimates are reasonably reliable. We added the following sentences to more clearly summarize these considerations (p. 22):

“In some settings errors in dietary recall could be worse than the repeat reliability of a biomarker, in which case our methods might harm rather than improve the accuracy of exposure assignment compared to using a single biomarker alone. We suspected that might be the case for our analysis based on separate consumption rates for different fish types, which is why we combined the fish types for our final model.”

Overall, we recognize that the method described makes simplifying assumptions and relies on data that have various limitations, but we believe that these limitations have been thoroughly and clearly articulated so that readers are aware of the potential sources of error and can make their own judgments about the suitability of this method in a variety of contexts.

Sincerely,
Stephen McKeen