

Author response to SHS & AB re: Ahlqvist et al.

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We appreciate SHS & AB's interest in our work, especially since we were inspired by their review on the topic¹ — and the reactions to their conclusions by experts on the topic²⁻⁵. The call for more detailed investigations into the question, using methods more robust to confounding, largely justifies several of our analyses. Conducting the largest analysis on the topic, and employing several different types of analysis, including but not limited to comparisons of full siblings, led us to conclude that there appears to be no causal link between acetaminophen and children's risk of autism, ADHD, or intellectual disability — which contrasts the conclusions that SHS & AB have drawn from previous literature.

We agree with SHS & AB, however, that measurement error may bias estimates towards the null under the assumption that the sample size is infinite, the error is nondifferential across all other measured and unmeasured factors, the exposure is binary, and there are no other biases whatsoever^{6,7}. However, as we describe in the study, if this were the case, we cannot explain why we would find similar estimates in our unadjusted analysis as those reported by previous studies.

We do not necessarily agree that our estimate of acetaminophen use is a severe underestimate, since it aligns with cohort data from both Sweden⁸ and Denmark⁹. However, we agree that some studies, such as those enrolling individuals with indications/preference for acetaminophen, have reported higher use (including the SELMA study¹⁰, as reported on by SHS¹¹, which was enriched for asthma/allergies—among which acetaminophen is often preferred in fear of reactions to nonsteroidal anti-inflammatory drugs). We also note that in Sweden, and Scandinavia in general, recommendations suggest that childbearing individuals should avoid painkillers unless necessary—resulting in lower than the global average estimates. For example, in the Copenhagen Pregnancy Cohort, 37% reported acetaminophen use in the 3 months prior to pregnancy, which dropped to 6% in the first trimester⁹, likely reflecting compliance with such recommendations. The lower use in Scandinavia should, however, be considered when transporting our findings to settings wherein the use may be more widespread.

Sibling-comparisons remain an invaluable method when studying early-life risk factors for neurodevelopmental conditions¹², as confounding has often been a key concern of such studies. However, as SHS & AB point out, some biases may be more pronounced in sibling-controls, and therefore one should not immediately conclude that nullification of results in sibling-control analysis is because it accounts for more confounding. It may, for example, be that measurement error is inflated in sibling analysis as only those classified as exposure and outcome discordant (possibly incorrectly so) fully contribute to the within-family estimate. As reported in our study, we performed a quantitative bias analysis to gauge the impact of exposure misclassification on the attenuation, leading us to conclude that even if most birthing parents incorrectly reported their use of acetaminophen, it would not explain the attenuation we observed in sibling comparisons.

Nonetheless, if SHS & AB are uncomfortable with the assumptions of sibling comparisons, then they may instead focus on the full cohort analysis, where we find a small difference after accounting for confounders. However, even after accounting for a wide range of confounders, it seems possible that such analysis would be affected by unmeasured or residual confounding – as the study is observational by nature, and even a small amount of confounding may fully eliminate this safety signal (i.e., an E-value of 1.28 for the associations with autism).

All in all, the findings from analysis of both 2.5 million children and 1.7 million full siblings support the position of most domain experts²⁻⁵; we find little evidence in support of a causal effect of acetaminophen use in pregnancy on children's neurodevelopmental outcomes. However, as (all?) pregnancy recommendations outline, and as SHS & AB have echoed, caution is always warranted when using drugs in pregnancy, and childbearing individuals are advised to ask their clinician if they experience symptoms or discomfort that may require treatment – even if there are limited reasons to believe that a treatment would be harmful.

References

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