

Response to Transmitter on Ahlqvist et al. APAP and neurodevelopment Cohort Study

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Several recent human epidemiologic studies suggest a link between acetaminophen (paracetamol) use during pregnancy and an increased risk of neurodevelopmental disorders in offspring, such as autism, ADHD, and intellectual disability. There are, however, concerns that these associations might not stem directly from acetaminophen use during pregnancy but may be the result of confounding by other factors, such as indication for use (the reason the acetaminophen was taken), parental health or genetic predisposition.

Ahlqvist and colleagues sought to “examine the associations of acetaminophen use during pregnancy with children’s risk of autism, ADHD, and intellectual disability” using a Swedish nationwide sample of 2,480,797 pregnancies from 1995 to 2019. This large study utilized clinical neurodevelopmental diagnoses and sibling comparisons to minimize confounding. They find that; “Acetaminophen use during pregnancy was not associated with children’s risk of autism, ADHD, or intellectual disability in sibling control analysis” and conclude that “associations observed in other models were attributable to familial confounding”. We disagree. While their findings suggest that the observed associations may not have been directly caused by acetaminophen use during pregnancy, we believe that the study’s limitations prevent it from providing conclusive evidence on causality.

The first important limitation of this study is the low reported usage of acetaminophen by pregnant women; 7.5%. This figure is far lower than what is reported in studies around the world. The global literature supports the conclusion that approximately 50% of women use acetaminophen at some point in their pregnancy.¹⁻⁴ Even within Sweden, several studies have reported acetaminophen exposure rates of over 50%, including studies that used biomarkers to verify exposure.⁵⁻⁸ As is well known, this exposure misclassification –unless it depended heavily on the outcome under study, which is not supported by the data–, would bias results toward the null, or “no effect”.⁹

This study uses a sibling-controlled design, where pairs of matched siblings discordant on exposure are used to further control for unobserved familial genetic and environmental confounding. If there is a causal effect, the acetaminophen-exposed sibling would be expected to have a higher risk of developing ADHD, for example, than the unexposed sibling. If the association is mainly explained by familial confounding factors, the ADHD risk should be similar in the two siblings. If the ADHD risk estimate is higher in the full cohort than the sibling analysis this would also suggest familial confounding. We have two concerns about the use of sibling-controlled analyses. The first relates to the use of sibling controls in a study with a high rate of exposure misclassification, as such measurement error has been shown to attenuate the association among discordant siblings even more than in the full cohort.^{10,11} This bias would make it difficult to draw any firm conclusions between the sibling-pair estimate and that derived from the full cohort.

Our second concern is that covariate control in a sibling control analysis may increase rather than reduce bias. It has been demonstrated that the sibling-control design eliminates the impact of shared family factors that operate as confounders but also eliminates family factors that operate as mediators.¹² While controlling for confounders is desirable, controlling for mediators may introduce bias.¹² A confounder is a third variable that influences both the exposure and disease outcome of interest and makes them seem related when they are not. It must not be affected by the exposure or the disease and cannot be an intermediate step on the causal pathway or chain of events between the exposure and disease.¹³ In contrast, a mediator lies on the causal pathway, is part of the chain of events and helps explain the underlying mechanism or process by which the exposure influences the disease outcome.¹⁴ Experimental studies have identified biologic mediators of the effects of prenatal acetaminophen on ADHD and autism that may cluster within families, these include endocrine disrupting effects, increased oxidative stress, and alterations in the prostaglandin and endocannabinoid systems.¹⁵⁻²² Taken together, this suggests the sibling control design might introduce rather than reduce bias.

Considering these limitations, we urge caution in interpreting the study's conclusions regarding the causal relationship between acetaminophen use during pregnancy and neurodevelopmental disorders.

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