Letters

COMMENT & RESPONSE

In Reply We are thankful for Dr Cramer's keen interest in our publication,[1] in which we concluded there appears to be no causal link between use of acetaminophen during pregnancy and the risk of autism, ADHD, or intellectual disability in children. Dr Cramer raises several points, many of which we have addressed in another correspondence,[2] which we believe deserve some contextualization.

First, as pointed out by O'Sullivan et al,[3] high exposure prevalences of acetaminophen use (eg, approximately 50%) may not accurately represent what we would typically define as "users"; such high prevalences more likely reflect sporadic single exposure during pregnancy. Consider the NINFEA (Nascita e INFanzia: gli Effetti dell'Ambiente) cohort of pregnant persons in Italy, where 31% reported some sporadic first-trimester acetaminophen use, but this use dropped to 5.5% if one instead defined "users" as those using acetaminophen for a minimum of 5 days during the first trimester.[4] Neglecting this context may lead to an exaggeration of perceived population prevalence and the associated public health risks.

We utilized maternal self-reports of drug use (both over-the-counter and prescription) and supplemented this information with prescription dispensation records. Analysis using data from either source indicated that 7.5% of pregnancies involved some acetaminophen use. This is consistent with previous reports, as discussed in our supplement.[1] The supplement[1] also discusses Nordic recommendations to minimize drug use during pregnancy. For instance, in the Copenhagen Pregnancy Cohort, 37% reported acetaminophen use in the 3 months prior to pregnancy, decreasing to 6% in the first trimester. Nevertheless, if we assume there is severe measurement error and therefore bias toward the null, as implied by Cramer, we cannot reconcile this percentage with the crude results. The previous largest study of acetaminophen and autism reported a crude hazard ratio of 1.22, while we reported a crude hazard ratio of 1.26. In other words, our study does not appear to be biased toward the null by measurement error in the exposure.

Sibling comparisons are an invaluable method for disentangling environmental risk from familial confounding. However, as Dr Cramer points out, nonshared confounding may be inflated in sibling analysis compared with cohort analysis, which is why we adjust for all measured time-varying confounders such as fevers and infections in the sibling analysis.

As Dr Cramer suggests, it may be worth emphasizing that our study has not examined all possible safety outcomes; rather, we focused solely on autism, ADHD, and intellectual disability. Because of the potential for confounding to explain associations of acetaminophen and other outcomes such as asthma,[4] we encourage future studies of other outcomes to adopt analytical strategies similar to ours.

The findings from our analysis of 2.5 million children and 1.7 million full siblings align with the consensus among most domain experts[3,5,6]; we find little evidence supporting a causal effect of acetaminophen use during pregnancy on autism, ADHD, or intellectual disability. However, as all pregnancy recommendations emphasize, caution is warranted when using any drugs during pregnancy and individuals expecting children are advised to consult their clinician, even if there are limited reasons to believe that a treatment would be harmful.

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