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LETTER TO THE EDITOR

Pledging my time: In utero exposure to acetaminophen and childhood neurodevelopment

Dear editor,

In the recent issue of PPE, Ricci et al.[1] present a systematic review and meta-analysis on in utero exposure to acetaminophen and childhood ADHD and ASD. It is a technically well designed and meticulous meta-analysis. It is well written with many appropriate considerations on limitations and cautiousness with respect to interpretation. Despite many similar papers in recent years, it is also a justifiable updated analysis given some new datasets. Unfortunately, I also believe that the authors do not address several major principal and paper-specific issues to a necessary extent.[2,3]

1. Hereditability of ADHD/ASD and the lack of or poor confounder control for almost all the papers included in the meta-analysis. The authors quote 'maternal migraine and fewer' as important confounders from the excellent bias analysis paper by Marsawa et al.[4] Upon adjustment for parental ADHD and ASD, these apparent associations were substantially attenuated.
2. This meta-analysis only in passing mentions heritability and confounding by parental ADHD/ASD.
3. Major methodological issues with, especially, Ji 2000,[3,5] but also some of the other papers included.
4. A major point of the very good paper by Ystrom[6] paper is not discussed. Preconceptional paternal exposure yielded similar associations as did maternal exposure during pregnancy. This is important as it substantiates the existence of a common denominator in the form of environmental and/or heritable factors.

The evolvement and use of systematic tools and guidelines to assess the quality and bias in observational research are an important progress. But sometimes, these tools do not suffice to evaluate the inherent quality of a study, i.e. according to the authors, the quality and risk of bias assessment of the Li 2000 paper qualify this for the meta-analysis. I flag this paper for severe selection bias to an extent that it does not hold any external validity and forcing these data through the meta-analysis funnel will not advance science, help our understanding of the issue or provide a fair or meaningful presentation. Other methodological issues reveal themselves below the surface of the GRADE, STROBE, PRISMA, SWiM and SAQOR tools. I encourage the authors to revisit the paper by Ji et al in detail and address these questions:

a. Why did every (996 of 996) single umbilical sample contain acetaminophen?
b. What comprises the control group in this study?
c. How is the author construct 'acetaminophen burden', essential to exposure stratification, validated?
d. To what extent is parental ADHD or ASD controlled for?
e. What are the consequences to the external validity of the study when the incidence of ADHD/ASD and combinations thereof is about 37% among all follow-ups, and only 33% were not assigned a 'developmental disability' diagnosis?
f. How many women received acetaminophen as an analgetic during birth?
g. In these cases, are umbilical cord acetaminophen concentrations meaningful or plausible in the context of childhood neurodevelopment?

I have no issues with different positions on the evaluation and synthesis of scientific papers. But it is important to address pivotal studies beyond the screening tools, especially on controversial issues.

CONFLICT OF INTEREST STATEMENT

The author declares no conflicts of interest.

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