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Published in:
American Journal of Epidemiology

DOI:
10.1093/aje/kwy202

Publication date:
2018

Document version
Peer reviewed version

Citation for published version (APA):
Letter to the Editor

Like a Rolling Stone: Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder.

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To the Editor

Like a Rolling Stone: Prenatal Exposure to Acetaminophen and Risk for Attention Deficit Hyperactivity Disorder and Autistic Spectrum Disorder.

I read with interest the systematic review and metaanalysis by Marsawa et al. on attention deficit hyperactivity disorder (ADHD), autistic spectrum disorder (ASD) and “hyperactivity symptoms” following in utero exposure to acetaminophen (1). I strongly applaud the authors call for more robust and validated outcome tools to study childhood neurodevelopment following in utero exposure to drugs. While perhaps not a complete unknown, the issue of acetaminophen during pregnancy and childhood neurodevelopment remain controversial and contested (2–5). An important contribution to our understanding of this subject was provided in a recent study (6). Ystrom and colleagues reported comparable weak signals for the risk of ADHD following maternal in utero exposure and paternal preconception acetaminophen exposure. This very important point, which should force the epidemiologically minded community to revisit the issue of causality and confounding on this matter, is not discussed by the authors of the present systematic review (1).

I challenge the decision to subject the studies selected for the systematic review to a meta-analysis, much less a meta-regression, approach. The authors state accurately, in their paragraph on study limitations, that assessments of the principal outcome variables as well as exposure are very heterogenous and subject to bias and confounding in the underlying studies. This describes a situation where the characteristics of the underlying data should discourage a meta-analysis approach for observational studies (7), hence the quite predictable and revealing $I^2$ values of 72, 14 and 92% for ADHD, ASD and “hyperactivity symptoms”, respectively. The apparent low heterogeneity for ASD is unsurprising given that this diagnosis carries a strong degree of heritability of 83-90% (8,9).

I find it inconsequential to 1) list a seemingly insurmountable obstacle of limitations, not least assessment of the primary outcome parameter of interest, which mitigate the findings of the underlying studies 2) state
appropriate substantial reservations with respect to interpretations of study findings and call for more research on the validity of the principal outcome parameters 3) yet perform a meta-analysis which forces these fundamentally incomparable data through the same rabbit hole. I believe the meta-analysis approach is inappropriate given the data at hand and the application thereof is more likely to have produced potential harmful statistical noise rather than contributed to a meaningful elucidation of the scientific questions posed.

Finally, the authors cite “...recent alarming evidence on the teratogenicity of acetaminophen...” in the section on implications for policy and practice. This is an exceptional and unnecessarily opinioned statement with substantial implications to healthcare professionals and pregnant women in pain. I am unaware of such “...recent alarming evidence on the teratogenicity of acetaminophen...” relevant to the clinical use of acetaminophen in pregnant women. The statement is not referenced and is not supported by any “evidence” that the authors bring forward in their paper. It is a necessity that this explicit and - I assume - deliberate choice of words be substantiated, appropriately referenced and justified by the authors.

References


