

HOT TOPIC

Disease of Conceit: Acetaminophen in Pregnancy and Neurodevelopmental Disorders

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A very recent review paper on the use of acetaminophen in pregnancy and the risk of adverse childhood neurodevelopment [1] has been given substantial attention among academic and clinical experts in the domain, in news media, in public and among policymakers.

This manuscript is now being directly quoted by the US Health Authorities [<https://youtu.be/YinEMgW-0Uc?si=JVUBM2PWhlPeLsiq&t=1408>; Accessed October 24, 2025] as a main justification to support an upcoming label change on the use of acetaminophen in pregnancy. Changes have already been implemented on the US CDC page [<https://www.cdc.gov/medicine-and-pregnancy/about/>; Accessed October 25, 2025]. The paper has subsequently been accessed more than 850 000 times, and while empirical evidence tells me that the lid on Pandora's Box cannot be put back, I refuse to let this stand unopposed.

The question of acetaminophen in pregnancy and childhood neurodevelopment, especially ASD and attention deficit hyperactivity disorder (ADHD), has remained a controversy for more than a decade. It is a shame then, that the paper by Prada et al. does not make any effort to reflect this or frame the presence of different positions that are widely documented [1]. Despite the authors' statements on scientific integrity, gold-standard framework and rigorous approach, the math does not check out. Most of these studies have been subject to critical peer commentaries, and the superficially substantiated position of the authors does not change the fact that most of these are severely hampered by methodological issues [2, 3]. My main points are:

1. A main issue with this 'review' is the application of the methodology itself. Surprisingly, the authors make no specific reference to the methodological framework but I assume they are referring to Woodruff et al. [4]. Unfortunately, the process in this manuscript compares poorly to the described method therein. I shall keep to major points here. From the Guideline:

Standardized and transparent documentation including expert judgment. Systematic reviews are not 'automated' or 'computerized' or otherwise conducted without applying judgment. The fundamental shift from existing methods of expert review in environmental health science is that *each step of the Navigation Guide is conducted in a thorough, consistent, and transparent manner, and all information, including judgments, is documented and displayed in the same way.* In short, the rationale for a decision is traceable, reproducible, and comprehensible.

Despite the reassuring words from Prada et al., few of these recommendations can be followed through the current manuscript. Of particular concern are the authors' untraceable judgements. Although a scoring sheet is provided, the rationale underlying each assigned score is not specified and should be articulated with greater specificity. Of all confounders listed,

the most important is missing. Accounting for parental disease is pivotal as ASD and ADHD have a very high degree of heritability. The authors nonchalantly dismiss an important point on accuracy of outcome measurements as they argue in favour of diagnoses assigned by proxy of questionnaires: *'While studies used different scales to assess ADHD in the offspring, and some of them relied on parental reports only, this pattern reflects real-life research..'* This is not a serious argument, and it does not make such questionnaire-based scoring systems valid for assigning a diagnosis of ASD or ADHD. I encourage the authors to visit the American Academy of Paediatrics diagnostic guidelines on ADHD and ASD. According to these guidelines, questionnaire-based tools are important, but they are primarily tools to identify children at risk. A definite diagnosis should be made by a primary care clinician or a specialist following individual assessment. It is important to screen for underlying causes and comorbidity such as anxiety, depression and sleep apnea [5, 6].

2. The authors invent a Likert-scale scoring system on the fly.

The framework has absolutely nothing on assigning numerical values to the itemized domain judgements, much less calculating averages of such assigned values. The latter is not in alignment with fundamentals of descriptive statistics to characterize data on an ordinal scale. What makes for an allocated score of -1? Who assigned this? Based on what? Despite framework claims of transparency there is little of such. We are not being told why the authors assign their different values to biases and on top of that they seem to invent an 'expert opinion' quantitative quality score as they go.

3. I challenge the author's contextual framing of 'biomarker exposure' and the significance thereof. The authors suggest that such measurement of exposure is objective and, consequently, these papers carry a substantial weight in the narrative summation and synthesis of the evidence. Umbilical cord- or meconium-based measurements of acetaminophen and metabolites are typically related to perinatal analgesic pain relief [7, 8], and the elimination half-life of acetaminophen and its metabolites are short. The authors implicitly suggest a plausible causal role of 1–4 single doses of acetaminophen administered in relation to delivery be relevant to CNS in utero and childhood neurodevelopment. This is counterintuitive as well as unsubstantiated.

4. The authors misrepresent an important reference. The reference by Masawa et al. in the reference list [9] is not the meta-analysis which is referenced in the text. The text cites results from a *previous* meta-analysis by Masarwa et al. [10] while the paper in the reference list is a much better reexamination of the studies from the meta-analysis. In *this* referenced paper, Masawa et al. apply a quantitative bias-analysis to account for—among other things—parental disease [9]. This approach strongly attenuates the results that the authors are citing here. This may be lack of attention. But it is *not* trivial, and this does not instal confidence to the meticulousness of the paper.

5. The authors include duplicate datasets for the assessment of ADHD (Table 4). This is particular to the studies by Yström [11] and Gustavsson [12]. These are from an identical dataset from the Norwegian MoBa-cohort only with a longer

follow-up for the latter. The Gustavsson paper reported null associations across various approaches with adjusted Hazard Ratios, stratified by duration of exposure, from 0.75 to 1.06 with fair precision and confidence intervals including unity. Of significant interest, the weak signal for an increased risk of ADHD (adjusted Hazard Ratio for any use 1.12; CI 1.02–1.24) reported in the Yström paper was also found for *paternal* exposure (adjusted Hazard Ratio 1.27; CI 1.08–1.24) prior to conception. This instantly raises a hypothesis of shared confounders such as heritability and familial circumstances.

6. For the 7 papers on ASD (Table 6), the paper cited by Alemany [13] is a meta-analysis and cannot be counted by the authors' own methodological assumptions. It includes the same Table 6 data as reported by Liew et al. [14] and Leppert et al. [15]. For the 6 individual papers, only three of them use a formal diagnosis assigned by a physician or a trained health-care professional [7, 14, 16] and others use inadequate proxy assessments. Commendably, two of these are appropriately flagged by the authors for high risk of bias [15, 17].

7. The authors misrepresent their own findings. From the 'ASD' heading, page 28: 'The reviewed studies consistently reported a positive association between prenatal acetaminophen use and ASD,..'. This 'consistently' is false. By their own table 2 (my opinion on the merits of the various papers notwithstanding) there are 8 studies (splitting the Ahlqvist study). Positive associations: Ahlqvist (overall); Alemany; Ji; Avella-Garcia; Liew. Null associations: Ahlqvist (sibling); Leppert; Saunders. By a simple count this makes for a 5–3 score which hardly qualifies as 'consistent'. Subtracting the Alemany reference, yields a very non-consistent 4–3 score.

8. The authors make a sustained effort to discredit the study by Ahlqvist et al. [16]. This is, effortlessly, the largest study of this kind and the ONLY study with population-wide data. The authors challenge the fundamentals of data collection in the Swedish midwife data-collection system where 98% of mothers get a visit within the first 12 weeks after birth and is systematically asked of medication use. Yes, some mothers asked may not see acetaminophen OTC as a medication, but the vast majority will. I dare the authors to point to a better dataset with population coverage of OTC drugs used in pregnancy [<https://www.socialstyrelsen.se/globalassets/share-point-dokument/dokument-webb/ovrigt/production-and-quality-mfr.pdf>; accessed October 24, 2025]. The point that sibling-studies are not without inherent methodological challenges is fair game. But this methodology has certainly value in terms of addressing familial and hereditary factors, both of which are important. The issue of low exposure rate and risk of exposure misclassification have been addressed by Ahlqvist [18] several times over [<https://www.thetransmitter.org/wp-content/uploads/2024/04/Author-response-to-SHS-AB.pdf>; accessed October 24, 2025], apparently eluding the authors. There is no specific reason to assume non-differential exposure misclassification and the direction of an ensuing 'true' point estimate is not clear.

9. The authors praise the study by Ji et al. [7] on their use of 'biomarker' exposure and assigns it the lowest risk of bias score, the highest 'Strength of Evidence' and the highest 'Expert Opinion Score'. I strongly disagree:

- APAP and/or metabolites were detected in 996/996 umbilical cord samples. I strongly question the validity of a 100% exposure rate. It is not stated how many of these mothers were given acetaminophen in direct relation to delivery. This may explain a 100% exposure rate but also nullifies any meaningful inferential analysis as the Bayesian prior value in such case is zero.
- In a different and independent sample of 810 patients from *the same* Boston Birth Cohort, acetaminophen and/or its primary metabolites were only detected in 29% of umbilical cords [19]. This discrepancy severely challenges the 100% exposure rate reported by Ji et al. [7].
- The 'APAP burden' used to stratify levels of exposure in tertiles is not validated. Actual levels of APAP and metabolites are not presented.
- The potential issue of sample stability is not discussed even though some samples had been stored for up to 20 years.
- Children in the cohort had extraordinarily high prevalences of neurodevelopmental disorders. 365/996 children (37%) were diagnosed with ADHD and/or ASD and just 327/996 (33%) children were NOT assigned a 'developmental disability' diagnosis. This is indicative of extreme selection bias.
- Parental ADHD/ASD was not sufficiently addressed

Based on the above points this study has no external validity and faces serious internal credibility challenges as well. Referencing an external framework for quality assessment does not absolve the authors from assessing the merits and validity of the study in context of the research question at hand.

10. Despite appropriately discharging the argumentation in the introduction the authors, inconsequentially, bring on the ecological fallacy argument in their conclusion: more acetaminophen consumed, more with ASD diagnosed. This is a fundamentally faulty argument.
11. COIs. These are *clearly* insufficiently detailed. I shall spare the readers the details, but refer to the Schachtman breakdown [<https://schachtmanlaw.com/2025/09/09/acetaminophen-autism-prada-review-misleadingly-claims-to-be-nih-funded/>; accessed October 24, 2025] and the New York Times [<https://www.nytimes.com/2025/09/23/health/harvard-dean-autism-tylenol-lawsuits-payment.html>; accessed October 24, 2025]. The self-clearing statement from Dr. Baccarelli is misconceived and inappropriate. List the specific 'expert witness' consultancies and the specific fees received. I am confident that readers are capable of processing this information in context.
12. Funding: This is a misrepresentation. This study was NOT funded by the NIH. [<https://schachtmanlaw.com/2025/09/09/acetaminophen-autism-prada-review-misleadingly-claims-to-be-nih-funded/>; Accessed October 24, 2025].

In summary, this manuscript is erroneous and internally inconsistent on pivotal issues. Consequently, it is misleading and forms an inappropriate substantiation for policy-making decisions.

Post-scriptum: a very recent Japanese population-based study found no association between acetaminophen in pregnancy and childhood ASD (propensity-score adjusted HR 1.06 [CI 0.98–1.15]; sibling design HR 0.85 [0.64–1.13]) [20].

Conflicts of Interest

The author declares no conflicts of interest.

Data Availability Statement

Data sharing not applicable to this article as no datasets were generated or analysed during the current study.

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