EDITORIAL

Acetaminophen and Neurodevelopmental Risk: A Commentary on Confounding, Causality, and Methodological Approaches

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In response to growing public concern about drug safety during pregnancy, acetaminophen use has become a focal point in clinical discussions. Renewed attention from health authorities and public figures—including statements by President Trump emphasizing the importance of maternal and child health—led the U.S. Food and Drug Administration (FDA) to issue a notice on September 22, 2025.[1] This advisory, attributed to Commissioner McCurry, urges physicians to limit the use of acetaminophen for mild fevers and to consider non-pharmacological alternatives when appropriate. In light of these developments, researchers have revisited studies dating back a decade to explore the origins of this concern. However, the issue has become increasingly politicized. During a press conference in November 2025, President Trump publicly questioned his Secretary of Health about whether he had altered his stance on acetaminophen use, as reported in the media. Such politicization risks compromising the objectivity and scientific rigor required to accurately assess the potential causal relationship between prenatal acetaminophen exposure and neurodevelopmental disorders in children.

The question of whether prenatal acetaminophen use contributes to neurodevelopmental disorders such as attention-deficit/hyperactivity disorder (ADHD) and autism spectrum disorder (ASD) has caused strong debate among scientists. Several studies offer complementary insights into this complex issue, using diverse methods to test whether the observed link is causal or confounded.

In his article *"Overdosing on Tylenol While Pregnant,"* Jeffrey Dach presents a critical examination of acetaminophen, arguing that its widespread use, especially during pregnancy, may carry underappreciated risks.[2] Drawing from scientific studies, clinical data, and public discourse, Dach builds a case that acetaminophen is not as benign as commonly believed. He aligns with a growing body of research suggesting links between prenatal exposure and serious outcomes such as liver toxicity, neurodevelopmental disorders, and impaired antioxidant defenses.

While some claims are grounded in peer-reviewed literature, others reflect Dach's speculative interpretations, particularly when connecting acetaminophen to maternal immune activation. Overall, his direction is clear: he agrees with and actively promotes the view that acetaminophen poses significant side effects and advocates for greater caution in its use, especially among pregnant individuals.

One of the strengths of the article is its attention to the specific metabolite of acetaminophen, *N* acetyl-p-benzoquinone imine (NAPQI), and its role in the pregnant body and developing fetus, which is essential for scientifically explaining the drug's potential impact.

Dach explains that acetaminophen overdose is a leading cause of liver failure in the U.S., citing data from the Centers for Disease Control and Prevention (CDC) and medical literature. The mechanism involves the formation of NAPQI, a toxic metabolite that depletes glutathione and causes liver necrosis. The antidote, *N* acetylcysteine (NAC), is well-established in clinical practice and supported by toxicology research.

The article cites a 2025 meta-analysis led by Dr. Andrea Baccarelli, which reviewed 46 studies and found that most showed a positive association between prenatal acetaminophen use and neurodevelopmental disorders. This analysis, published in a reputable journal, adds weight to concerns about acetaminophen safety during pregnancy.

Dach discusses research showing that many children with autism have autoantibodies that block folate transport into the brain. He references studies by Dr. Quadros and Dr. Frye (2013), published in peer-reviewed journals, which support the use of activated folate (Leucovorin) to improve symptoms in affected children.

He also introduces a speculative hypothesis combining two known biological processes: maternal immune activation and glutathione depletion caused by acetaminophen. While maternal immune activation, triggered by fever, infection, or vaccination, is well-supported in scientific literature, the idea that Acetaminophen's impact on glutathione levels could

amplify this immune response and lead to fetal brain inflammation remains not confirmed by large-scale studies and remains theoretical.

Dach recommends natural anti-inflammatory agents such as curcumin, boswellia, omega-3s, white willow bark, CBD oil, and magnesium. While some of these have supportive evidence in pain management, their safety and efficacy during pregnancy are not universally established.

Prada et al. conducted a comprehensive evaluation using the Navigation Guide methodology to assess the relationship between prenatal acetaminophen use and neurodevelopmental disorders (NDDs), including ADHD and ASD.[2] The authors systematically reviewed 46 human epidemiological studies, of which:

- 27 reported positive associations (significant links to NDDs),
- 9 showed null associations (no significant link),
- 4 indicated negative associations (suggesting protective effects).

The review concluded that the majority of studies support a positive association between acetaminophen exposure during pregnancy and increased risk of NDDs. The strength of evidence was rated as sufficient, and the quality as moderate, indicating a credible link despite limitations in study design and exposure measurement. The authors emphasized biological plausibility, citing mechanisms such as oxidative stress, endocrine disruption, glutathione depletion, and altered neurotransmitter activity. Findings from animal studies and mechanistic data reinforced these conclusions, suggesting that acetaminophen may impair neurodevelopment through multiple pathways.

Importantly, the authors acknowledged the challenges of confounding and exposure misclassification, particularly the reliance on maternal self-reporting. Nevertheless, the consistency of findings across diverse populations and study designs led them to recommend greater caution in the use of acetaminophen during pregnancy. They called for improved exposure assessment, biomarker validation, and further research to clarify causal pathways and inform public health guidance.

Several key studies, such as those by Liew et al. (2016, 2019),[4,5] Ji et al. (2020),[6] Ahlqvist et al. (2024),[7] and others, were included in the systematic review by Prada et al. (2025)[3] and discussed in Dach's (2025)[2] commentary; however, a more detailed examination of their confounding controls, causal inference strategies, and methodological limitations is warranted to fully understand the strength and implications of their findings.

Liew et al., (2016)[5] conducted a prospective cohort study using the Danish National Birth Cohort to investigate the relationship between maternal acetaminophen use during pregnancy and the risk of autism spectrum disorders (ASD) in children. They tracked over 64 000 mother-child pairs and assessed acetaminophen use through prenatal interviews, while ASD diagnoses were obtained from national health registries. The study found a modest association between prenatal acetaminophen use and increased risk of ASD with hyperkinetic symptoms, particularly with long-term use exceeding 28 days. No significant association was found with ASD without hyperkinetic symptoms. To account for potential bias, the researchers adjusted for several confounding factors, including maternal age, education, smoking, alcohol use, psychiatric history, and child sex and birth year. These adjustments aimed to isolate the effect of acetaminophen use from other maternal traits or behaviors. However, the reliance on self-reported exposure introduces potential recall bias, and the possibility of residual confounding remains—especially if the underlying reasons for acetaminophen use, such as fever or infection, are themselves linked to neurodevelopmental outcomes. Additionally, the absence of advanced causal inference methods, such as sibling comparisons or instrumental variable analysis, limits the ability to determine whether the observed associations reflect a true causal relationship. While the findings suggest a possible pregnancy-specific effect, further research is needed to confirm causality and rule out alternative explanations.

A large-scale Swedish study involving 2.4 million children was studied by Ahlqvist et al. (2024).[7] By comparing siblings where only one was exposed to acetaminophen during pregnancy, the researchers aimed to control family-level confounding such as genetics and shared environment. Although initial data showed increased risks for ASD (21%), ADHD (30%), and intellectual disability (ID) (15%) among exposed children, these associations disappeared in sibling comparisons. This suggests that earlier findings may be explained by familial factors rather than a direct effect of acetaminophen. Complementing the findings of Ahlqvist et al. (2024),[7] the *JAMA* article "*Acetaminophen Use in Pregnancy—Study Author Explains the Data*", authored by Kate Schweitzer (2025),[8] revisits the same large-scale analysis led by Lee, who collaborated with Ahlqvist on the research. The article features a discussion between Lee and *JAMA* Deputy Editor Linda Brubaker, MD, MS, and reemphasizes that earlier associations may have been overstated due to methodological limitations. It further aligns the study's conclusions with guidance from major health organizations, including the American College of Obstetricians and Gynecologists (ACOG) and the Society of Obstetricians and Gynaecologists of Canada (SOGC), reaffirming that acetaminophen remains the recommended treatment for pain and fever during pregnancy when used appropriately.

Liew et al. (2019)[4] used a U.S. cohort of nurse mothers and applied a "negative control" approach. They compared acetaminophen use before pregnancy, when it cannot affect fetal development, with use during pregnancy. The study found no link between pre-pregnancy use and ADHD, which supports the idea that the pregnancy-specific link may be real, and not simply due to shared maternal traits or behaviors. However, the study emphasizes that further evidence is needed to confirm a causal relationship.

A biomarker-based approach by measuring acetaminophen levels in umbilical cord blood within a

prospective birth cohort was conducted by Ji et al. (2020).[6] Their findings revealed a strong dose-response relationship: higher acetaminophen levels were associated with increased risks of ADHD and ASD. Importantly, acetaminophen was detectable in all samples, even among mothers who reported low usage. These results support a biological link, though the study lacks sibling comparisons to fully eliminate confounding.

Together, these studies highlight the strengths and limitations of different methodological strategies used to investigate the potential neurodevelopmental risks of prenatal acetaminophen exposure. Prospective cohort studies such as Liew et al. (2016)[5] and the Baccarelli meta-analysis (2025)[2] provide population-level associations and suggest a pregnancy-specific link, though they are limited by potential confounding and reliance on self-reported exposure. Speculative and mechanistic interpretations, as presented by Dach (2025),[2] offer hypotheses about biological pathways—such as glutathione depletion and maternal immune activation—but require empirical validation. Sibling comparisons (Ahlqvist et al., 2024)[7] are powerful for controlling family-level confounding, while biomarker-based studies (Ji et al., 2020)[6] provide precise exposure data but cannot fully account for hidden factors. Negative control designs (Liew et al., 2019)[4] help test whether associations are due to shared maternal behaviors or traits. A systematic review by Prada et al. (2025),[3] using the Navigation Guide methodology, rated the evidence linking prenatal acetaminophen exposure to neurodevelopmental disorders as "sufficient" in strength and "moderate" in quality, reinforcing the need for caution and further mechanistic research.

To strengthen future research, combining biomarker data with sibling comparisons would offer the most reliable evidence. Upcoming studies should aim to:

- Use clinically confirmed diagnoses of ADHD and ASD, rather than relying solely on maternal reports.
- Investigate biological mechanisms through laboratory studies.

Such integrative approaches will be crucial for clarifying the potential risks of prenatal acetaminophen use and guiding public health recommendations.

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