The Journal of Child Psychology and Psychiatry

Journal of Child Psychology and Psychiatry 66:11 (2025), pp 1621–1626 doi:10.1111/jcpp.70064

Editorial: The acetaminophen scare: association vs causation

With high twin concordance and sibling recurrence risk, the influence of genetic factors in the etiology of autism is not disputed. The contribution of environmental risk to the etiology of autism is less well established. While the prevalence increase observed worldwide has fueled beliefs of an epidemic driven by environmental changes, the evidence for such interpretations of the secular change in prevalence is lacking (Fombonne, 2025). In epidemiological surveys, no clustering in time or space has been reported that could point to candidate exposures. Thus, observational (cohort and case–control) studies have been wide-ranging and exploratory rather than hypothesis-driven. In light of growing evidence of atypical development occurring in the first months of life (Dawson et al., 2023), environmental risk research in autism has focused on prenatal or periconceptional exposures. In the last 20 years, a myriad of associations have been reported between autism risk and prenatal exposure to: pesticides, phthalates, air pollutants, maternal fever or infection during pregnancy, inter-pregnancy interval, lack of folic acid supplementation, vitamin D deficiency, maternal diet, advancing parental age, exposure to heavy metals, prenatal exposure to antidepressants, valproic acid, benzodiazepines, acetaminophen, maternal smoking, cannabis or alcohol use during pregnancy, maternal obesity and excessive gestational weight gain, prematurity, low birth weight, maternal immune activation, C-section, use of oxytocin, assisted reproductive technologies, and countless others. With few exceptions (advanced parental age, prenatal exposure to valproic acid), associations have not been replicated, or when they have, their causal nature has not been established. The proliferation of disparate environmental putative 'causes' makes it difficult for practitioners and families to form a reasoned opinion.

Like correlation, association is not causation. Associations between environmental risk factors and autism only represent statistical relationships between variables that must be carefully assessed to determine their causal nature. Nonspecialized readers can be confused in interpreting this literature especially as investigators tend to overemphasize features of their findings that are 'consistent' with a causal relationship (often using the Bradford Hill viewpoints as a framework) albeit not a proof for it. Often, these arguments are purely hypothetical,[1] they depart from the data and study results at hand, and put a spin on the findings that, instead of promoting cautious explanations and entertaining alternative interpretations, unduly elevate their importance. The usual cautionary statements (e.g., 'our observational study cannot establish causality'; 'we cannot exclude residual confounding') are buried at the end of articles in the limitations section, and their message washed out by prior unrestricted speculations on causality. Replication of results may provide a false sense of confidence when adoption of the same research apparatus fails to unmask unforeseen sources of bias inherent to any observational study. Worse, confirmation bias also occurs through a proliferation of low-quality and overlapping meta-analyses that impress with more precise (albeit not more valid) estimates that are not less biased than those of the constituent studies. If input estimates of a meta-analysis are biased, the meta-analytical estimate is too.

If the genetic factors that influence the maternal environment of the fetus are also genetic risk factors for autism, the association between an environmental risk factor and autism risk might be spurious and would attenuate or disappear if shared genetic influences could be adjusted for.

Acetaminophen studies

Among prenatal medication exposures, acetaminophen has been studied (since 1987) in relation to a range of neurodevelopmental outcomes, including autism, ADHD, and intellectual disability. Results have largely been inconsistent, and the causal nature of statistically significant associations has not been established. In fact, reviews by professional organizations have regularly identified methodological weaknesses in studies arguing for a causal link (Damkier et al., 2025). Medical associations have monitored this literature and not changed their guidelines on its use with pregnant women (e.g., ACOG, 2025).

As compared to other medication exposures, the study of acetaminophen is especially difficult. Acetaminophen may be obtained through medical prescriptions but is mostly accessed as an over-the-counter medication. Therefore, estimating the overall exposure of a pregnant woman during pregnancy cannot rely solely on insurance claims or prescriptions databases. Instead, maternal self-reports have been relied upon. Recall for acetaminophen use that can be employed for different

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reasons (fever, pain, headache, migraine) and for variable doses and durations is of questionable accuracy. In fact, most studies could not characterize well the duration of exposure, its precise timing during pregnancy, and the dosage involved. Moreover, outcome assessments have often relied on symptom checklists as opposed to professionally confirmed autism diagnoses. Adjustment on covariates that could confound the association estimate has also been variable across studies. For example, studies have shown that acetaminophen use is raised 2.7 fold among pregnant women with psychiatric disorders (Taagaard et al., 2023), which are independently associated with offspring autism risk; however, adjustment on maternal psychiatric disorders (including autistic traits) has been inconsistent. In addition, a tenet of pharmacoepidemiology is to evaluate if a significant association between drug exposure and an outcome reflects a direct effect of the drug on the developing fetus as opposed to be accounted for by the reason (indication) for which the drug is taken. Evaluating confounding by indication has proved difficult because acetaminophen may be used for mild medical ailments that are not registered in medical records and are easily forgotten by informants. Therefore, most associations can be assumed to remain confounded even after sophisticated statistical adjustment on available measured confounders.

In this context, it came as a surprise that, in order to 'prevent autism', the US HHS Secretary summoned pregnant-to-be women with a new injunction: 'Do not take Tylenol!' The decision was precipitated by a recent review article (Prada, Ritz, Bauer, & Baccarelli, 2025) that requires, therefore, careful re-evaluation.[2]

Following the Navigation Guide Methodology (a modified version of systematic reviews), Prada et al. (2025) evaluated eight autism-acetaminophen associations[3] and rated study features (participant selection, exposure and outcome assessments, confounding, etc.) and overall risk of bias. No quantitative analysis was performed. A very 'low risk of bias' rating was given to four studies supporting a positive association (Alemany et al., 2021; Avella-Garcia et al., 2016; Ji et al., 2020; Liew, Ritz, Virk, & Olsen, 2016) and a 'high risk of bias' rating to the four studies with negative results (Leppert et al., 2019; Saunders, Woodland, & Gander, 2019; Ahlqvist et al., 2024 (twice)). Our own assessment led to very different grades and conclusions.

The first 'low risk of bias' study was, in fact, a meta-analysis of six European cohorts (Alemany et al., 2021) where caregiver-completed screening questionnaires were used to assess outcome (defined as scoring above the screener cut-off). Several studies used the CBCL autism subscale that is notoriously poor at screening for autism (Havdahl, von Tetzchner, Huerta, Lord, & Bishop, 2016). Across studies, the median proportion of high scorers was 7.2%, a figure much higher than diagnosed autism prevalence, indicating that the vast majority of participants with a 'positive' outcome, in fact, did not have autism.[4] In five cohorts, associations were statistically non-significant; the meta-analytical estimate only reached significance due to the last oversized cohort. The second 'low risk of bias' study relied on the CBCL, one of the worst possible outcomes for assessment (Avella-Garcia et al., 2016). In the third study (Ji et al., 2020), exposure was measured only once in the cord blood of 996 infants from the Boston Birth cohort. Given the short half-life of acetaminophen (<3 h) and sampling at the time of delivery, it was not surprising that acetaminophen was detected in *all* participants, preventing an unexposed group from being formed as a referent. The relevance for autism etiology of a brief exposure to the antalgic at the time of delivery is debatable. In the fourth study of the Danish registry (Liew et al., 2016), participation was low (60%), exposure assessment relied on maternal recall through three telephone interviews, and over a third of the sample was excluded for missing complete exposure data. Adjustment for confounders was rudimentary for maternal mental health and absent for common indications of acetaminophen use such as pain, headaches, or migraines. There was no further attempt to detect confounding or control for genetic factors. Thus, upon closer scrutiny and despite the varnish of objectivity provided by quantitative grading of study features, 'low risk of bias' ratings in those four studies were questionable. We also note that some studies were counted twice,[5] raising concern about duplication of the evidence.

Turning to the three 'high risk of bias' studies, one small case–control study with poor ratings was indeed non-contributory due to lack of power and proper analyses, combined with poor exposure and outcome assessment (Saunders et al., 2019). Using the ALSPAC cohort data ($N = 7{,}921$), the second study showed no association between prenatal use of acetaminophen assessed for the 2 halves of pregnancy through maternal self-reports and a diagnosis of autism (relative risk = 0.76; 95% CI: 0.51–1.13) (Leppert et al., 2019). Analyses were adjusted on multiple covariates and for multiple comparisons. Prada et al.'s poor ratings for exposure assessment and confounding appeared unjustified. The third study was a large study of >2.4 million Swedish children born 1995–2019 (Ahlqvist et al., 2024). Acetaminophen exposure was assessed through midwives interviews and prescription records, and analyses were adjusted on a large array of covariates and potential confounders, including many maternal indications for using antalgics. Compared with non-users, women ever using acetaminophen had higher rates of obesity, smoking, history of psychiatric disorders, and indications such as fever, infections, headaches, chronic pain, asthma, rheumatoid

arthritis, and migraine. All these maternal characteristics have been associated with autism risk in independent studies, calling for tight adjustment in modeling associations. The full cohort analyses first showed mild significant increase in the risk for autism in ever-exposed mothers compared with unexposed mothers (hazard ratio (HR) = 1.05; 95% CI: 1.02–1.08).

This study then employed two approaches to further detect confounding in this association. Using comparator antalgics, similarly significant increases in autism risk were found in relation to prenatal use of aspirin, non-steroid anti-inflammatory drugs, opioids and antimigraine drugs, suggesting that the reason for taking antalgics, and not their intrauterine effect, accounted for the association. Second, in order to adjust on unmeasured shared familial confounders, the association was re-estimated in a large sample of sibling pairs (N = 16,267 unique siblings) discordant for both acetaminophen exposure and autism. The association disappeared, was no longer statistically significant, and yielded an estimate <1 (HR = 0.98; 95% CI: 0.93–1.04), showing that shared familial influences accounted for the association observed in the full cohort. Rigorous quantitative bias analyses further established that results were robust to known limitations of sibling comparisons, including carry over effects, exposure under ascertainment and misclassification. Authors concluded 'acetaminophen use during pregnancy was not associated with children's risk of autism in sibling control analysis…' suggesting '…that associations observed in other models may have been attributable to familial confounding'. For several design and analytical features, this study stands as the most informative observational study. The poor ratings for 'risk of bias' and 'strength of the evidence' in Prada's et al. review were therefore stunning and indeed biased.

Prada et al.'s overall conclusion that their review 'demonstrated evidence consistent with an association between exposure to acetaminophen during pregnancy and offspring autism' is unreliable. Their own final admission that 'observational limitations preclude definitive causation' and 'unmeasured or residual confounding remains a potential source of bias' makes it even less comprehensible that this review was pivotal in prompting FDA to make label changes to acetaminophen and alert physicians to its presumed dangerosity.

Of note, another large population-based cohort study was just published that replicated Ahlqvist et al. (2024) findings of no causal association between acetaminophen use during pregnancy and autism (Okubo, Hayakawa, Sugitate, & Nariai, 2025). In a prospective study of 217,602 children born 2005–2022, with 40% of mothers being ever-users of acetaminophen, there was a mild increase in the risk of ASD in offspring (HR = 1.06; 95% CI: 0.98–1.15) in the full cohort analysis. Associations were also estimated for alternative antalgics (aspirin, NSAIDs) and pre- and post-pregnancy exposure periods as negative control exposure. When sibling comparisons were performed (N = 23,593, siblings discordant for exposure), the association disappeared with the point estimate going way below the null value (HR = 0.85; 95% CI: 0.64–1.23) again demonstrating that unmeasured shared familial influences (including genetic factors) confound estimates of associations.

The combined findings of two well-executed population-based large cohort studies converge in showing that acetaminophen-autism associations are not causal.[6] In each, investigators supplemented the full cohort analyses by conducting additional analyses (comparing acetaminophen exposure in pregnancy to comparator drugs or to exposure in periods outside pregnancy; or adjusting on shared familial confounders in sibling comparisons), designed to test the robustness of initial results and refute a premature causal interpretation. These two studies differed for several aspects of their methodology and were conducted in very different populations (likely different for their confounding structure). Nevertheless, estimates of association in the full cohort were shifted towards the null in sibling comparisons, a very telling convergence that speaks to the internal and external validity of sibling comparisons findings. These two studies provide strong and replicated evidence that there is no causal association between acetaminophen and autism.

De-confounding associations

The acetaminophen story has implications for the evaluation of findings of studies investigating all prenatal risk factors in autism. In observational studies, estimates of associations can be biased due to the lack of full comparability of exposed and unexposed groups. Despite the availability of multiple statistical techniques (stratification, matching, restriction, propensity scores, etc.) to reduce confounding, confounding always remains a concern (residual confounding) due to the imperfect measurement of confounders and to unmeasured confounders. There are study designs and analytical steps that investigators can take to detect confounding and bias and thereby refine their causality assessment.

Use of *negative controls* (exposure or outcome) has been helpful in detecting confounding and testing the causal nature of observed associations. *Negative control exposures* are chosen for having no plausible causal biological pathway to the outcome. In drug exposure studies, pre-pregnancy exposure periods can serve as negative control exposures. If associations are comparable in both exposure periods, it suggests that the pregnancy exposure association is spurious and confounded by shared background factors, whether known and measured or not. These

approaches have been contributing to refute or support causality in several autism studies. For example, in SSRI-autism studies, the association between antidepressant use *before* pregnancy was significant and stronger than the non-significant association during pregnancy, ruling out a causal link in the maternal drug–offspring autism relation (Hviid et al., 2013). Conversely, the fact that the association between valproic acid and autism reported during pregnancy was not observed for other anti-epileptic drugs and was nullified among women exposed to VPA *before* but *not during* pregnancy provided more evidence for a true causal effect (Christensen et al., 2013). Contrasting associations estimated from maternal versus paternal exposure during pregnancy is also an efficient approach to detect confounding. When both estimates are comparable, they point at confounding in the maternal exposure association since paternal exposure cannot directly impinge on fetal neurodevelopment, as illustrated for maternal smoking (Langley, Heron, Smith, & Thapar, 2012) or acetaminophen use (Ystrom et al., 2017), this time in relation to ADHD. *Negative control outcomes* may also be informative when, for a given prenatal risk factor, the risk of offspring neurodevelopmental disorder is also examined for a completely different outcome (e.g., appendicectomy) for which no biological pathway exists that could connect it to the exposure. The prediction here is that if an association with autism is valid, none should be observed for the negative control outcome.

Many variables that capture the maternal lifestyle, behavior, or intrauterine environment reflect genetic-environmental correlations and question the environmental nature of observed associations. If the genetic factors that influence the maternal environment of the fetus are also genetic risk factors for autism, the association between an environmental risk factor and autism risk might be spurious and would attenuate or disappear if shared genetic influences could be adjusted for. What looks initially like an environmental effect might not be environmental at all. However, most observational studies on prenatal environmental risk cannot disentangle genetic and environmental effects unless family-based and genetically sensitive designs are employed, as well articulated elsewhere (D'Onofrio, Sjölander, Lahey, Lichtenstein, & Öberg, 2020; Thapar & Rice, 2021). One possible design is to compare, within a cohort, siblings born from the same parents, with one exposed and the other unexposed in their respective pregnancy. Because siblings share 50% of their genes and many family-level environmental factors, the association estimated in sibling pairs discordant for exposure controls for these shared genetic and environmental influences. While sibling comparisons have their own limitations, they are powerful tools to strengthen causality assessment. When a significant association first reported in main cohort analyses comparing unrelated individuals attenuates or disappears in sibling comparisons within the same cohort, the non-causal nature of the association is revealed. The usefulness of sibling comparisons was well illustrated in several autism studies. For example, in a large (N = 668,000) Danish prospective cohort, maternal use of SSRIs during pregnancy was associated with a statistically significant increase of offspring autism risk (HR = 1.6; 95% CI: 1.3–2.0) in the main cohort that disappeared in sibling analyses (HR = 0.9; 95% CI: 0.4–2.0) (Sørensen et al., 2013). In a recent large study of 1.1 million children born 1998–2015, 42 out of 236 maternal health conditions during pregnancy were found to be associated with an increased offspring autism risk (Khachadourian et al., 2025). Most associations attenuated or disappeared in comparisons of discordant sibling pairs. Using a twin sample, obstetric complications were raised among affected twins compared with unaffected twin controls (Gómez-Vallejo et al., 2022); however, unaffected co-twins also had raised obstetric complications compared with controls but did not differ from their affected co-twins. This pattern of results was consistent with the association between obstetric complications and autism reflecting shared familial confounding rather than a causal association.

Sibling comparisons allow controlling for shared genetic liability without obtaining direct measures of genetic susceptibility. With the advances in genetic studies and the more frequent inclusion of DNA collection in cohort studies, maternal genetic liability to autism or other developmental disorders can be measured through polygenic risk scores and their relationship with prenatal environmental variables examined. Interestingly, in one such study set in the ALSPAC cohort (Leppert et al., 2019), maternal genetic liability to ADHD was associated with maternal body mass index, infections, blood levels of mercury and cadmium, and increased use of acetaminophen in late pregnancy. Polygenic risk scores for autism were associated with maternal history of severe depression and rheumatism, stressful life events during pregnancy, and more weakly with pre-eclampsia and low Apgar scores. Similar results were obtained in the MoBa cohort (Havdahl et al., 2022) with autism polygenic risk scores being associated with pregnancy-related risk factors such as lifetime depression, anxiety/depression symptoms, and migraine and urinary tract infections (both indications of acetaminophen). Both sets of results concur with those of discordant sibling pairs analyses in illustrating that associations between neurodevelopmental disorders and pregnancy-related risk factors must be evaluated in the context of genetically informative studies. Adjustment for shared genetic liability should improve with future larger genome-wide association studies of autism and related disorders that will augment the accuracy

of polygenic risk scores and with methods more fully accounting for genetic liability.

The two recent acetaminophen studies employed negative control strategies and sibling comparisons in order to de-confound association estimates. While each approach to detect confounding is not problem-free or sufficient in itself, what matters is the ability within a study and across studies to employ different study designs and analytical strategies to adjust for measured and unmeasured confounders. A key to their success was to generate and test competing hypotheses to interpret associations, allowing for triangulation of the evidence that is much needed for evaluating causality.

Conclusion

Most associations between prenatal exposures and autism risk in the offspring should not be interpreted as implying a causal relationship between said exposures and autism. There is abundant evidence that residual confounding and confounding by genetic factors is pervasive. The recent history of widely publicized associations (e.g., antidepressant use by pregnant women) that turned out to not be causal needs to be borne in mind. The case of acetaminophen is similar. Studies have shown inconsistent associations with autism (and with other neurodevelopmental outcomes), heterogeneity of studies is high and estimates in most studies remain confounded by unmeasured factors, including genetic liability. In two recent well-executed studies of very large population-based cohorts, investigators could go a step further in detecting bias by employing different strategies to de-confound observed associations. Both concluded that the evidence was not consistent with a causal relationship between prenatal acetaminophen exposure and risk of autism. With a worldwide estimated 40%–60% of women ever using acetaminophen during pregnancy and no evidence for a causal association, singling out acetaminophen use to 'prevent' autism was unscientific and truly irresponsible. After having been treated of 'refrigerator mothers', asked to stop working and give up their careers to deliver Lovaas' intervention around the clock, summoned to remove gluten/casein from the family diet and to not adhere to the child immunization schedule, or even blamed for lack of progress of their child in caregiver-mediated interventions, women are now targeted for seeking pain reduction during pregnancy.[7] At the core of all these missteps, were erroneous causal inferences made after observing correlations or associations between variables without experimental control. The new acetaminophen-induced autism scare follows that same path.

Pregnant mothers do not need to 'tough it out'; they should listen to their doctor, not to the spin doctors.

Conflict of interest statement

Dr. Fombonne was an expert witness in trials on childhood vaccines and autism risk on behalf of the US Department of Justice and Department of Human & Health Services and of vaccine manufacturers (2003–2009). He is consulting on behalf of defendants in litigation relating to heavy metals in baby food and in litigation related to acetaminophen. His research has been funded by INSERM, MRC, CIHR, Autism Speaks, Simons Foundation, and NIMH. None of his research was funded by industry. The author declares that no funds, grants, or other support were received during the preparation of this manuscript.

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Endnotes

1. Typically, listing biological effects of exposures in animal models (oxidative stress, apoptosis, microglia activation, etc.) that resemble those reported in some autism studies is often used to assert "biological plausibility." However, the parallel does *not* make it *more likely* that the exposure is causally related to autism. Autisms are heterogeneous; there is no biological signature of autism; biological disturbances reported in autism are non-specific and not proven to be causal; and superficial similarity of effects does not dispense to demonstrate in human studies that the biological mechanisms are operant in autism.
2. The review paper addresses other neurodevelopmental outcomes than autism, such as ADHD, and other developmental indices (motor, cognitive, behavioral). Due to space constraints, we focus here on studies of autism. However, the methodological issues discussed apply as well to other outcomes.
3. There were seven different studies, but findings from Ahlqvist et al. (2024) were split in two separate estimates.
4. Assuming a population prevalence of 1.5% in these European populations at that time, and assuming that all truly autistic children would be screen positive (an unlikely performance), the proportion of autistic children in the positive outcome group would be ≈20% (1.5%/7.2%) at best. Four out of 5 children with the "autism" outcome under study could not have autism.
5. For example, Avella-Garcia et al. (2016) study was included in the meta-analysis of Alemany

et al. (2021) *and* presented as a separate independent study.
6. In both studies, the pattern of results for ADHD and intellectual disability was similar to that for autism.
7. An alternative, more evidence-based and equally actionable slogan could have been: "Old men, stop having babies!"...

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Accepted for publication: 6 October 2025