Acetaminophen Use During Pregnancy and Children's Risk Of Autism, ADHD, And Intellectual Disability. Ahlqvist Vh, Et Al. *Jama*. 331(14):1205-1214. April, 2023

Acetaminophen (paracetamol/Tylenol) is the most recommended analgesic and antipyretic in pregnancy. The FDA and EMA have historically considered it low risk for fetal development. However, in 2021, an international statement urged more cautious use, citing observational signals linking prenatal exposure with later neurodevelopmental disorders such as autism spectrum disorder (ASD) and attention-deficit/hyperactivity disorder (ADHD). Those prior studies were frequently limited by small cohorts and susceptibility to confounding, particularly "*confounding by indication*" (fever, infection, or migraine prompting acetaminophen use), as well as parental health/genetic factors that are shared within families.

This JAMA study addresses these limitations by leveraging Sweden's linked national health and demographic registers to assemble an almost nation-wide birth cohort and, crucially, by applying a sibling-control design that holds constant shared familial factors. Medication exposures were recorded prospectively during routine antenatal care and, from 2005 onward, supplemented by the national Prescribed Drug Register. Neurodevelopmental outcomes were ascertained using ICD codes in the National Patient Register.

Because familial genetics and home environment are strong determinants of both medication use patterns and child neurodevelopment, within-family (matched full-sibling) analyses can test whether small associations observed in conventional models persist after controlling for those shared factors. Dose–response analyses using dispensed prescription dose (where available) and comparisons with other analgesics further probe whether any association looks causal or instead reflects residual confounding.

Clinical Question: Among children born in Sweden, is prenatal acetaminophen exposure associated with increased risk of autism, ADHD, or intellectual disability (ID)?

- **Population:** All singleton liveborn children in Sweden from July 1, 1995, to December 31, 2019.
    - **Exclusions:** Children with missing data on the birthing parent's birth country, age, region of residence, or household education or income.
- **Exposure:** Any acetaminophen use during pregnancy, prospectively recorded at antenatal visits (over-the-counter and prescription) and later antenatal documentation.
- **Comparison**: No acetaminophen use during pregnancy.
- **Outcomes:** ASD, ADHD, and ID diagnoses from the National Patient Register (ICD-9/10). ADHD was also identified via dispensed ADHD medications.
- **Type of study:** Nationwide population-based cohort with within-family (full-sibling) control analysis. An observational design using prospectively collected registry data.

Authors' Conclusions: *"Acetaminophen use during pregnancy was not associated with children's risk of autism, ADHD, or intellectual disability in sibling control analysis. This suggests that associations observed in other models may have been attributable to familial confounding."*

Quality Checklist for Observational Studies:

1. **Clearly focused issue? Yes.** The objective specified acetaminophen exposure in pregnancy and risk of ASD/ADHD/ID in offspring.
2. **Appropriate method? Yes.** A large registry cohort with sibling controls is appropriate when an RCT is not feasible and familial confounding is plausible.
3. **Cohort recruited acceptably? Yes.** Near-complete inclusion of all eligible singleton births with minimal exclusions.
4. **Exposure accurately measured to minimize bias? Unsure.** Antenatal records captured use prospectively, but dose/timing were incomplete, and OTC use may be misclassified.
5. **Outcome accurately measured to minimize bias? Unsure.** Autism coding has prior validation; ADHD and ID coding in these registers had not been validated in this data set.
6. **Important confounders identified/adjusted? Yes.** Extensive covariates and sibling control for shared familial factors; E-values reported.
7. **Follow-up complete enough? Yes.** Median follow-up 13.4 years with nationwide registers capturing outcomes.
8. **Precision of results? Yes.** Very large sample with narrow 95% CIs, especially in sibling analyses hovering around null.
9. **Do you believe the results? Yes.** Conventional models show small risk increases that disappear with sibling controls, and no dose-response remains, consistent with confounding.
10. **Applicable to local population? Yes.** Findings from Sweden's universal-care setting are likely applicable to similar high-income settings (Canada and US), though local prescribing/OTC patterns may differ.
11. **Fit with other evidence? Yes.** Aligns with sibling-controlled MoBa findings for ADHD and suggests prior positive associations in conventional designs reflect confounding.
12. **Who funded the study?** The Article Information notes author funding, including grants reported from the Swedish Research Council during the conduct of the study.
13. **Conflicts of interest declared? Yes.** Disclosures include, for example, a coauthor's startup affiliation and grant support as listed in Article Information.

Results: The final analytic sample consisted of 2,480,797 singleton births. A sibling sub-cohort included 1,773,747 full siblings from 780,839 families. There were only 8,924 births excluded, which means 99.6% were retained in the analysis.

Among 2,480,797 singleton births, 185,909 (7.5%) were exposed to acetaminophen in utero. Exposure was more common among births to parents with lower education/income, higher early-pregnancy BMI, smoking, and with psychiatric or neurodevelopmental diagnoses, as well as in those with diagnoses representing indications for analgesics and relevant co-prescriptions. Sex distribution was roughly even; median follow-up was 13.4 years.

Key Result: No statistical difference in hazard ratios for ASD, ADHD or ID in matched sibling analysis.

- **Outcome:** Hazard Ratio (HR) for ASD, ADHD and ID
    - Fully adjusted population models (no sibling control), prenatal acetaminophen use was associated with slightly higher hazards of ASD (HR 1.05), ADHD (HR 1.07), and ID (HR 1.05), translating to very small absolute risk differences at age 10 (e.g., +0.09% for ASD).
    - In matched full-sibling analyses, all associations were null: ASD HR 0.98 (95% CI, 0.93–1.04), ADHD HR 0.98 (95% CI, 0.94–1.02), ID HR 1.01 (95% CI, 0.92–1.10).
    - No dose–response remained in sibling models, and associations for other analgesics similarly attenuated to null, except for aspirin. Aspirin showed an inverse association in sibling analyses and was hypothesized to reflect selection and perinatal effects (preeclampsia prevention).

Five Things that Threaten the Validity of the Study:

1. Residual & Time-Varying Confounding: These may persist despite high-quality control. Sibling analyses neutralize shared familial (genetic & environmental) confounders, but they cannot fully adjust for pregnancy-specific, time-varying indications. Examples include infections, fever, migraines, or pain severity that may differ between pregnancies and correlate with both acetaminophen use and neurodevelopmental risk. The authors document incomplete capture of such indications (especially those not requiring formal care), so confounding by indication may still bias estimates even in sibling models, albeit likely toward small positive associations in conventional analyses.

2. Exposure Misclassification: Antenatal records captured any use but not precise timing, duration, or OTC dose, and prescription registers do not equal ingestion. Self-report is prone to under-reporting. Such non-differential misclassification typically biases associations toward the null and complicates dose–timing inference. The authors' simulations suggest that even substantial under-ascertainment would be unlikely to create the null sibling findings, but it still reduces confidence in estimating effects tied to gestational windows or higher cumulative doses.

3. Outcome Misclassification: While autism coding has prior validation within these registers, ADHD and ID diagnoses in this data set had not been specifically validated, and

registry-based case capture depends on help-seeking and diagnostic practices that changed over the study period. Misclassification can bias hazard ratios in either direction and complicates comparisons over time or across subgroups.

4. Sibling-Control: Within-family analyses require families discordant for exposure and outcomes, which may limit generalizability and can be affected by carryover effects (one pregnancy affecting the next child's outcome or exposure). The authors found no evidence of carryover for ASD/ID but could not fully exclude it for ADHD. In addition, sibling estimates may be less precise for subgroups and assume that unshared confounding is adequately modelled.

5. External Validity: This is a Swedish registry-based study within a universal health-care system with specific antenatal practices and OTC availability patterns. Both the background risk of neurodevelopmental diagnoses and acetaminophen use behaviours may differ elsewhere. Although the huge population-based cohort strengthens external validity, clinicians should still consider local prescribing norms, diagnostic thresholds, and access to care when applying these results.

SGEM Bottom Line: In this large Swedish cohort using a rigorous sibling-control design, prenatal acetaminophen exposure was not associated with ASD, ADHD, or ID. It is still reasonable to recommend the use of acetaminophen during pregnancy when clinically indicated, at the lowest effective dose, and for the shortest reasonable duration.

Clinical Context: This study doesn't rule out harm from extreme dosing or time windows (early first trimester). However, the burden of proof is on those claiming that acetaminophen causes ASD, ADHD or ID. There is insufficient evidence to warrant accepting the claim currently.