Prenatal paracetamol exposure and child neurodevelopment: a systematic review and meta-analysis

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Summary

Background Concerns have emerged about the impact of paracetamol use in pregnancy on child neurodevelopment, particularly in relation to autism spectrum disorder. We aimed to synthesise available evidence to investigate associations between prenatal paracetamol exposure and autism spectrum disorder, attention-deficit hyperactivity disorder (ADHD), and intellectual disability.

Methods For this systematic review and meta-analysis, we searched MEDLINE, Embase, ClinicalTrials.gov, and the Cochrane Library from inception to Sept 30, 2025, for cohort studies reporting adjusted estimates of the risk of autism spectrum disorder, ADHD, and intellectual disability. Eligible studies used validated questionnaires or medical records to define outcomes, reported maternal comorbidities and treatments, and compared pregnancies with and without paracetamol exposure, whereas unadjusted studies were excluded. Quality assessment of the included studies was conducted using the Quality In Prognosis Studies (QUIPS) tool. The primary outcomes were the associations between prenatal paracetamol exposure and the likelihood of autism spectrum disorder, ADHD, and intellectual disability. Analyses were restricted to sibling-comparison studies with adjusted estimates, and odds ratios (OR) were calculated. Random-effects meta-analyses used the generic inverse variance method. Subgroup analyses were performed when possible (trimester, duration of use, offspring sex, and follow-up length). This study was registered with PROSPERO, CRD420251156690.

Findings 43 studies were included in the systematic review, and 17 studies in the meta-analysis. When considering sibling comparison studies, paracetamol exposure during pregnancy was not associated with the risk of autism spectrum disorder (OR 0·98, 95% CI 0·93–1·03; p=0·45), ADHD (0·95, 0·86–1·05; p=0·31), or intellectual disability (0·93, 0·69–1·24; p=0·63). There was also no association between paracetamol intake during pregnancy and autism spectrum disorder (OR 1·03, 95% CI 0·86–1·23; p=0·78), ADHD (0·97, 0·89–1·05; p=0·49), or intellectual disability (1·11, 0·92–1·34; p=0·28) when considering only studies at low risk of bias according to QUIPS. This absence of association persisted when considering all studies with adjusted estimates and those with more than 5 years of follow-up.

Interpretation Current evidence does not indicate a clinically important increase in the likelihood of autism spectrum disorder, ADHD, or intellectual disability in children of pregnant individuals who use paracetamol as directed, supporting existing recommendations on its safety.

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Introduction

Paracetamol, or acetaminophen, is the most commonly used analgesic and antipyretic during pregnancy, recommended globally as a first-line option for pain relief and fever reduction. Its safety profile is generally more favourable than that of non-steroidal anti-inflammatory drugs and opioids, making it the preferred choice in obstetric care.[1,2] However, concerns have arisen regarding its potential impact on child neurodevelopment, including conditions such as autism spectrum disorder.[3–5]

The public debate gained traction in September, 2025, when the US Government suggested that prenatal exposure to paracetamol might contribute to autism, citing a review linking acetaminophen use in pregnancy to neurodevelopmental outcomes.[6,7] This review was limited by data variability and significant differences in how studies defined exposure and outcomes. Despite these concerns, major professional organisations, such as the American College of Obstetricians and Gynecologists (USA) and the Royal College of Obstetricians and Gynaecologists (UK), continue to endorse the safe use of paracetamol during pregnancy when used appropriately.[8,9]

Conflicting findings in the literature stem from variability in evaluating neurodevelopmental outcomes and the timing of acetaminophen use.[10–15] A 2024 meta-analysis[10] suggested small associations between prenatal paracetamol exposure and increased risks of autism spectrum disorder and attention-deficit hyperactivity disorder (ADHD), but these were often based on studies prone to biases. More rigorous studies, including a

Research in context

Evidence before this study

We searched MEDLINE, Embase, ClinicalTrials.gov, and the Cochrane Library from database inception to Sept 30, 2025, using combinations of Medical Subject Headings and keywords including "paracetamol", "pregnancy", "autism", "neuropsychological", and "outcome*". We restricted inclusion to cohort studies that reported adjusted risk estimates for the association between prenatal paracetamol exposure and neurodevelopmental outcomes. Study quality was evaluated using the Quality in Prognosis Studies (QUIPS) tool. Earlier meta-analyses suggested small increases in autism or attention-deficit hyperactivity disorder (ADHD) risk after prenatal paracetamol exposure, but were highly heterogeneous and subject to residual confounding and exposure misclassification. In contrast, previous large registry-based cohorts using sibling-comparison designs generally reported null associations, suggesting that familial and genetic confounding might explain earlier findings. Across the literature, exposure definitions and outcome ascertainment varied considerably across studies and diagnostic eras.

Added value of this study

This study is, to our knowledge, the first systematic review and meta-analysis to prioritise sibling-comparison designs and to apply the QUIPS tool to assess prognostic-factor bias across the entire evidence base. It provides a clear hierarchy of evidence, by separating analyses of sibling-comparison studies, low-risk-of-bias studies, and all adjusted studies. Across all analyses, most notably in sibling-comparison studies, prenatal paracetamol exposure was not associated with increased risks of autism spectrum disorder, ADHD, or intellectual disability. These findings remained stable when restricting to studies with longer follow-up and those judged to be at low risk of bias. The study clarifies that previously reported associations in conventional observational studies are likely to reflect residual confounding from maternal illness, fever, genetic susceptibility, or environmental factors rather than a causal effect of paracetamol.

Implications of all the available evidence

Taken together with large-scale sibling-controlled studies from Sweden and Japan published in 2024 and 2025, our findings support the safety of paracetamol when used appropriately during pregnancy. They reinforce the guidance of major professional and regulatory bodies, including the American College of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynaecologists, and the European Medicines Agency, which continue to recommend paracetamol as the first-line analgesic and antipyretic in pregnancy. Avoiding paracetamol based on inconclusive or biased evidence might increase the risk of maternal fever or untreated pain, both of which can harm pregnancy outcomes. Future research should focus on improving exposure measurement, standardising outcome definitions, and integrating mechanistic and family-based designs to clarify any residual uncertainties.

Swedish cohort of 2·48 million births, found no association between prenatal paracetamol use and these disorders when accounting for familial confounding.[10] A Japanese cohort study suggested minor risk increases for ADHD and autism spectrum disorder, but further analyses indicated these were likely due to confounding and misclassification.[11]

See Online for appendix

Considering the widespread use of paracetamol in pregnancy, even a small causal effect on neurodevelopment could have major public health implications. At the same time, avoiding paracetamol might expose mothers and fetuses to the risks associated with untreated pain and fever, such as miscarriage, preterm birth, or congenital defects.[12] Thus, the politicisation of scientific uncertainty creates confusion among pregnant people and clinicians. In this systematic review and meta-analysis, we aimed to rigorously assess the available literature to clarify the association between prenatal paracetamol exposure and neurodevelopmental outcomes, such as autism spectrum disorder, ADHD, and intellectual disability.

Methods

Search strategy and selection criteria

For this systematic review and meta-analysis, we searched MEDLINE, Embase, the Cochrane Library, and ClinicalTrials.gov, from database inception to Sept 30, 2025, for articles published in English, adopting different combinations of the following relevant medical subject heading terms and keywords: "paracetamol" AND "pregnancy" AND "autism" AND "neuropsychological" AND "outcome*". Full search strategies are in the appendix (pp 2–5). In case of analyses published from the same cohort, we extracted the data from the publication with the longer follow-up or, if the length of follow-up was identical, with the largest sample size. Reference lists of relevant articles and reviews were hand-searched for additional reports.

Studies were eligible if they had (1) a cohort design; (2) available information on acetaminophen exposure among pregnant women, either performed through the assessment of biomarkers or medical records, or self-reported; (3) an explicit definition of the primary and if applicable, the secondary outcomes, diagnosed using validated questionnaires or medical records; (4) available adjusted estimates comparing pregnancy outcomes in individuals taking paracetamol versus those not taking paracetamol during pregnancy; and (5) available information on underlying comorbidities and pharmacological treatments during or before pregnancy.

The following outcomes were examined: (1) autism spectrum disorder, understood as a form of neurodevelopmental diversity characterised by differences in social communication, interaction, and behavioural expression;[16–18] (2) ADHD, understood as a neurodevelopmental condition involving differences in attention regulation, activity level, and impulse control;[19] and (3) intellectual disabilities, defined as a neurodevelopmental condition involving differences in intellectual functioning and adaptive skills.[20] We decided not to include studies reporting language anomalies in children as developmental language disorders in this analysis, since these do not necessarily reflect broader development.

Although the most reported definitions of autism spectrum disorder, ADHD, and intellectual disability in children are those provided by the Diagnostic and Statistical Manual of Mental Disorders, fifth edition (DSM-5), numerous diagnostic guidelines are used in the published literature and no specific restriction on how to define any of the observed outcomes was applied. Considering the heterogeneity of outcome ascertainment across studies, we classified ICD or DSM-coded outcomes as autism spectrum disorder, and treated screening-based or questionnaire-based measures as indicators of autistic traits rather than diagnostic autism spectrum disorder.

Quality assessment of the included studies was conducted using the Quality In Prognosis Studies (QUIPS) tool, which evaluates the risk of bias in prognostic factor research.[21] The tool examines six domains: study participation, study attrition, prognostic factor measurement, study confounding, outcome measurement, and statistical analysis and reporting. In each domain, studies are rated as having a high, moderate, or low risk of bias. Two authors (FD and MEF) independently graded risk of bias (high, moderate, or low risk of bias) for each domain of the QUIPS tool for each study (appendix pp 5–6). These assessments were then compared, and disagreements resolved by discussion or by a third reviewer (AK).[21]

Our primary analysis aimed to elucidate the association between paracetamol exposure during pregnancy and the risk of autism spectrum disorder, ADHD, and intellectual disabilities, and included only sibling comparison studies. The rationale behind this choice is based on the fact that sibling comparison studies can reduce potential confounders by addressing shared familial factors, such as parental genetics, socioeconomic status, and home environment, thus potentially providing a more robust estimation of the possible association between a specific prognostic factor and later development of these neurodevelopmental outcomes.[22] However, we also explored the observed outcomes by including studies not reporting sibling comparison in their analysis and in studies with a low risk of bias according to QUIPS assessment.

Considering the multifactorial nature of autism spectrum disorder and ADHD, with several parental or child characteristics potentially affecting the reported risks, we excluded studies reporting only unadjusted estimates.

This review was conducted according to a protocol designed a priori and recommended for systematic reviews and meta-analysis.[23] This study adhered to PRISMA guidelines[24] and was registered with PROSPERO, CRD420251156690.

Data analysis

Two authors (FD and LDV) independently screened titles and abstracts, with discrepancies resolved by a senior reviewer (AK). Each included article was independently evaluated by two reviewers (FD and MEF), who extracted the study characteristics and measures of effect. In cases of discrepancies in data extraction, a third author (AK) was contacted, and consensus was achieved through discussion. Case reports, conference abstracts, and case series with fewer than ten cases (five per group) were excluded. Cases were defined as offspring identified with autism spectrum disorder, ADHD, or intellectual disability according to the diagnostic criteria or validated records used in each primary study (appendix pp 9–22).

The units of the meta-analysis were single comparisons of pregnant women taking versus not taking paracetamol predicting: (1) autism spectrum disorders; (2) ADHD; and (3) intellectual disability. The likelihood of each outcome was assessed, using only adjusted estimates from studies that reported sibling comparisons, in studies at low risk of bias according to QUIPS assessment, in all studies reporting adjusted estimates and in those with a follow-up longer than 5 years. When possible, we performed several additional meta-analyses stratified by: trimester of paracetamol intake (first, second, and third); duration of intake (<1 week, 1 week–30 days, >30 days); sex of the newborn; and duration of follow-up. We did not include studies reporting the risk of each of the observed outcomes in a subset of women and children with assessment of paracetamol metabolites in different biological samples in the meta-analysis, because they might not be representative of the entire population, especially when the risk of an adverse outcome was not reported in those patients who did not have such a biological assessment.

Data were combined using a random-effects generic inverse variance approach to account for between-study heterogeneity.[25] Results were reported as odds ratios (ORs) and 95% CIs. If a study reported the results of different multivariable models, the most stringently controlled estimates (those from the model adjusting for more factors) were extracted. If different models controlled for the same number of covariates, the model containing the highest number of clinical covariates (either genetics, sociodemographics, perinatal, or environmental) was used for the analysis.[19] In case a study

only reported separate estimates by subgroup, the overall estimate of risk was computed from the separate relative risks using the fixed-effect model for generic inverse variance outcomes.[25] Between-study heterogeneity was quantified using the I^2 statistic. For each outcome, the total number of publications included in the meta-analyses was less than ten, thus we were not able to assess publication bias, either graphically, through funnel plots, or formally, through Egger's regression asymmetry test (in such cases, the power is too low to distinguish chance from real asymmetry). All meta-analyses were performed using RevMan software (version 5.4).

Role of the funding source

There was no funding source for this study.

Results

Our initial search yielded 4147 articles, of which 4092 were excluded because the reported outcomes were not relevant; 55 studies were obtained for full-text review. An additional 12 articles were excluded after full review; therefore, 43 articles[10,11,26–66] were included in the systematic review (figure 1; appendix pp 5–6). Of these, 17 studies were included in the meta-analysis.[10,11,14,27,32,34,37,42,44,47–49,52,54,55,60,66]

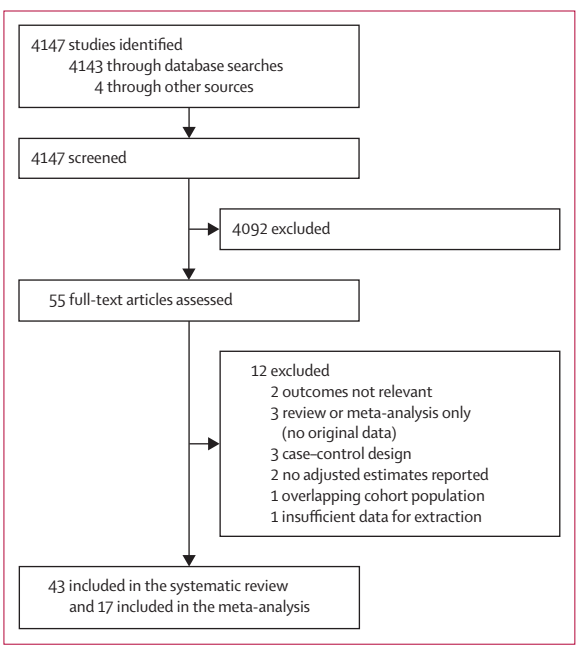

Figure 1: **Study selection**

11 studies were at low, 23 at moderate, and nine at high risk of bias (appendix pp 4–6). The major limitations of the included studies were the heterogeneity in reporting the exposure to paracetamol during pregnancy, timing, and type of follow-up, and absence of stratification by paracetamol intake and drug dosage, which was a common feature for most of the included studies (appendix pp 9–22).

When considering sibling comparison studies, paracetamol exposure during pregnancy was not associated with the risk of autism spectrum disorder (OR 0·98, 95% CI 0·93–1·03; p=0·45; I^2=0%; figure 2; table) The absence of association between paracetamol intake during pregnancy and autism spectrum disorder persisted when considering studies at low risk of bias according to QUIPS (1·03, 0·86–1·23; p=0·78), all studies with adjusted estimates (1·08, 0·95–1·22; p=0·30), or those with more than 5 years of follow-up (1·09, 0·95–1·26; p=0·22; table).

Maternal use of paracetamol was not associated with an increased risk of ADHD among children when considering sibling comparison studies (OR 0·95, 95% CI 0·86–1·05; p=0·31; I^2=18%), those at low risk of bias according to QUIPS (0·97, 0·89–1·05; p=0·49), all published studies with adjusted estimates (1·10, 0·99–1·23; p=0·08), or those with a follow-up of longer than 5 years (1·09, 0·95–1·25; p=0·21; figure 3; table).

No association was identified between paracetamol intake during pregnancy and intellectual disability, when considering sibling comparison studies (OR 0·93, 0·69–1·24; p=0·63; I^2=48%; figure 4), those at low risk of bias according to QUIPS (1·11, 0·92–1·34; p=0·28), all studies with adjusted estimates (1·04, 0·99–1·11; p=0·14), or those with a follow-up longer than 5 years (1·11, 0·98–1·25; p=0·10).

It was not possible to perform subgroup analyses according to trimester at intake, fetal sex, or frequency of drug intake for all three outcomes explored when considering studies with sibling comparison or those at low risk of bias, because few studies reported these stratified data within these methodologically stringent

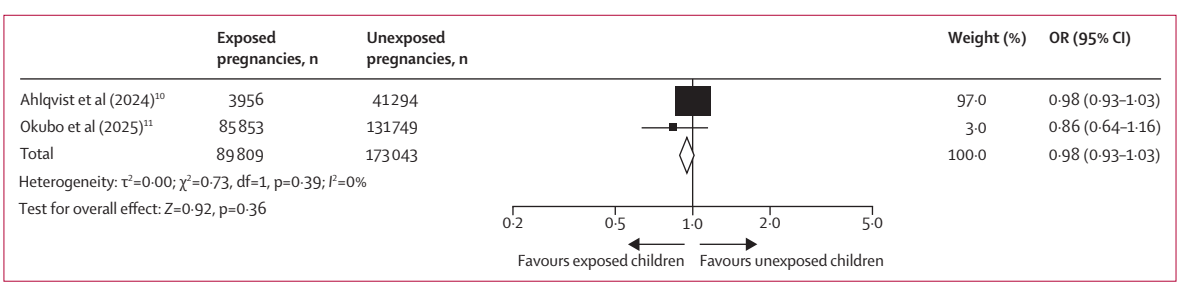

Figure 2: **Risk of autism spectrum disorder in children with in-utero exposure to paracetamol versus unexposed children**
Only sibling comparison studies were included in this analysis. df=degrees of freedom. OR=odds ratio.

subsets, resulting in insufficient statistical power and unstable estimates.

Discussion

This systematic review and meta-analysis found no evidence that maternal paracetamol use during pregnancy increases the risk of autism spectrum disorder, ADHD, or intellectual disability among children. The null findings remained consistent when analyses were harmonised to studies with longer follow-up, those employing sibling comparisons, and those at low risk of bias.

A comprehensive literature search across major databases, exploration of a multitude of outcomes, and stratified analysis by timing and duration of exposure, and follow-up period, represent the main strengths of the present systematic review.

Nevertheless, several limitations warrant consideration. Few studies used sibling or family-based designs, limiting our ability to account for genetic and shared environmental confounders, which might influence both use of analgesics and later neurodevelopment. Heterogeneity in exposures and outcome assessment, adjustment strategies used, and variability in the type of neurodevelopmental assessment tools adopted to characterise neurodevelopmental outcomes represent the main weakness of the present systematic review.

Explaining the potential causal relationship between paracetamol and conditions such as autism, ADHD, or intellectual disability is challenging. Our results should be interpreted in the context of the broader literature. Earlier meta-analyses suggested increased likelihood of autism spectrum disorder (pooled risk ratio (RR) approximately 1·19) and ADHD (pooled RR approximately 1·34), but these were characterised by high heterogeneity (I^2>70%) and by reliance on conventional observational designs susceptible to residual confounding. By contrast, the largest and most methodologically rigorous studies provide strong evidence against a causal link.

In a Swedish population-based cohort of 2·48 million births using sibling comparisons, no increased likelihood of autism spectrum disorder (hazard ratio [HR] 0·98, 95% CI 0·93–1·04), ADHD (0·98, 0·94–1·02), or intellectual disability (1·01, 0·92–1·10) was identified with prenatal paracetamol use.[11] Similarly, in a nationwide Japanese cohort of more than 217 000 children, small likelihood increases in conventional analyses were reported for ADHD (HR 1·22, 95% CI 1·09–1·36).[10] However, these associations did not hold or were reversed in sibling analyses and were further attenuated by probabilistic bias modelling and negative-control exposures. Together with our pooled results, these findings suggest that previously reported associations might be artifacts of unmeasured confounding, such as underlying maternal pain, discomfort, fever, or genetic liability, rather than direct drug effects.

	Datasets, n	Total sample, n	Pooled estimates		
			OR (95% CI)	p value	I^2, %
Autism spectrum disorder					
All studies	8	339 040	1·08 (0·95–1·22)	0·30	57%
Studies with sibling comparisons only	2	262 852	0·98 (0·93–1·03)	0·45	0
Studies with low risk of bias (QUIPS)	4	328 413	1·03 (0·86–1·23)	0·78	75%
Studies with follow-up >5 years only	6	337 038	1·09 (0·95–1·26)	0·22	
ADHD					
All studies	9	426 629	1·10 (0·99–1·23)	0·076	51%
Studies with sibling comparisons only	3	335 255	0·95 (0·86–1·05)	0·31	18%
Studies with low risk of bias (QUIPS)	4	341 659	0·97 (0·89–1·05)	0·49	10%
Studies with follow-up >5 years only	7	332 924	1·09 (0·95–1·25)	0·22	
Intellectual disabilities					
All studies	9	502 217	1·04 (0·99–1·11)	0·14	50%
Studies with sibling comparisons only	2	406 681	0·93 (0·69–1·24)	0·63	48%
Studies with low risk of bias (QUIPS)	5	236 781*	1·11 (0·92–1·34)	0·28	57%
Studies with follow-up >5 years only	6	455 666	1·11 (0·98–1·25)	0·10	50%

Sibling-comparison meta-analyses represent the primary evidence, since they account for shared familial and genetic factors; all other analyses (overall adjusted estimates, low-risk-of-bias studies, and longer follow-up subsets) are presented as secondary supportive analyses. All meta-analyses used a generic inverse variance random-effects model. ADHD=attention-deficit hyperactivity disorder. OR=odds ratio.QUIPS= Quality In Prognosis Studies. *The reported total sample is incomplete, since one or more of the studies included in the meta-analysis did not report the raw data for the subgroup.

Table: **Primary and secondary pooled analyses of autism spectrum disorder, ADHD, and intellectual disabilities among children with in-utero paracetamol exposure versus unexposed children**

It is also important to recognise that heterogeneity in diagnostic eras, reflecting changes over time in diagnostic criteria, instruments, and assessment practices, is inevitable across the included studies. Neurodevelopmental diagnoses have evolved substantially over time,[67] and the outcomes reported here represent neurodevelopmental diagnoses as defined in their time, rather than a single uniform construct. Within this framework, the most reassuring null findings consistently come from large, registry-based cohort studies employing sibling-comparison designs, which minimise confounding from shared familial, genetic, and environmental factors. By contrast, smaller questionnaire-based studies are more susceptible to exposure misclassification, recall bias, and variability in diagnostic thresholds, and therefore tend to produce more heterogeneous and less reliable associations.

Importantly, although prolonged analgesic use might coincide with underlying maternal health conditions, the null findings in sibling designs indicate that familial and genetic factors, including the well established tendency for autistic traits to run in families, are more plausible explanations for previously observed associations than any direct effect of paracetamol. These findings, therefore, cannot be taken as evidence of causality, but instead highlight the complexity of distinguishing medication effects from underlying maternal and familial factors.

Biological mechanisms proposed to link paracetamol with neurodevelopmental outcomes include endocrine

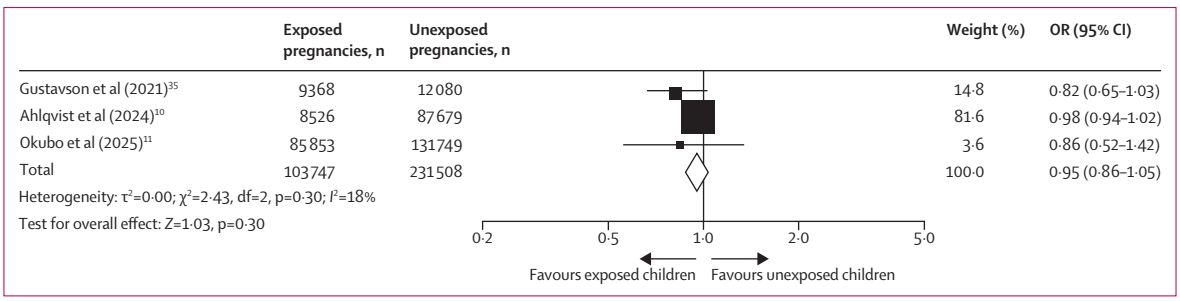

Figure 3: **Risk of attention-deficit hyperactivity disorder in children with in-utero exposure to paracetamol versus unexposed children**
Only sibling comparison studies were included in this analysis. df=degrees of freedom. OR=odds ratio.

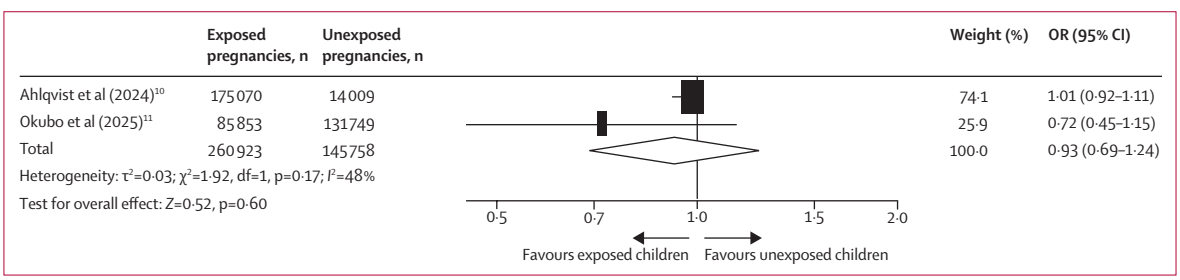

Figure 4: **Risk of intellectual disability in children with in-utero exposure to paracetamol versus unexposed children**
Only sibling comparison studies were included in this analysis. df=degrees of freedom. OR=odds ratio.

disruption and oxidative stress mediated by the metabolite N-acetyl-p-benzoquinone imine, altered prostaglandin signalling, and epigenetic modifications. The immature fetal liver has limited detoxification capacity, potentially increasing susceptibility to these pathways.[68–70] Paracetamol also crosses the placental barrier, with fetal concentrations approximating maternal levels. Although these mechanisms are plausible, most supporting evidence has been obtained from animal or in-vitro studies, and no human data have established causality.

Our results have clear clinical relevance. Paracetamol remains one of the most widely used medicines in pregnancy, commonly taken for pain or fever, and is included on the WHO List of Essential Medicines.[71] In many settings, it is the only safe and accessible option for treating fever and pain. Avoidance of paracetamol based on inconclusive evidence could expose pregnant women and their babies to known risks associated with untreated fever or severe pain. Untreated maternal fever, in particular, has been linked to miscarriage, congenital anomalies, preterm birth, and differences in neurodevelopment.[9,72–74] For this reason, discouraging the appropriate use of paracetamol has the potential to cause greater harm than the drug itself.

Our findings align with the guidance issued by leading professional organisations, including the American College of Obstetricians and Gynecologists, the Royal College of Obstetricians and Gynaecologists, the International Federation of Gynaecology and Obstetrics, and the Society for Maternal-Fetal Medicine.[8,75–77] These organisations continue to recommend paracetamol as the first-line analgesic and antipyretic in pregnancy when used as directed. Regulatory agencies such as the European Medicines Agency, the UK Medicines and Healthcare products Regulatory Agency, and Health Canada hold similar positions.[77–79]

Our review highlights several weaknesses in the existing literature and available data. Many existing analyses rely on maternal self-report of paracetamol use, which is susceptible to recall bias and misclassification, particularly as mothers of children later identified with a neurodevelopmental condition might be more likely to recall or over-report medication use. Exposure assessment should ideally incorporate pharmacy dispensing records or biomarker validation to improve accuracy. Outcome definitions also varied widely across studies, with some relying on survey-based assessments rather than validated diagnostic criteria.

Large longitudinal studies often lose substantial numbers of participants (ie, due to adherence decline and substantial loss to follow-up) over time due to factors such as condition progression, lack of support, or differences in socioeconomic status. Additionally, the assessment of neurodevelopment over time might be impacted by changes in diagnostic criteria, variations in diagnostic tools, and the use of different informants (parents *vs* teachers). Therefore, standardising diagnostic methods and ensuring long-term follow-up could improve comparability and strengthen pooled estimates.

Furthermore, when calculating the prevalence of neurodevelopmental outcomes, it is crucial to consider the baseline risk of such conditions within families. Family-based designs, such as sibling comparisons,

represent a valuable approach to controlling for shared genetic and environmental factors. Although these studies mitigate bias from between-family confounding, they also face reduced statistical power, as only discordant sibling pairs contribute to identification, and potential influence from time-varying confounders across pregnancies. Computation of a specific neurodevelopmental outcome in patients exposed to a specific drug suspected of influencing such outcomes should ideally take into account the concentration of a drug in maternal or neonatal circulation. In this scenario, future studies should stratify their analysis according to the degree of drug exposure through biomarker assessment.

Considering the extensive observational evidence already available and the impracticality of further large-scale prospective studies or randomised trials, future progress in this field is likely to come from mechanistic research, improved exposure measurement, and genetically informed or quasi-experimental designs that can better distinguish causal effects from residual confounding. Importantly, future research should also be guided by the autistic community, to ensure that priorities, independence, and outcomes reflect lived experience.

Paracetamol is typically used only intermittently, and its prolonged use raises questions about whether the underlying health condition prompting extended use might be more important in shaping neurodevelopmental outcomes rather than the drug itself. Future research should therefore prioritise dose–response analyses, trimester-specific exposure, and integration of mechanistic and epidemiological approaches to clarify whether experimental hypotheses such as oxidative stress or endocrine disruption, potentially exacerbated by immature fetal liver metabolism, translate into clinically meaningful effects in humans.

Our findings should be interpreted in the context of recently published evidence. A 2025 meta-analysis including 16 studies examined the association between prenatal paracetamol exposure and autism spectrum disorder and ADHD.[80] By contrast, our review incorporated a larger body of evidence and extended the scope to include intellectual disabilities. Furthermore, by restricting analyses to cohort studies and conducting sensitivity analyses limited to studies at low risk of bias and with long-term follow-up, our study provides an updated and methodologically more rigorous synthesis of the current evidence.[80]

Future studies should employ designs that minimise confounding by indication, such as sibling or other quasi-experimental approaches, and, where feasible, incorporate biomarker-based exposure assessment to improve the precision of exposure measurement and strengthen causal inference.

Maternal use of paracetamol during pregnancy does not seem to increase the likelihood of autism spectrum disorder, ADHD, or intellectual disability. This finding supports the recommendations made by major medical organisations regarding its use.

Contributors

FD and MEF contributed equally to this work and share joint first authorship. FD and LDV performed the literature search, extracted data, and contributed to data verification, interpretation, and manuscript drafting. FD and MEF designed the study, drafted the manuscript, and carried out statistical analyses. SP contributed to data verification, interpretation, and manuscript drafting. LM provided methodological oversight and contributed to data synthesis and statistical validation. AS contributed to data synthesis and manuscript drafting, and critically reviewed the final manuscript. AK conceived the study, supervised all stages of the project, drafted the manuscript, and critically reviewed the final manuscript. All authors had full access to all data in the study and had final responsibility for the decision to submit for publication. FD, LDV, and MEF had direct access to, and verified all data.

Declaration of interests

We declare no competing interests. No author has received financial or personal support that could have influenced the findings of this work. The study was conducted independently, and no funding is relevant to this study.

Data sharing

No new data were generated for this meta-analysis. All data analysed were extracted from published studies and are available from the original publications cited in this Article. Requests for access to individual participant data should be directed to the corresponding authors of the original studies, in accordance with their data sharing policies.

References

1 American College of Obstetricians and Gynecologists' Committee on Practice Bulletins—Obstetrics. ACOG practice bulletin no 209: obstetric analgesia and anesthesia. *Obstet Gynecol* 2019; **133:** e208–25.

2 Bisson DL, Newell SD, Laxton C. Antenatal and postnatal analgesia: scientific impact paper no 59. *BJOG* 2019; **126:** e114–24.

3 Bauer AZ, Swan SH, Kriebel D, et al. Paracetamol use during pregnancy - a call for precautionary action. *Nat Rev Endocrinol* 2021; **17:** 757–66.

4 Khan FY, Kabiraj G, Ahmed MA, et al. A systematic review of the link between autism spectrum disorder and acetaminophen: a mystery to resolve. *Cureus* 2022; **14:** e26995.

5 Nilsen K, Staff AC, Krogsrud SK. Paracetamol use in pregnancy: not as safe as we may think? *Acta Obstet Gynecol Scand* 2023; **102:** 652–56.

6 Halpert M, Yousif N. Trump urges pregnant women to avoid Tylenol over unproven autism link. BBC News. Sept 22, 2025. https://www.bbc.co.uk/news/articles/cx20d4lr67lo (accessed Dec 17, 2025).

7 Prada D, Ritz B, Bauer AZ, Baccarelli AA. Evaluation of the evidence on acetaminophen use and neurodevelopmental disorders using the Navigation Guide methodology. *Environ Health* 2025; **24:** 56.

8 Royal College of Obstetricians and Gynaecologists. The Royal College of Obstetricians and Gynaecologists issues advice for pregnant women and people on the use of paracetamol to manage fever and pain. Royal College of Obstetricians and Gynaecologists. Sept 23, 2025. https://www.rcog.org.uk/news/the-royal-college-of-obstetricians-and-gynaecologists-issues-advice-for-pregnant-women-and-people-on-the-use-of-paracetamol-to-manage-fever-and-pain/ (accessed Oct 10, 2025).

9 American College of Obstetricians and Gynecologists. Acetaminophen use in pregnancy and neurodevelopmental outcomes. September, 2025. ACOG Practice Advisory. https://www.acog.org/clinical/clinical-guidance/practice-advisory/articles/2025/09/acetaminophen-use-in-pregnancy-and-neurodevelopmental-outcomes (accessed Oct 10, 2025).

10 Ahlqvist VH, Sjöqvist H, Dalman C, et al. Acetaminophen use during pregnancy and children's risk of autism, ADHD, and intellectual disability. *JAMA* 2024; **331:** 1205–14.

11 Okubo Y, Hayakawa I, Sugitate R, Nariai H. Maternal acetaminophen use and offspring's neurodevelopmental outcome: a nationwide birth cohort study. *Paediatr Perinat Epidemiol* 2025; published online Sept 2. https://doi.org/10.1111/ppe.70071.

12 Dreier JW, Andersen AM, Berg-Beckhoff G. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. *Pediatrics* 2014; **133:** e674–88.

13 Antoun S, Ellul P, Peyre H, et al. Fever during pregnancy as a risk factor for neurodevelopmental disorders: results from a systematic review and meta-analysis. *Mol Autism* 2021; **12:** 60.

14 Gustavson K, Ask H, Ystrom E, et al. Maternal fever during pregnancy and offspring attention deficit hyperactivity disorder. *Sci Rep* 2019; **9:** 9519.

15 Wood ME. Associations between prenatal acetaminophen exposure and child neurodevelopment: truth, bias, or a bit of both? *Paediatr Perinat Epidemiol* 2020; **34:** 233–36.

16 Lordan R, Storni C, De Benedictis CA. Autism spectrum disorders: diagnosis and treatment. In: Grabrucker AM, ed. Autism spectrum disorders. Exon Publications, 2021: 17–32.

17 Koutsoklenis A, Honkasilta J. ADHD in the DSM-5-TR: what has changed and what has not. *Front Psychiatry* 2023; **13:** 1064141.

18 Lord C, Brugha TS, Charman T, et al. Autism spectrum disorder. *Nat Rev Dis Primers* 2020; **6:** 5.

19 Cabral MDI, Liu S, Soares N. Attention-deficit/hyperactivity disorder: diagnostic criteria, epidemiology, risk factors and evaluation in youth. *Transl Pediatr* 2020; **9** (suppl 1): S104–13.

20 Committee to Evaluate the Supplemental Security Income Disability Program for Children with Mental Disorders, and the Board on the Health of Select Populations. Board on Children, Youth, and Families; Institute of Medicine; Division of Behavioral and Social Sciences and Education; The National Academies of Sciences, Engineering, and Medicine. Clinical characteristics of intellectual disabilities. In: Boat TF, Wu JT, eds. Mental disorders and disabilities among low-income children. National Academies Press, 2015: 89–118.

21 Hayden JA, van der Windt DA, Cartwright JL, Côté P, Bombardier C. Assessing bias in studies of prognostic factors. *Ann Intern Med* 2013; **158:** 280–86.

22 Andrade C. Discordant sibling pair comparisons in observational studies: a research design simply explained. *J Clin Psychiatry* 2025; **86:** 25f15843.

23 Henderson LK, Craig JC, Willis NS, Tovey D, Webster AC. How to write a Cochrane systematic review. *Nephrology (Carlton)* 2010; **15:** 617–24.

24 Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *Syst Rev* 2021; **10:** 89.

25 DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials* 1986; **7:** 177–88.

26 Anand NS, Raghavan R, Wang G, et al. Perinatal acetaminophen exposure and childhood attention-deficit/hyperactivity disorder (ADHD): exploring the role of umbilical cord plasma metabolites in oxidative stress pathways. *Brain Sci* 2021; **11:** 1302.

27 Avella-Garcia CB, Julvez J, Fortuny J, et al. Acetaminophen use in pregnancy and neurodevelopment: attention function and autism spectrum symptoms. *Int J Epidemiol* 2016; **45:** 1987–96.

28 Baker BH, Bammler TK, Barrett ES, et al. Associations of maternal blood biomarkers of prenatal APAP exposure with placental gene expression and child attention deficit hyperactivity disorder. *Nat Ment Health* 2025; **3:** 318–31.

29 Baker BH, Lugo-Candelas C, Wu H, et al. Association of prenatal acetaminophen exposure measured in meconium with risk of attention-deficit/hyperactivity disorder mediated by frontoparietal network brain connectivity. *JAMA Pediatr* 2020; **174:** 1073–81.

30 Bornehag CG, Reichenberg A, Hallerback MU, et al. Prenatal exposure to acetaminophen and children's language development at 30 months. *Eur Psychiatry* 2018; **51:** 98–103.

31 Brandlistuen RE, Ystrom E, Nulman I, Koren G, Nordeng H. Prenatal paracetamol exposure and child neurodevelopment: a sibling-controlled cohort study. *Int J Epidemiol* 2013; **42:** 1702–13.

32 Chatzi L, Leventakou V, Vafeiadi M, et al. Cohort profile: the mother-child cohort in Crete, Greece (Rhea study). *Int J Epidemiol* 2017; **46:** 1392–93.

33 Golding J, Tunstall H, Gregory S, Lies-Gaven Y. Maternal prenatal paracetamol ingestion and scholastic attainments of the offspring. *Front Pharmacol* 2023; **14:** 1116683.

34 Golding J, Gregory S, Clark R, Ellis G, Iles-Caven Y, Northstone K. Associations between paracetamol (acetaminophen) intake between 18 and 32 weeks gestation and neurocognitive outcomes in the child: a longitudinal cohort study. *Paediatr Perinat Epidemiol* 2020; **34:** 257–66.

35 Gustavson K, Ystrom E, Ask H, et al. Acetaminophen use during pregnancy and offspring attention deficit hyperactivity disorder—a longitudinal sibling control study. *JCPP Adv* 2021; **1:** e12020.

36 Havdahl A, Wootton RE, Leppert B, et al. Associations between pregnancy-related predisposing factors for offspring neurodevelopmental conditions and parental genetic liability to attention-deficit/hyperactivity disorder, autism, and schizophrenia: the Norwegian Mother, Father and Child Cohort Study (MoBa). *JAMA Psychiatry* 2022; **79:** 799–810.

37 Inoue K, Ritz B, Ernst A, et al. Behavioral problems at age 11 years after prenatal and postnatal exposure to acetaminophen: parent-reported and self-reported outcomes. *Am J Epidemiol* 2021; **190:** 1009–20.

38 Ji Y, Riley AW, Lee LC, et al. Maternal biomarkers of acetaminophen use and offspring attention deficit hyperactivity disorder. *Brain Sci* 2018; **8:** 127.

39 Ji Y, Azuine RE, Zhang Y, et al. Association of cord plasma biomarkers of in utero acetaminophen exposure with risk of attention-deficit/hyperactivity disorder and autism spectrum disorder in childhood. *JAMA Psychiatry* 2020; **77:** 180–89.

40 Laue HE, Shen Y, Bloomquist TR, et al. In utero exposure to caffeine and acetaminophen, the gut microbiome, and neurodevelopmental outcomes: a prospective birth cohort study. *Int J Environ Res Public Health* 2022; **19:** 9357.

41 Laue HE, Cassoulet R, Abdelouahab N, et al. Association between meconium acetaminophen and childhood neurocognitive development in GESTE, a Canadian cohort study. *Toxicol Sci* 2019; **167:** 138–44.

42 Liew Z, Kioumourtzoglou MA, Roberts AL, O'Reilly EJ, Ascherio A, Weisskopf MG. Use of negative control exposure analysis to evaluate confounding: an example of acetaminophen exposure and attention-deficit/hyperactivity disorder in Nurses' Health Study II. *Am J Epidemiol* 2019; **188:** 768–75.

43 Liew Z, Ritz B, Rebordosa C, Lee PC, Olsen J. Acetaminophen use during pregnancy, behavioral problems, and hyperkinetic disorders. *JAMA Pediatr* 2014; **168:** 313–20.

44 Liew Z, Ritz B, Virk J, Olsen J. Maternal use of acetaminophen during pregnancy and risk of autism spectrum disorders in childhood: a Danish national birth cohort study. *Autism Res* 2016; **9:** 951–58.

45 Liew Z, Bach CC, Asarnow RF, Ritz B, Olsen J. Paracetamol use during pregnancy and attention and executive function in offspring at age 5 years. *Int J Epidemiol* 2016; **45:** 2009–17.

46 Liew Z, Ritz B, Virk J, Arah OA, Olsen J. Prenatal use of acetaminophen and child IQ: a Danish cohort study. *Epidemiology* 2016; **27:** 912–18.

47 Lye JM, Knight JA, Arneja J, et al. Maternal acetaminophen use and cognitive development at 4 years: the Ontario Birth Study. *Pediatr Res* 2023; **93:** 959–63.

48 Parker SE, Collett BR, Werler MM. Maternal acetaminophen use during pregnancy and childhood behavioural problems: discrepancies between mother- and teacher-reported outcomes. *Paediatr Perinat Epidemiol* 2020; **34:** 299–308.

49 Porta D, Fantini MP. Prospective cohort studies of newborns in Italy to evaluate the role of environmental and genetic characteristics on common childhood disorders. *Ital J Pediatr* 2006; **32:** 350–57.

50 Rifas-Shiman SL, Cardenas A, Hivert MF, Tiemeier H, Bertoldi AD, Oken E. Associations of prenatal or infant exposure to acetaminophen or ibuprofen with mid-childhood executive function and behaviour. *Paediatr Perinat Epidemiol* 2020; **34:** 287–98.

51 Ruisch IH, Buitelaar JK, Glennon JC, Hoekstra PJ, Dietrich A. Pregnancy risk factors in relation to oppositional-defiant and conduct disorder symptoms in the Avon Longitudinal Study of Parents and Children. *J Psychiatr Res* 2018; **101:** 63–71.

52 Skovlund E, Handal M, Selmer R, Brandlistuen RE, Skurtveit S. Language competence and communication skills in 3-year-old children after prenatal exposure to analgesic opioids. *Pharmacoepidemiol Drug Saf* 2017; **26:** 625–34.

53 Smith-Webb RS, Barnard-Mayers R, Werler MM, Parker SE. Prenatal exposure to acetaminophen and adolescent assessment of behavior: discrepancies by age and reporter. *Front Pharmacol* 2023; **14:** 1084781.

54 Snijder CA, Kortenkamp A, Steegers EA, et al. Intrauterine exposure to mild analgesics during pregnancy and the occurrence of cryptorchidism and hypospadia in the offspring: the Generation R Study. *Hum Reprod* 2012; **27:** 1191–201.

55 Stergiakouli E, Thapar A, Davey Smith G. Association of acetaminophen use during pregnancy with behavioral problems in childhood: evidence against confounding. *JAMA Pediatr* 2016; **170:** 964–70.

56 Sznajder KK, Teti DM, Kjerulff KH. Maternal use of acetaminophen during pregnancy and neurobehavioral problems in offspring at 3 years: a prospective cohort study. *PLoS One* 2022; **17:** e0272593.

57 Theunissen G, D'Souza S, Peterson ER, Walker C, Morton SMB, Waldie KE. Prenatal determinants of depressive symptoms in childhood: evidence from Growing Up in New Zealand. *J Affect Disord* 2022; **302:** 41–49.

58 Thompson JM, Waldie KE, Wall CR, Murphy R, Mitchell EA, ABC study group. Associations between acetaminophen use during pregnancy and ADHD symptoms measured at ages 7 and 11 years. *PLoS One* 2014; **9:** e108210.

59 Tovo-Rodrigues L, Carpena MX, Martins-Silva T, et al. Low neurodevelopmental performance and behavioural/emotional problems at 24 and 48 months in Brazilian children exposed to acetaminophen during foetal development. *Paediatr Perinat Epidemiol* 2020; **34:** 278–86.

60 Tovo-Rodrigues L, Schneider BC, Martins-Silva T, et al. Is intrauterine exposure to acetaminophen associated with emotional and hyperactivity problems during childhood? Findings from the 2004 Pelotas birth cohort. *BMC Psychiatry* 2018; **18:** 368.

61 Trønnes JN, Wood M, Lupattelli A, Ystrom E, Nordeng H. Prenatal paracetamol exposure and neurodevelopmental outcomes in preschool-aged children. *Paediatr Perinat Epidemiol* 2020; **34:** 247–56.

62 Vlenterie R, Wood ME, Brandlistuen RE, Roeleveld N, van Gelder MM, Nordeng H. Neurodevelopmental problems at 18 months among children exposed to paracetamol in utero: a propensity score matched cohort study. *Int J Epidemiol* 2016; **45:** 1998–2008.

63 Olstad EW, Nordeng HME, Lyle R, Gervin K. No impact of prenatal paracetamol and folic acid exposure on cord blood DNA methylation in children with attention-deficit/hyperactivity disorder. *Front Genet* 2023; **14:** 1204879.

64 Woodbury ML, Geiger SD, Schantz SL. The relationship of prenatal acetaminophen exposure and attention-related behavior in early childhood. *Neurotoxicol Teratol* 2024; **101:** 107319.

65 Woodbury ML, Cintora P, Ng S, Hadley PA, Schantz SL. Examining the relationship of acetaminophen use during pregnancy with early language development in children. *Pediatr Res* 2024; **95:** 1883–96.

66 Ystrom E, Gustavson K, Brandlistuen RE, et al. Prenatal exposure to acetaminophen and risk of ADHD. *Pediatrics* 2017; **140:** e20163840.

67 Lord C, Brugha TS, Charman T, et al. Autism spectrum disorder. *Nat Rev Dis Primers* 2020; **6:** 5.

68 Kearns GL, Abdel-Rahman SM, Alander SW, Blowey DL, Leeder JS, Kauffman RE. Developmental pharmacology—drug disposition, action, and therapy in infants and children. *N Engl J Med* 2003; **349:** 1157–67.

69 Pacifici GM. Placental transfer of antibiotics administered to the mother: a review. *Int J Clin Pharmacol Ther* 2006; **44:** 57–63.

70 Nitsche JF, Patil AS, Langman LJ, et al. Transplacental passage of acetaminophen in term pregnancy. *Am J Perinatol* 2017; **34:** 541–43.

71 WHO. Paracetamol (acetaminophen). Electronic Essential Medicines List. World Health Organization, 2023. https://list.essentialmeds.org/medicines/15 (accessed Oct 10, 2025).

72 Moretti ME, Bar-Oz B, Fried S, Koren G. Maternal hyperthermia and the risk for neural tube defects in offspring: systematic review and meta-analysis. *Epidemiology* 2005; **16:** 216–19.

73 Dreier JW, Andersen AM, Berg-Beckhoff G. Systematic review and meta-analyses: fever in pregnancy and health impacts in the offspring. *Pediatrics* 2014; **133:** e674–88.

74 Antoun S, Ellul P, Peyre H, et al. Fever during pregnancy as a risk factor for neurodevelopmental disorders: results from a systematic review and meta-analysis. *Mol Autism* 2021; **12:** 60.

75 International Federation of Gynecology and Obstetrics. Paracetamol (acetaminophen) use during pregnancy and autism risk: evidence does not support causal association. International Federation of Gynecology and Obstetrics, 2021. https://www.figo.org/paracetamol-acetaminophen-use-during-pregnancy-and-autism-risk-evidence-does-not-support-causal (accessed Oct 10, 2025).

76 Society for Maternal-Fetal Medicine. SMFM response to administration announcement on acetaminophen use during pregnancy and autism. Society for Maternal-Fetal Medicine, 2025. https://www.smfm.org/news/smfm-statement-on-acetaminophen-use-during-pregnancy-and-autism (accessed Oct 10, 2025).

77 European Medicines Agency. Use of paracetamol during pregnancy unchanged in the EU. Sept 23, 2025. September. https://www.ema.europa.eu/en/news/use-paracetamol-during-pregnancy-unchanged-eu (accessed Oct 10, 2025).

78 Medicines and Healthcare products Regulatory Agency. MHRA confirms taking paracetamol during pregnancy remains safe and there is no evidence it causes autism in children. Medicines and Healthcare products Regulatory Agency. https://www.gov.uk/government/news/mhra-confirms-taking-paracetamol-during-pregnancy-remains-safe-and-there-is-no-evidence-it-causes-autism-in-children (accessed Oct 10, 2025).

79 Health Canada. Acetaminophen: recommended treatment for fever and pain during pregnancy. Health Canada. https://recalls-rappels.canada.ca/en/alert-recall/acetaminophen-recommended-treatment-fever-and-pain-during-pregnancy (accessed Oct 10, 2025).

80 Bérard A, Cottin J, Leal LF, et al. Systematic review and meta-analysis: acetaminophen use during pregnancy and the risk of neurodevelopmental disorders in childhood. *J Am Acad Child Adolesc Psychiatry* 2025; published online Oct 6. https://doi.org/10.1016/j.jaac.2025.09.031.