



FAST TRACK

Maternal paracetamol (acetaminophen) use during pregnancy and risk of autism spectrum disorder and attention deficit/hyperactivity disorder in offspring: umbrella review of systematic reviews

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Additional material is published online only. To view please visit the journal online.

Cite this as: *BMJ* 2025;391:e088141
<http://dx.doi.org/10.1136/bmj-2025-088141>

Accepted: 04 November 2025

ABSTRACT

OBJECTIVE

To assess the quality, biases, and validity of evidence on maternal paracetamol (acetaminophen) use during pregnancy and the risk of autism spectrum disorder (referred to as autism) and attention deficit/hyperactivity disorder (ADHD) in offspring.

DESIGN

Umbrella review of systematic reviews.

DATA SOURCES

Medline, Embase, PsycINFO, and the Cochrane Database of Systematic Reviews, along with grey literature, Epistemonikos, and the reference lists of included studies (inception to 30 September 2025).

INCLUSION CRITERIA

Systematic reviews of randomised trials and cohort, case-control, or cross sectional studies that reported maternal paracetamol use during pregnancy and the diagnosis of autism or ADHD in offspring. Details of the primary studies included in the reviews are reported, including adjustments for key confounders (maternal characteristics, indication for paracetamol use, and familial factors) and unmeasured confounders and ascertainment of outcomes.

RESULTS

Nine reviews (40 studies) reporting on autism (six studies) and ADHD (17 studies) in offspring were

included. Four reviews undertook meta-analysis. The overlap of primary studies included in the reviews was very high (corrected covered area 23%). The reviews reported a possible to strong association between maternal paracetamol intake and autism or ADHD or both in offspring. Seven of the nine reviews advised caution when interpreting the findings owing to the potential risk of bias and confounding in the included studies. Confidence in the findings of the reviews was low (two reviews) to critically low (seven reviews) based on the AMSTAR 2 (A MeaSurement Tool to Assess Systematic Reviews) criteria. Only one review included studies (n=2) reporting autism and ADHD in offspring that appropriately adjusted for familial factors and unmeasured confounding through sibling controlled analyses. In both studies, the increased risk of autism in offspring (one study, hazard ratio 1.05, 95% confidence interval 1.02 to 1.08) and ADHD (two studies, 1.07, 1.05 to 1.10 and 2.02, 1.17 to 3.25) observed in the whole cohort analyses did not persist in sibling controlled analyses for autism (0.98, 0.93 to 1.04) and ADHD (0.98, 0.94 to 1.02 and 1.06, 0.51 to 2.05).

CONCLUSION

Existing evidence does not clearly link maternal paracetamol use during pregnancy with autism or ADHD in offspring.

SYSTEMATIC REVIEW REGISTRATION

PROSPERO CRD420251154052.

WHAT IS ALREADY KNOWN ON THIS TOPIC

Paracetamol (acetaminophen) is the recommended treatment for pain and fever in pregnancy and is considered safe by regulatory agencies worldwide

Systematic reviews and primary studies vary in their reporting on maternal paracetamol use during pregnancy and risk of autism spectrum disorder (autism) and attention deficit/hyperactivity disorder (ADHD) in offspring

Familial factors, maternal health and behaviour, and socioeconomic environment influence the neurodevelopmental outcomes of babies

WHAT THIS STUDY ADDS

Confidence in the findings of published systematic reviews on maternal paracetamol use during pregnancy and risk of autism and ADHD in offspring, with a very high overlap of primary studies, is low to critically low

Existing evidence does not show a clear link between in utero exposure to paracetamol and autism and ADHD in offspring

Any apparent effect observed after in utero exposure to paracetamol on autism and ADHD in childhood might be driven by familial genetic and environmental factors and unmeasured confounders

Introduction

Paracetamol (acetaminophen) is one of the most commonly used drugs in pregnancy worldwide.^{1 2} It is the recommended treatment for pain relief and fever in pregnancy.^{3 4} In September 2025, the US president advised against using Tylenol (acetaminophen) during pregnancy, citing risks of autism in children exposed to the drug in utero.⁵ The announcement caused considerable concern among pregnant women and mothers of children with autism.⁶ Withholding paracetamol use for high fever risks poor pregnancy outcomes.^{7 8 9} Worldwide, regulatory health agencies and expert bodies, such as the UK's Medicines and Healthcare Products Regulatory Agency, the European Medicines Agency, and the Australian Therapeutic Goods Administration, responded with reassurance about the safety of paracetamol use during pregnancy.¹⁰⁻¹² Professional bodies and health organisations advised women to contact

their healthcare practitioners for evidence based information on the safety of maternal paracetamol use during pregnancy.^{13 14}

To date, numerous systematic reviews have synthesised the evidence on the risks of prenatal exposure to maternal paracetamol use and autism spectrum disorder (referred to as autism) and attention deficit/hyperactivity disorder (ADHD) in childhood.¹⁵⁻¹⁷ These reviews, based on observational studies, vary in methodological quality, findings, and the interpretation of evidence.¹⁶ Primary studies that do not adjust for key confounders such as familial genetic and environmental factors, maternal health, indications for paracetamol use, and potential unmeasured confounders cannot accurately estimate the effects of in utero exposure to paracetamol on neurodevelopment in children.¹⁸ Erroneous conclusions could arise from ignoring the biases in primary studies and from inadequate definition and ascertainment of exposures and outcomes.^{19 20} Given the heterogeneous quality and reporting of studies, a robust overview of existing evidence is urgently needed to guide healthcare professionals, women, and families in interpreting the risks of paracetamol use during pregnancy.²¹ We therefore conducted an umbrella review of systematic reviews to assess the overall quality and validity of existing evidence and the strength of association between paracetamol use during pregnancy and the risks of autism and ADHD in offspring.

Methods

Literature search and study selection

Our umbrella review is based on a prospective protocol (registered on PROSPERO, 26 September 2025) and follows the recommended methods for rapid reviews.²² Our findings are reported in line with the Preferred Reporting Items for Overviews of Reviews guidelines (see supplementary appendix 1).²³ We searched Medline, Embase, PsycINFO, the Cochrane Database of Systematic Reviews, grey literature, and Epistemonikos from inception to 30 September 2025 for systematic reviews and meta-analyses of studies reporting maternal paracetamol use and autism spectrum disorder and ADHD outcomes. The search terms “paracetamol” or “acetaminophen” were combined with “pregnancy”, “antenatal”, or “maternal” that represented the population, which were further combined with terms for the outcome such as “child development”, “developmental disabilities”, “neurodevelopment”, “learning disorders”, “autism spectrum”, “attention deficit”, and “ADHD” (see supplementary appendix 2). We supplemented the electronic searches with a manual search of the reference lists. No language restrictions were applied.

A two stage process was used to select the reviews. Firstly, two reviewers (JA, JS) independently screened the titles and abstracts to identify eligible reviews and then retrieved and assessed the full texts of relevant citations. Disagreements were resolved through discussion with a third reviewer (JZ). We included

systematic reviews of randomised trials and cohort, case-control, or cross sectional studies that reported the effects of maternal paracetamol use during pregnancy on risk of autism and ADHD in offspring. We excluded narrative reviews, reviews of studies that focused solely on animal research, case series, conference abstracts, and studies that did not report outcomes related to autism or ADHD. When reviews contained overlapping primary studies, we documented the overlap.

Quality assessment

Two independent reviewers (MNP and HMB) assessed the methodological quality of the included reviews using AMSTAR 2 (A MeaSurement Tool to Assess Systematic Reviews).²⁴ Disagreements were resolved by discussion with a third reviewer (JZ). The tool evaluates the following domains, seven of these (marked with an asterisk) were considered critical: *a priori design or protocol registration, *comprehensive literature search strategy, use of publication status (eg, inclusion of grey literature) as an inclusion criterion, duplicate study selection and data extraction, *list and justification of excluded studies, characteristics of the included primary studies, *assessment and documentation of the quality or risk of bias of included studies, *appropriate use of study quality in interpreting and formulating conclusions, *appropriate statistical methods for combining study findings, *assessment of the likelihood of publication bias, and disclosure of conflicts of interest by the review authors. Following the proposed framework, we categorised our overall confidence in the results of the reviews as high (no critical weaknesses and at most one non-critical weakness), moderate (no critical weaknesses but more than one non-critical weakness), low (one critical weakness), or critically low (more than one critical weakness).

Data extraction and analysis

We extracted data independently and in duplicate (SS and JA) using a piloted standardised form. Information was extracted on review characteristics (year, review type, number and design of included studies, population characteristics), exposure (timing, duration, method of ascertainment of paracetamol use), type of outcomes (autism, ADHD) and their definition, the confounders considered, risk of bias assessment of the primary studies and the tools used, methods of synthesis, effect estimates and confidence intervals of the included primary studies, and the overall and subgroup findings. When reviews undertook meta-analysis, we extracted data on effect estimates, heterogeneity measures, and any publication bias.

A narrative synthesis of the included systematic reviews was undertaken. To address overlap, we constructed a citation matrix to map primary studies included in each systematic review and quantified the overlap using the corrected covered area method.²⁵ The degree of overlap was categorised as slight (0-5%), moderate (6-10%), high (11-15%), and very high

(>15%). To avoid overrepresentation of individual primary studies, we interpreted the findings with consideration of the extent of duplication. For each outcome we reported the pooled effect estimates with 95% confidence intervals as provided in the meta-analyses. We extracted information on the characteristics of the primary studies included in the reviews, their adjustment for key confounders such as maternal characteristics, indications for paracetamol use, familial genetic and environmental factors, and unmeasured confounding, and the methods used to ascertain autism and ADHD outcomes in offspring, such as clinician diagnosis, medical records, or validated parent completed or teacher completed questionnaires.

Patient and public involvement

We involved a carer of a child and grandchild with autism and a woman with lived experience of ADHD. Both provided input into our research question, reviewed the manuscript, and helped interpret the findings. They shared their lived experience of having a diagnosis of ADHD and how it affects many members of the family. They felt that recognising the strong familial and genetic links can reduce misplaced blame and reassure families that neurodivergence in their children is not caused by anything the mother did during pregnancy. The contributors highlighted the need for a comprehensive evidence

base for paracetamol use during pregnancy and clear dissemination of the findings.

Results

From 663 citations, we included nine systematic reviews^{16 17 26-32} that reported the findings from 40 primary studies (37 prospective cohorts, two case-control studies,^{33 34} and one ecological study³⁵); four were meta-analyses.^{17 27 30 31} Figure 1 provides the flow chart of the review identification process.

Characteristics of the included reviews

All reviews were published in the past 10 years and focused on maternal paracetamol intake throughout pregnancy, with one including both antenatal and postnatal use.³² Seven reviews included only cohort studies²⁶⁻³² and two included cohort and case-control studies.^{16 17} Two reviews included studies with inappropriate designs, such as multivariate predictive model and ecological study, to assess the exposure-outcome association.^{16 32} One review included a study that assessed maternal genetic ADHD risk and paracetamol use in pregnancy.¹⁶ Table 1 and supplementary appendix 3 provide the characteristics of the reviews, criteria for the inclusion of primary studies, the tools used for quality assessment, and the outcomes reported. Of the 40 studies included in the reviews, six reported on autism and 17 on ADHD. Supplementary appendix 4 provides the characteristics of the primary studies included in the reviews. Only one review, a narrative synthesis, included studies (n=2) that adjusted for shared familial factors and unmeasured confounding using sibling controlled analysis for autism (one study) and ADHD (two studies) outcomes in offspring.¹⁶ The two sibling controlled studies involved populations from Sweden (Ahlqvist et al)³⁶ and Norway (Gustavson et al)³⁷ and provided estimates by dose and duration of paracetamol use (see supplementary appendix 5).^{36 37} Supplementary appendix 6 provides the list of the excluded systematic reviews and the rationale for exclusion.

Quality of the included reviews

The methodological quality of the nine included systematic reviews revealed substantial weaknesses across several critical domains (fig 2). Most reviews lacked a previously registered protocol (item 2), did not provide a comprehensive literature search strategy (item 4), and did not present a list of excluded studies with justifications (item 7). Furthermore, the assessment and consideration of risk of bias in primary studies were frequently absent or partially present. None of the systematic reviews used the recommended tool to assess the risk of bias of non-randomised trials (either ROBINS-E or ROBINS-I) (item 9). Appropriate statistical methods for meta-analysis were rarely applied. The meta-analysis adjusted for confounding effect estimates in only one review (item 11). The impact of risk of bias on the interpretation of results was addressed only in three systematic reviews (item 13).

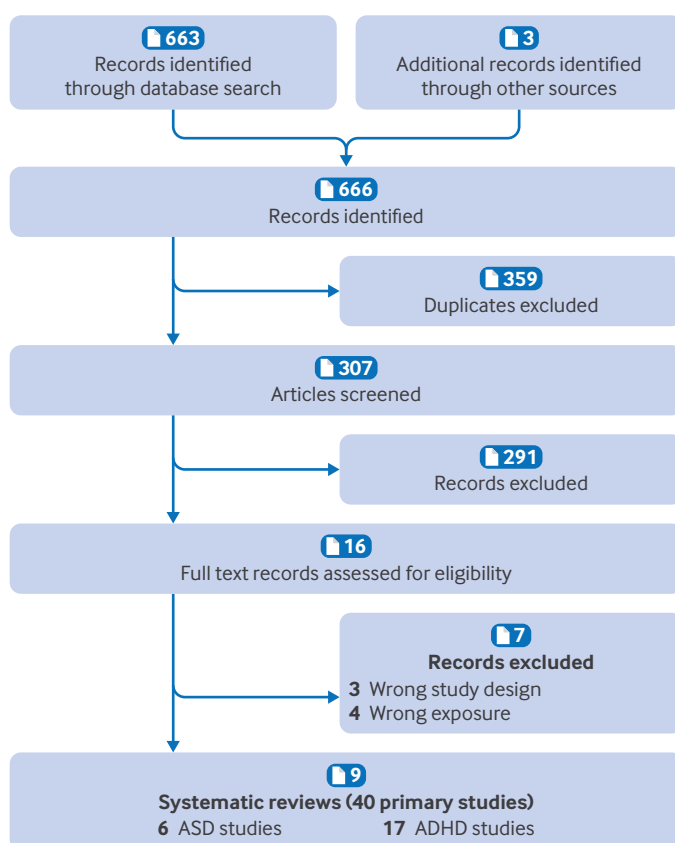


Fig 1 | Flow chart of review identification process. ADHD=attention deficit/hyperactivity disorder; ASD=autism spectrum disorder

Table 1 | Characteristics of systematic reviews included in the umbrella review on maternal paracetamol (acetaminophen) use during pregnancy and risk of ASD and ADHD in offspring

Reference	No of databases searched (search end)	No of included studies	Inclusion criteria	Exclusion criteria	Exposure assessment	Outcomes reported	Outcome assessment	Adjusted studies*	Synthesis	Interpretation of evidence	RoB tool (quality/RoB of included studies)
Bauer 2018	4 (Feb 2017)	9	Maternal paracetamol use during pregnancy and its association with ASD, ADHD, hyperkinetic disorder, and IQ in offspring	Studies with unexposed comparison, studies reporting no effect estimates, studies with overlap of cohorts	Maternal self-reported use (questionnaire/interviews)	ASD, ADHD, hyperactivity symptoms, IQ	Parental report, standard assessment	No	Narrative synthesis: nine prospective studies showed that prenatal exposure to paracetamol was associated with increased risks of adverse neurodevelopmental outcomes, including ADHD-like behaviours and autism	Increased risk of ASD and ADHD in offspring; further precise details needed on indications and exposure assessment	NOS (7 high quality, 2 moderate quality)
Gou 2019	4 (Nov 2018)	8	Maternal paracetamol use during pregnancy and ADHD risk in offspring	No overlap of cohorts, no effect size estimates, case or case series reports, no raw data	Maternal self-reported use (questionnaire/interviews); maternal biomarker	ADHD	Parental reports; standard assessment	No	Random effects meta-analysis: RR 1.25 (95% CI 1.17 to 1.34), $I^2=2$	Moderate association with ADHD in offspring; caution advised on causality owing to potential unmeasured and inadequately controlled confounder	NOS (6 high quality, 2 moderate quality)
Hoover 2015	3 (Jun 2015)	4	Maternal paracetamol use and development of ADHD and hyperactivity in offspring	Animal studies	Maternal self-reported use (questionnaire/interviews)	ADHD, ADHD-like behaviour	Parental reports; standard assessment	No	Narrative synthesis: three prospective studies showed a mild but statistically significant association between prenatal use and increased ADHD diagnoses or symptoms, while one found no effect	Possible mild association, but many variables unaccounted; evidence insufficient to attribute ADHD in offspring to maternal paracetamol use	Not stated
Khan 2022	5 (Not stated)	13	Women in reproductive years aged >16 years taking paracetamol in pregnancy and child neurodevelopment	Grey or unpublished literature, adult male studies, animal studies	Maternal self-reported use (questionnaire/interviews); cord and maternal plasma biomarkers	ASD, ADHD, IQ, isolated language, attention, executive function, communication, behaviour, and psychomotor development	Parental reports; standard assessment; genotype data; maternal polygenic risk scores	No	Narrative synthesis: all included studies reported associations between exposure to paracetamol and adverse outcomes, with stronger associations seen for longer duration, higher dose, and more frequent use	Association with adverse neurodevelopment, including ASD; more research needed	Not stated
Masanwa 2018	3 (Jan 2017)	7	Cohort studies and case-control studies reporting effect estimates for ADHD or ASD in offspring of women exposed to paracetamol during pregnancy	Case reports, cross sectional studies, letters, editorial	Maternal self-reported use (questionnaire/interviews)	ASD, ADHD, hyperactivity symptoms, conduct disorder	Parental reports; standard assessment	No	Random effects meta-analysis: ADHD: RR 1.34 (95% CI 1.21 to 1.47), $I^2=7.2\%$; ASD: RR 1.19 (1.14 to 1.25), $I^2=14\%$; cautioned the interpretation of results owing to RoB and potential confounding factors	Association with ASD and ADHD; caution advised in interpretation owing to RoB and potential confounding factors	NOS (6 moderate quality, 1 poor quality)
Masanwa 2020	4 (Dec 2018)	7	Observational studies examining paracetamol use during pregnancy and ADHD risk in offspring	Not stated	Maternal self-reported use (questionnaire/interviews)	ADHD	Parental reports; standard assessment	No	Updated random effects meta-analysis: ADHD: RR 1.31 (95% CI 1.23 to 1.39), $I^2=48\%$	Association with offspring ADHD likely due to unmeasured confounding	Not stated
Patel 2022	3 (Aug 2021)	12	Any study describing use of paracetamol in prenatal or neonatal period and examined child neurodevelopmental outcomes	Animal studies, duplicate studies	Maternal self-reported use (questionnaire/interviews); cord and maternal plasma biomarkers; ecological evaluation	ASD, ADHD, behavioural performance, intelligence, executive and psychomotor function problems	Parental reports; standard assessment	No	Narrative synthesis: 11 studies found that prenatal exposure to paracetamol was associated with increased risks of neurodevelopmental adverse outcomes	Possible association; limited evidence and prone to biases such as confounding by indication of modern cross sectional ecologic study)	NOS (11 high quality; 1 high quality)

Prada 2025	4 (Feb 2025)	33†	Observational studies focusing on prenatal paracetamol exposure and neurodevelopmental disorders outcomes in children	Postnatal exposure, animal studies and studies presenting results from same cohort or dataset	Maternal self- reported use (questionnaire/ interviews); cord and maternal plasma biomarkers; pharmacy registry	ADHD, ASD, other neurodevelopmental disorders	Parental reporting; standard assessment; genotype data maternal polygenic risk scores	Yes (2 studies)	Narrative synthesis: Of the 20 cohorts on ADHD, 14 reported positive associations, 3 null, 1 inverse, and 2 mixed associations. Of the 8 studies on ASD, 5 reported positive associations, 2 null, and 1 mixed association	Strong consistent association with ASD and ADHD	Navigation Guide's RoB assessment (ADHD: 18 low RoB, 1 probably low, and 1 probably high; ASD: 4 low RoB, 1 probably low, and 3 high)
Ricci 2023	4 (Aug 2022)	22	Observational studies of babies exposed to paracetamol in utero in comparison group of unexposed children	Conference abstracts, letters, case reports	Maternal self- reported use (questionnaire/ interviews); cord and maternal plasma biomarkers; pharmacy records	ADHD, delays or disorders in communication, motor, social, and other development	Parental reporting; standard assessment	No	Random effects meta- analysis; unadjusted ADHD: RR 1.32 (95% CI 1.20 to 1.44), $I^2=47\%$; adjusted for maternal and infant characteristics ADHD: RR 1.47 (1.12 to 1.92), $I^2=80\%$; adjusted for maternal and infant characteristics and confounding by indication ADHD: RR 1.34 (1.15 to 1.55), $I^2=50\%$	Small to moderate association not explained by confounding by indication; need for high quality studies and adjust for unmeasured confounding	SAQOROR (3 high, 13 moderate, 5 low quality)

ADHD=attention deficit/hyperactivity disorder; ASD=autism spectrum disorder; CI=confidence interval; IQ=intelligence quotient; NOS=Newcastle-Ottawa Scale; RoB=risk of bias; RR=relative risk; SAQOROR=Systematic Assessment of Quality in Observational Research.

*Studies adjusted for familial factors and unmeasured confounding for ASD and/or ADHD outcomes in offspring.

†Included two sibling controlled studies.

Review	Item	1. PICO components in research question	2. Protocol established before review, deviations justified*	3. Study design justification	4. Comprehensive literature search*	5. Selection in duplicate	6. Extraction in duplicate	7. List and justification of excluded studies*	8. Characteristics of included studies in detail	9. Adequate risk of bias assessment in individual studies*	10. Report sources of funding for primary studies	11. Appropriate statistical methods for synthesis*	12. RoB in meta-analysis	13. Consider RoB of primary studies in discussion*	14. Explanation/discussion of heterogeneity	15. Publication bias*	16. Conflicts of interest/funding for review	Overall confidence
Bauer 2018		No	No	No	No	No	No	No	Partial yes	Partial yes	No	No MA	No MA	No	No	No MA	Yes	Critically low
Gou 2019		No	No	No	No	No	Yes	No	Yes	Partial yes	No	No	No	No	Yes	Yes	Yes	Critically low
Hoover 2015		No	No	No	No	No	No	No	Partial yes	No	No	No MA	No MA	No	No	No MA	Yes	Critically low
Khan 2022		No	No	No	No	Yes	Yes	No	Partial yes	Partial yes	No	No MA	No MA	No	No	No MA	Yes	Critically low
Masarwa 2018		Yes	Partial yes	No	Yes	Yes	No	No	Yes	Partial yes	No	No	Yes	Yes	Yes	No	Yes	Critically low
Masarwa 2020		Yes	Partial yes	No	Yes	Yes	No	No	Yes	No	No	Yes	No	No	No	No	Yes	Critically low
Patel 2022		Yes	Partial yes	No	Partial yes	Yes	Yes	No	Yes	Partial yes	No	No MA	No MA	Yes	No	No MA	Yes	Low
Prada 2025		Yes	Partial yes	No	Partial yes	Yes	No	No	Yes	Partial yes	No	No MA	No MA	Yes	Yes	No MA	Yes	Low
Ricci 2023		Yes	Partial yes	No	No	Yes	Yes	Yes	Yes	Partial yes	No	No	No	No	No	No	Yes	Critically low

Fig 2 | Methodological quality of reviews. Overall confidence in the results of the review are classified: High: Zero or one non-critical weakness: the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest. Moderate: More than one non-critical weakness: the systematic review has more than one weakness, but no critical flaws. It may provide an accurate summary of the results from the available studies included in the review. Low: One critical flaw with or without non-critical weaknesses: the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest. Critically low: More than one critical flaw with or without non-critical weaknesses: the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies. Notes: Item 1: The current study rated this as “no” when the review did not include a section that explicitly specified the components of the PICO question. If these components were not stated in the review but were available in the published protocol, the current study rated this item as “yes.” Item 3: The current study rated this item as “no” when the review did not justify the choice of study design(s). If the review merely listed the types of studies to be included, or stated that all types of studies were eligible, it was also rated as “no.” Item 9: Given that the ROBINS-I and ROBINS-E tools are the standard for evaluating risk of bias in non-randomised studies, the use of alternative instruments was rated as “partial yes,” since they do not provide the same level of methodological rigour and comprehensiveness. Item 11: Since one of the conditions for scoring this item as “yes” is either that adjusted data were included in the pooled analysis or that the use of raw data was justified when adjusted data were unavailable, the current study rated this item as “no” when these conditions were not met. Masarwa 2020 is an update of Masarwa 2018. This review focused on unmeasured confounding and provided limited details on the review methodology, stating that the same methods as the previous review were followed. *Critical domains. AMSTAR-2=A MeaSurement Tool to Assess systematic Reviews 2; MA=meta-analysis; PICO=population, intervention, comparison and outcome; RoB=risk of bias; ROBINS-E=Risk Of Bias In Non-randomised Studies-of Exposure; ROBINS-I=Risk Of Bias In Non-randomised Studies-of Interventions

Likewise, only one review adequately investigated publication bias when quantitative synthesis was undertaken (item 15). Owing to these issues in multiple critical domains, the overall confidence in the results was rated as critically low in seven systematic reviews^{17 26-31} and low in two systematic reviews.^{16 32} The corrected covered area was 23%, indicating a very high overlap among the reviews, with the nine reviews mostly based on the same primary studies (see supplementary appendix 7).

Effects of maternal paracetamol use on autism and/or ADHD in offspring

All reviews reported a positive association between maternal paracetamol use in pregnancy and adverse

neurodevelopmental outcomes in offspring. The conclusions of seven of the nine reviews warned against interpreting a causal link between maternal paracetamol use and autism or ADHD, or both in offspring, citing lack of data, bias in the primary studies, and unmeasured or inadequately controlled confounders (table 1). The four reviews that performed meta-analyses reported pooled relative risks or odds ratio for ADHD ranging between 1.2 and 1.4, and smaller but positive estimates for autism.^{17 27 30 31} Subgroup and sensitivity analyses in three meta-analyses showed stronger associations with longer duration or higher frequency of paracetamol use^{27 30} and with exposure during the third trimester.²⁷ Risk of bias and unmeasured confounding in the primary

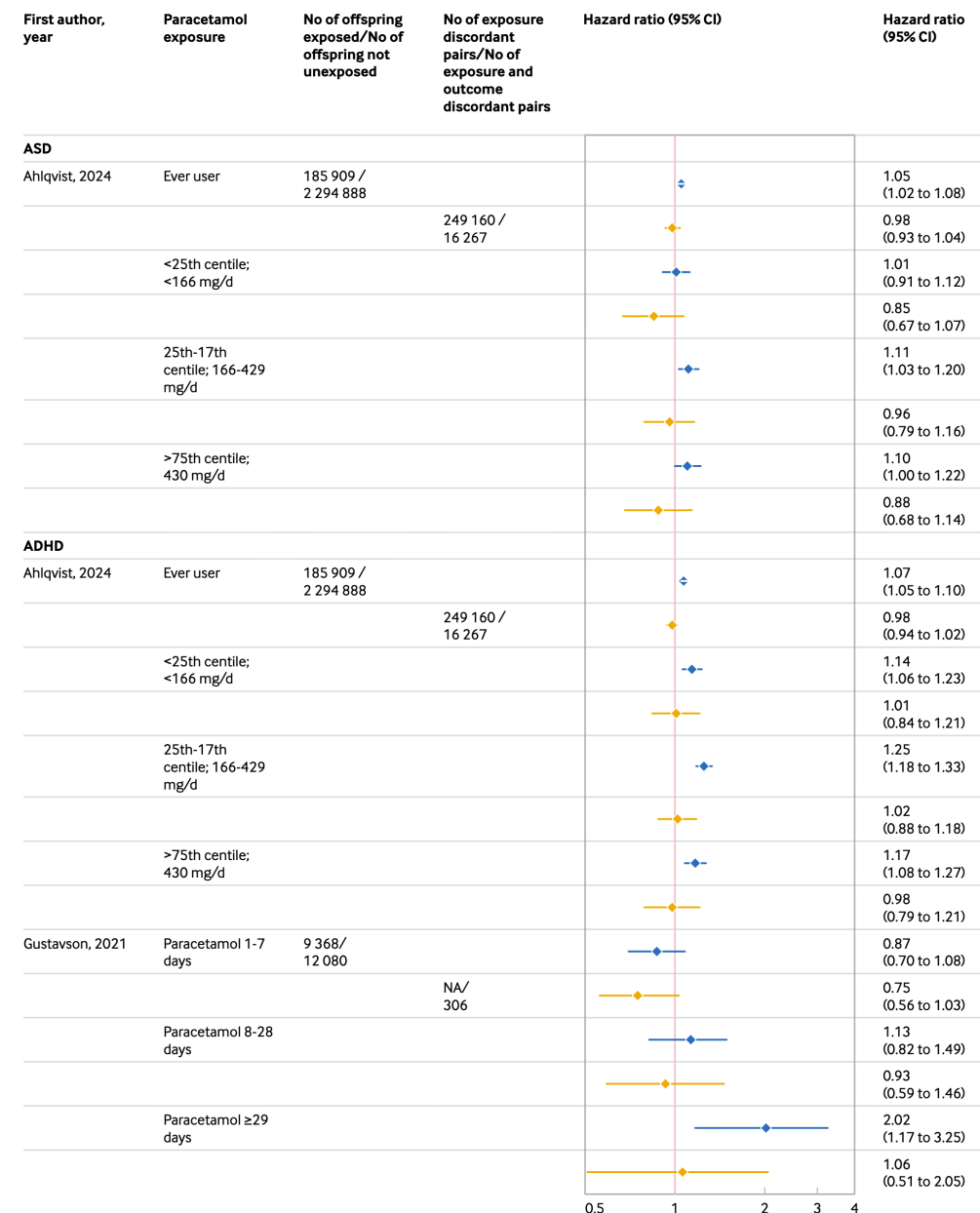
Maternal paracetamol (acetaminophen) use during pregnancy

Association with ASD and ADHD in offspring by whole cohort analysis (blue) and sibling controlled analysis (yellow) in primary studies included in the reviews



All ASD ADHD

Whole cohort analysis Sibling analysis



Article DOI: 10.1136/bmj-2025-088141 • Download data

ADHD=attention deficit/hyperactivity disorder; ASD=autism spectrum disorder; CI=confidence interval; NA=not available

Fig 3 | Maternal paracetamol (acetaminophen) use during pregnancy and association with autism spectrum disorder and attention deficit/hyperactivity disorder. An interactive version of this graphic is available at <https://public.flourish.studio/visualisation/26019505/>

studies were considered to influence the results in two of the four meta-analyses.^{30 31} None of the studies in the meta-analysis adjusted for shared familial factors and unmeasured confounding.

In the two studies that adjusted for shared familial factors and unmeasured confounding using sibling controlled analysis for autism and ADHD outcomes in offspring, we observed a consistent pattern (fig 3). In

both studies, the whole cohort analyses yielded small, positive associations—often with dose or duration gradients—whereas sibling comparisons (adjusted for time varying maternal factors) shifted the estimates towards a null effect. For ADHD, the hazard ratio for ever use of paracetamol in the study by Ahlqvist et al was 1.07 (95% confidence interval (CI) 1.05 to 1.10) in the whole cohort that reduced to 0.98 (0.94 to 1.02) in siblings; the ≥ 29 day category hazard ratio estimates in the study by Gustavson et al decreased from 2.02 (95% CI 1.17 to 3.25) to 1.06 (0.51 to 2.05) in sibling controlled analysis.^{36 37} The same attenuation was observed for autism: in the study by Ahlqvist et al, the hazard ratio for ever use of 1.05 (1.02 to 1.08) was reduced to 0.98 (0.93 to 1.04) in sibling controlled analysis.³⁶ The dose specific contrasts showed a similar leftward shift. For example, the hazard ratio of the 75th centile paracetamol dose exposure was 1.10 (1.00 to 1.22) and decreased to 0.88 (0.68 to 1.14). In the best powered sibling analyses (Ahlqvist et al), the upper bounds rule out more than very small increases ($\leq 2\%$ for ADHD; $\leq 4\%$ for autism).³⁶

Discussion

Existing systematic reviews on prenatal exposure to paracetamol and risk of autism and ADHD in offspring included heterogeneous studies, and many suggested a positive association. But few reviews accounted for the study quality, appropriate control of relevant confounders, and rigorous ascertainment of drug use and outcomes in the primary studies when interpreting the evidence. Also, the overlap of primary studies in these reviews was substantial. Our confidence in the review findings is low to critically low. In the primary studies that appropriately adjusted for familial factors through a sibling controlled design, and for key time varying maternal characteristics and indications for paracetamol use, the observed association between exposure to paracetamol and risk of autism and ADHD in childhood disappeared or attenuated. This disappearance of association in the sibling analyses, previously observed in the whole cohort, suggests that shared family factors, such as parental mental health, genetic predisposition, and socioenvironmental background, explain much of the observed risk.^{38–40}

Strengths and limitations of this review

Our overview brings together all relevant evidence and applies established methods to assess quality. We rigorously evaluated the quality and the degree of overlap in primary studies between reviews, showing the very low quality of previous syntheses and the high degree of redundancy.^{24 25} This justified our strategy to focus on primary studies with better control of bias that used a sibling (within family) design, because autism and ADHD show strong familial aggregation,^{41 42} making it important to control for unmeasured genetic and stable family factors. The sibling fixed effects absorb these shared influences without the need to measure them, whereas standard approaches (eg, propensity score, inverse probability of treatment

weighting) address only the measured confounders. Although sibling models are less precise because only discordant pairs contribute data, the largest cohort still provided narrow confidence intervals.³⁶ These studies were at low risk of bias, with limited concerns about missing data. Many studies used standardised tools (some more valid than others) as indicators for autism or ADHD, to indicate that children might have one of these conditions.^{43 44} To be confident in a diagnosis, best practice guidelines always recommend a clinician's diagnosis supported by evidence from well validated tools.

Our work has limitations. The included systematic reviews differed in scope and methods. We restricted outcomes to only autism and ADHD, in direct response to the recent announcements around the safety of paracetamol use in pregnancy.^{5 6} Therefore, we were unable to report the effects of paracetamol use on other neurodevelopmental outcomes. We depended on published tables and appendices and did not contact authors owing to the rapid nature of our review. Hence, some exposure or covariate details may be misclassified or inconsistently defined. Although we measured overlap across reviews and performed a comprehensive search, residual redundancy and missed sources are still possible. Finally, the pooriness of reporting limited the exploration of effect modifiers (eg, indication, timing, dose).

Comparison with existing evidence

A previous umbrella review, by Kwok et al,¹⁵ examined the effect of prenatal exposure to various analgesic drugs and the risk of autism and ADHD in childhood and included four systematic reviews on paracetamol.^{26–28 30} Our overview focused only on prenatal exposure to paracetamol and included five additional systematic reviews.^{16 17 29 31 32} We excluded the study by Alemany et al that was included in the Kwok et al umbrella review as it was not a systematic review.⁴⁵ Kwok et al considered the four included systematic reviews to be of moderate or high quality, whereas in our analysis, we rated these four reviews as critically low quality.¹⁵ We were unable to verify the reasons for this discrepancy, as Kwok et al reported only the overall AMSTAR 2 ratings.¹⁵

Until now, systematic reviews of mainly conventional whole cohort studies have been of very low quality, with inconsistent results. But sibling comparisons, especially when applied to large registry based cohorts and combined with extensive sensitivity analyses, give stable and conservative estimates. In addition to those published in the included reviews, we are aware of one additional prospective cohort study, by Okubo et al, published after the completion of the last review.⁴⁶ The study involved a Japanese population and adjusted for key confounders and familial factors using sibling controlled analysis. Similar to the two existing sibling controlled studies in the included reviews, Okubo et al reported an attenuated association between maternal ever use of paracetamol and ADHD in offspring, with hazard ratios decreasing from 1.32 (95% CI 1.16 to

1.51) to 0.86 (0.52 to 1.44), and between ever use and autism, with hazard ratios decreasing from 1.09 (1.00 to 1.19) to 0.85 (0.64 to 1.13) in sibling controlled analysis. The study had a relatively short follow-up period ($\approx 50\%$ observed for <4.4 years) compared with the Nordic cohorts.⁴⁶ This short follow-up leaves many children without outcome information at older ages, increasing the potential for bias. The Japanese study adds important new evidence by replicating these findings in an Asian population and by conducting extensive sensitivity analyses to test for alternative explanations.⁴⁶ In the best powered sibling analyses (Ahlqvist et al), the upper bounds rule out more than very small increases ($\leq 2\%$ for ADHD; $\leq 4\%$ for autism), whereas smaller cohorts cannot exclude modest effects (eg, up to 44% for ADHD in Okubo et al and 13% for autism).^{36 46} Overall, the triangulation suggests that familial and related confounding factors are likely to largely explain the apparent positive signals observed in conventional cohorts, while small residual effects cannot be entirely ruled out in the less precise sibling estimates.

Several criticisms of sibling designs have been raised,^{16 57} which we consider in detail below. The first is over-adjustment—that is, sibling models may remove a real causal effect together with confounding. Ahlqvist et al, however, showed that not only paracetamol but also other analgesics (non-steroidal anti-inflammatory drugs, opioids, antimigraine drugs) displayed the same pattern—small associations in whole cohort models that disappeared in sibling controlled models.³⁶ Sibling designs show a consistent finding across countries, despite differences in populations, health systems, and data sources. This consistency strongly suggests that sibling designs remove family level bias, particularly given the increasing evidence of high genetic linkage observed in autism and ADHD, and does not negate a real effect. A second criticism is the role of non-shared confounders, such as maternal infections or stress, which can vary between pregnancies. Gustavson et al addressed this by comparing sibling similarity in exposure to paracetamol with similarity in confounders such as maternal education, smoking, body mass index, and psychiatric history.³⁷ Confounders were more strongly correlated with exposure than the exposure itself, meaning the sibling design reduces bias more than it introduces it. Okubo et al added further evidence by adjusting for a wide range of pregnancy specific conditions and applying statistical methods, such as propensity scores and inverse probability weighting, and found the results to be unchanged.⁴⁶ A third criticism is measurement error, since misclassification could bias the association to the null, attenuating within family contrasts more than cohort models. Gustavson et al performed simulations that showed measurement error explains some attenuation but cannot account for the large attenuation observed.³⁷ Ahlqvist et al used prescription and antenatal records to minimise recall bias, and they performed sensitivity analyses excluding combination products.³⁶ Okubo et

al addressed over-the-counter misclassification using probabilistic bias analysis and showed that missing information on exposure would bias conventional models away from the null rather than toward it.⁴⁶ A fourth criticism was low statistical power. The finding that sibling estimates consistently shifted toward the null, with the best powered study³⁶ showing narrow 95% CIs that excluded clinically meaningful effects, indicated the removal of familial confounding bias rather than a loss-of-power issue. Finally, selection bias is a concern, as families with discordant siblings may not be representative of the entire population. However, the studies by Ahlqvist et al and Gustavson et al were based on nationwide registries that included almost all births, and Okubo et al directly assessed for selection bias using inverse probability weights and bounding factors and found minimal impact on the findings.^{36 37 46} In the study by Gustavson et al,³⁷ out of the 29 090 siblings initially identified, 2477 were excluded owing to missing information on exposure and 5165 for missing information on covariates, which totalled about 25% of the sibling sample. The main analyses relied on complete cases. However, multiple imputation yielded estimates similar to the complete case results, suggesting that any bias from missing covariates would likely not materially change conclusions.

One additional earlier sibling study, by Brandlistuen et al, from the same Norwegian cohort on maternal paracetamol use in pregnancy and parent reported externalising symptoms in children, reported poorer child development at three years and that associations appeared stronger in their sibling analysis.⁴⁷ This conflicts with the later study by Gustavson et al, which used the same cohort with longer follow-up and registry based diagnoses of ADHD and autism and showed attenuation in sibling analyses. Several factors can explain the divergence: Brandlistuen et al studied early developmental traits reported by mothers, not clinical diagnoses of ADHD; they used an earlier, less mature dataset with fewer siblings and shorter follow-up; and the number of discordant sibling pairs was small, which makes estimates unstable.⁴⁷

Implications for clinical practice and policy

Our review shows the lack of robust evidence linking paracetamol use in pregnancy and autism and ADHD in offspring. Regulatory bodies, clinicians, pregnant women, parents, and those affected by autism and ADHD should be informed about the poor quality of the existing reviews and the likelihood that positive associations reported in studies were driven by familial confounding. Given that alternative classes of drugs for relief of pain and fever, such as non-steroidal anti-inflammatory drugs, are known to adversely affect the fetal vascular system and can cause complications such as oligohydramnios and premature closure of the ductus arteriosus,^{48–50} and considering the harmful effects of pyrexia on pregnancy, women should be advised to take paracetamol when needed to treat pain and pyrexia in pregnancy.⁵¹

To date, no well established molecular mechanisms link exposure to paracetamol with autism or ADHD in childhood. A quantitative review of animal studies found no consistent evidence that developmental exposure to paracetamol at therapeutic or non-toxic doses results in neurodevelopmental harm.⁵² Various hypotheses based on animal, in vitro, and in silico work have proposed that paracetamol could influence fetal brain development through oxidative stress⁵³; mitochondrial effects⁵⁴; prostaglandin, endocannabinoid, or TRPV1 signalling⁵⁵; or epigenetic changes.⁵⁶ But it is important to note that data from human studies to support any of these putative mechanisms is lacking. Such a lack of evidence around medicine use during pregnancy remains a critical and longstanding problem resulting from the historical and ongoing underinvestment in women's health research, particularly in pregnancy, perpetuating an evidence gap.²¹

Implications for research

In the future, studies reporting the effects of paracetamol use in pregnancy on neurodevelopment in children should ensure both reliable assessment of exposure and rigorous ascertainment of outcomes, address bias due to confounding that includes indication bias, and prioritise adjustment for genetic and shared environmental factors, preferably through sibling cohorts. Lastly, studies should triangulate results across complementary analyses, including population models, sibling comparisons, negative controls, and sensitivity analyses, to minimise biases inherent to any single approach.

Conclusion

Reviews have reported an association between maternal paracetamol use during pregnancy and autism or ADHD in offspring, but quality was low. The current evidence base is insufficient to definitively link in utero exposure to paracetamol with autism and ADHD in childhood. High quality studies that control for familial and unmeasured confounders can help improve evidence on the timing and duration of paracetamol exposure, and for other child neurodevelopmental outcomes.

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We thank CW and JP, two public and patient partnership members who provided their valuable lived experiences and input into the study, and Alexander Davies and Caroline Dale at the University of Liverpool for their support during preparation of this manuscript.

Contributors: JS, JA, and SS are joint first authors and contributed equally to this work. ST and JZ are joint last authors and contributed equally to this work. JS, JA, SS, HN, FN, MNP, and HMB conducted study selection, data extraction, and analysis and wrote the manuscript. ST and JZ designed the study, supervised the project, and revised the manuscript. MNP and HMB assisted with detailed statistical analysis. All authors reviewed and approved the final version of the manuscript. ST is the guarantor. The corresponding author (ST) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Funding: ST is a senior investigator for the National Institute for Health and Care Research (NIHR). SS is funded by the NIHR Midlands Patient Safety Research Collaboration. The views expressed are those of the author(s) and not necessarily those of the NIHR or the Department of Health and Social Care. HMB is supported by the Instituto de Salud Carlos III through a Río Hortega contract (CM24/00152), co-funded by European Social Fund Plus.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/disclosure-of-interest/ and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: Not required.

Data sharing: All data relevant to the study is included in the article or uploaded as supplementary information.

Transparency: The lead author (the manuscript's guarantor) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Dissemination to participants and related patient and public communities: The findings of this study will be disseminated to the public through institutional press releases, academic and public facing blogs, and social media platforms to maximise accessibility and engagement. The results will also be shared with relevant patient and public involvement networks and organisations focused on maternal and child health. All outputs will be published open access to ensure broad availability.

Provenance and peer review: Not commissioned; externally peer reviewed.

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Supplementary information: Appendices 1-7