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Analgesic drug use in pregnancy and neurodevelopment outcomes: an umbrella review

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ABSTRACT

Emerging evidence from reviews suggests that analgesic drug exposure during pregnancy may contribute to child neurodevelopment outcomes. A comprehensive overview of existing evidence is needed for firm conclusions to inform clinical guidelines. This umbrella review aims to synthesise high-quality evidence on prenatal analgesic drug exposure and risk of ASD and ADHD in children. Seven databases were searched from inception to May 2021 to identify relevant reviews of any design. The AMSTAR 2 and the GRADE quality assessments were used to evaluate risk of bias and heterogeneity. A narrative synthesis approach was used to summarise findings. Five systematic reviews and meta-analyses met the inclusion criteria. All reviews reported significant associations between maternal prenatal acetaminophen use and ADHD outcomes (risk ratio range: 1.08–1.34; no pooled incidence rate), with a potential dose-dependent relationship. Potential sources of heterogeneity included usage timing and dosage. Findings suggest minimisation of prenatal acetaminophen exposure due to risk for ADHD outcomes. Future studies should include assessing potentially interacting mechanisms associating acetaminophen use with future neurodevelopmental outcomes.

1. Background

Literature suggests that around 90% of women take some form of medication during pregnancy (Elsabbagh et al., 2012; Thomas et al., 2015), with approximately 56% of women reporting using analgesic drugs during pregnancy (Lupattelli et al., 2014), making them the most common class of drugs used during pregnancy (Servey and Chang, 2014; Henry and Crowther, 2000). Given its widespread use, it is critical that there is clarity on the potential harms of analgesic drug use during pregnancy. The purpose of the current study is to synthesise the evidence from existing meta-analyses and systematic reviews, to provide a comprehensive overview of the evidence on the links between prenatal maternal analgesic use and key neurodevelopmental outcomes: autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD). This study aims to summarise findings in the form of a narrative review on how analgesic drug use during pregnancy affects risk for ASD and ADHD outcomes.

Drug absorption increases during pregnancy through the mother's increased cardiac output and blood flow (Feghali et al., 2015; Sachdeva et al., 2009). This bioavailability then leads to some unbound drugs with characteristics of lipid solubility, lower ionization, and lower molecular weight (<500 g/mol) crossing the placenta and entering the fetal blood circulatory system in large concentrations, directly affecting the fetal brain (Griffiths and Campbell, 2015; Gedeon and Koren, 2006). Drugs within this category include aspirin, ibuprofen, naproxen, and acetaminophen (paracetamol). While previous research has suggested neurodisruptive properties of certain drugs on the fetus (Masarwa et al., 2018), some of these drugs are still not classified human teratogens and are easily accessible to the public. Current clinical guidelines are still based on dated and limited evidence regarding the long-term effects of these drugs on the fetus (Guidance for Industry on Establishing Pregnancy Exposure Registries, 2002).

Abbreviations: ASD, Autism Spectrum Disorder; ADHD, Attention-Deficit Hyperactivity Disorder; AMSTAR 2, A MeaSurement Tool to Assess systematic Reviews (2nd edition); DSM-5, Diagnostic and Statistical Manual of Mental Disorders (5th edition); FDA, Food and Drug Administration (United States); HKD, Hyperkinetic Disorder; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; PROSPERO, International Prospective Register of Systematic Reviews.

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It is critical to examine how drugs such as acetaminophen, which are easily accessible and commonly found over the counter, can potentially affect child neurodevelopmental outcomes. Increasing clinical evidence suggests that prenatal exposure to medication could have lasting effects on fetal development, such as neurological, reproductive, and urogenital disorders (Bauer et al., 2021). A recent review suggested that medications such as acetaminophen can act as an endocrine disruptor, and has associations with variety of risks ranging from genital malformations (Mazaud-Guittot et al., 2013), cognitive and behavioural difficulties (Rifas-Shiman et al., 2020), and hormonal disruption causing early puberty onset during adolescence (Bauer et al., 2021). Within this review, positive associations were found in 26 out of 29 studies of 220,000 mother-child pairs when examining maternal acetaminophen use and potential adverse neurodevelopment effects such as ADHD, ASD, decreased IQ and conduct disorders. In 16 out of 19 studies within the review, possible dose-response associations were found (Bauer et al., 2021).

Other reviews have found links between maternal prenatal analgesic drug use and increased risk of neurodevelopmental disorders between the ages of 18 months and 12 years old (Masarwa et al., 2018; Bauer et al., 2018). However, bias analyses performed to studies that failed to adjust for relevant confounders such as parental ADHD and maternal migraine found no such link. Findings may therefore be influenced by unmeasured confounding. As the existing evidence on links between maternal use of analgesic drugs in pregnancy and children's neurodevelopmental outcomes seems mixed, the aims of this umbrella review are to: a) examine and synthesise findings from the current literature of systematic reviews or meta-analyses on links between analgesic drug use in pregnancy and neurodevelopmental disorders in children, specifically ASD and ADHD; b) use high-quality evidence to inform guidelines and clinical practices regarding the use of analgesic drugs in pregnancy and neurodevelopmental outcomes of ASD and ADHD; and c) to identify possible gaps in the literature providing further opportunities to better inform recommendations for future research in this area.

2. Methods

2.1. Study design

An umbrella review examining the associations between analgesic drug use during pregnancy and ASD or ADHD outcomes was conducted and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses Protocols (PRISMA-P) statement. The study protocol was previously published (Kwok et al., 2020) and has also been registered in the International Prospective Register of Systematic Reviews (PROSPERO) database (CRD42020179216).

2.2. Search Strategy and Selection Criteria

A search was performed by one reviewer through the following major databases: Embase, Global Health, PsycINFO, PsycARTICLES, PubMed, and Cochrane Library from inception to 30 May 2021 (Supplement 1). Boolean operators of "AND" and "OR" were used for linking search terms, with specific syntax adapted for different databases. Search filters were employed and presented sequentially, with key terms searched for in the title or abstract fields. Relevant subject headings were also included in the search such as using MeSH ID numbers. These included analgesics (D000700), aspirin (D001241), acetaminophen (D000082), ibuprofen (D007052), naproxen (D009288), diclofenac (D004008), ketoprofen (D007660). Reference lists of selected reviews, reviews in-press (derived from scanning pre-print archives or discussion with field experts), manual searches of grey literature (such as Open Grey, Virtual Health Library), and preprint platforms (such as arXiv.org, medRxiv.org, PsyArXiv.com, Open Science Framework [OSF] preprints) were also scanned for articles fitting the eligibility criteria.

Articles included systematic reviews and meta-analysis examining associations between analgesic drugs and the outcomes of ASD, ADHD or ASD and ADHD in human offspring. Animal models were not included in this review. Reviews were not restricted to those containing primary studies of a particular research design, such as longitudinal or cross-sectional designs. Rather, methodological differences were highlighted and discussed. Only the main analysis of meta-analysis or systematic reviews articles that were relevant to the topic of this umbrella review were considered. Opinion articles, primary empirical articles or non-systematic reviews were excluded. Articles published in languages other than English were also excluded due to the language capabilities of the team. More details on the inclusion and exclusion criteria can be found in the registered PROSPERO protocol (CRD42020179216) and the published protocol (Kwok et al., 2020).

2.3. Data extraction

One reviewer (JK) searched the databases for titles or abstracts that fit the eligibility criteria. Two reviewers (JK and EL) independently compared each extracted article to make sure eligibility criteria were met before assessing all the articles. A third reviewer (HAH) was available if consensus was not reached by the two reviewers or to resolve any discrepancy during this process.

The following data were extracted from all eligible reviews: first author, publication year, standard identifier of PMID and DOI, study title, database name, number of participants, and data extraction approach. Reviewers independently used a standardised coding sheet to record further details on article methodology: data synthesis method (quantitative, qualitative, or mixed), any missing essential information, presentation format (descriptive, graphical, table, or other types), study design type, and if publication bias was present. Next, reviewers used the eligibility criteria stated previously to determine whether each review was to be included for final analysis and stated reasons if it was not included (Fig. 1).

All reported effect sizes (odds ratios, hazard ratios, relative risk, standardised mean difference) were converted to risk ratios, as well as their corresponding 95% confidence intervals. Additionally, it was noted for each review whether articles adjusted for confounding variables.

2.4. Quality assessments

A quality assessment of each review was first assessed independently by both reviewers, followed by a meeting where reviewers came to a consensus about the study quality scores. The quality assessment was based on the AMSTAR (A Measurement Tool to Assess Systematic Reviews) 2. The AMSTAR 2 tool consists of 16 items which evaluate search strategies, data extraction techniques, risk of bias, appropriate methodology, and the interpretation and discussion of results.

The AMSTAR 2 tool was modified to suit this umbrella review topic through critical appraisal of meta-analysis and systematic reviews instead of randomised control trials. Seven domains in the AMSTAR 2 were identified as critical in affecting the validity of the review. These were items 2, 4, 7, 9, 11, 13, 15, with a maximum score of 11 points for meta-analyses, and 9 points for systematic reviews. A scoring scheme was also designed to categorise confidence in results, consisting of 'High', 'Moderate', 'Low' and 'Critically Low'. Articles rated as 'Critically Low' signified two or more critical flaws in the review article, and was included but given significantly less weight in the narrative synthesis. Articles rated as 'Low' signified one critical flaw and were included in the synthesis, with conclusions given less weight. Meta-analyses were scored on a strict scale due to emphasis on methodology: "High = 9–11″, "Moderate = 7–8″, "Low = 5–6″, "Critically Low = <5″. Systematic reviews were scored using the following scale: "High = 7–9″, "Moderate = 4–6″, "Low = 3–4″, "Critically Low = <3″. For systematic reviews, more emphasis was placed on data synthesis in the discussion or conclusion section in order to fulfil study aims of providing a scoping review involving not only methodological appraisal,

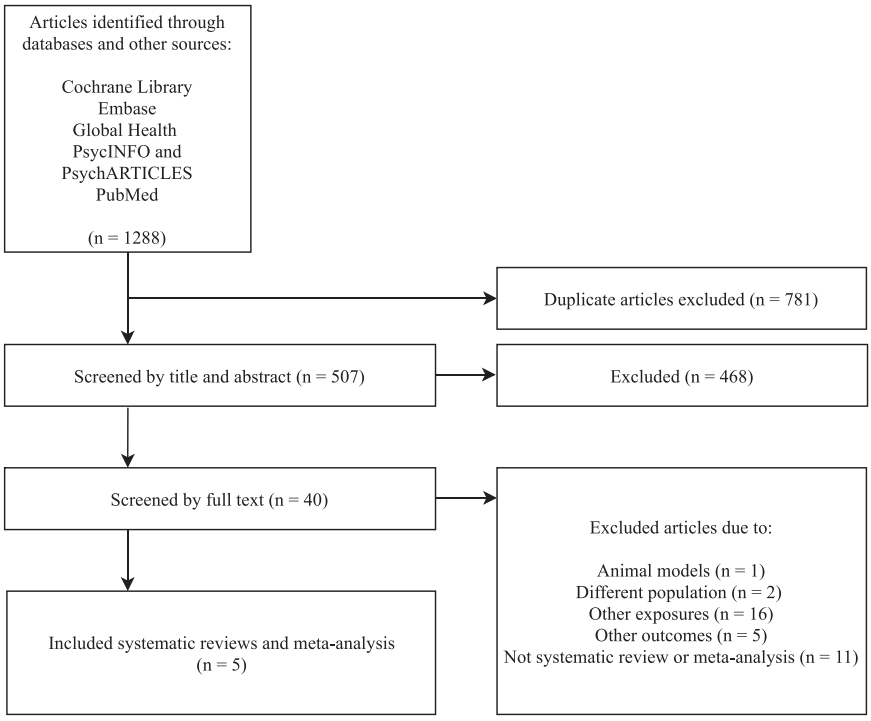

Fig. 1. Flowchart of Selected Review Articles Tables.

but also interpretation and conclusions of results.

2.5. Data synthesis

A narrative synthesis method was used in this umbrella review. Included articles are placed in overall descriptive tables (Tables 2 and 3). These tables include key features for both the data extraction process and methodology (i.e. variations in data selection, study designs, indication of bias present, adjustments for covariates or confounders). Separate tables are provided for the AMSTAR 2 and GRADE assessments (Table 4) and key findings (Table 5). A narrative synthesis was carried out with the purpose of providing a clear and integrated summary of the combined literature of qualitative and quantitative reviews on the topic of the effects of analgesic drugs on ASD and ADHD diagnosis.

2.6. Confidence in cumulative evidence

Confidence in the cumulative evidence was assessed through Grading of Recommendations, Assessment, Development and Evaluations (GRADE) certainty ratings guidelines. Each review was carefully assessed and assigned two ratings: 1) certainty rating ("Very Low" = true effect different from estimated effect"; "Low" = true effect possibly different from estimated effect; "Moderate" = true effect close to estimated effect, and "High" = true effect similar to estimated effect), and 2) decision making ("Critical = 7–9″, "Important but Not Critical = 4–6″, and "Of Limited Importance = 1–5″). The following domains were assessed for certainty of evidence: risk of bias, publication bias, imprecision of true effects, inconsistency of effects, and indirectness of outcomes. As per the GRADE guidelines, certainty was either down-rated or up-rated based on the above-mentioned several domains. Scores were then summed, and decision-making importance was assigned to one of the following categories: "Critical", "Important but not critical", "Of limited importance". The domains for certainty and decision-making importance are stated in Table 1.

Table 1
GRADE certainty and decision-making criteria.

Certainty down-rated for	Certainty up-rated for	Decision-making
a) Risk of bias b) Publication bias c) Imprecision d) Inconsistency e) Indirectness	a) Large magnitude of effect b) Dose-response gradient c) Plausible confounding that reduces demonstrated effect d) Possible confounding suggesting spurious effect when actual results show no effect	a. **Critical:** highly likely that results are a reasonable and accurate representation of data b. **Important but not critical:** likely that results are a reasonable and accurate representation of data c. **Of limited importance:** not clear if results are a reasonable and accurate representation of data

3. Results

A total of 1288 articles were identified through six databases and grey literature searches. After duplicates were excluded, and with articles screened by title, abstract, and full text, forty articles remained. A further thirty-five articles were excluded due to one of the following classifications: animal models, different population, other exposures or outcomes, and non-systematic reviews or meta-analysis. A total of five systematic reviews and meta-analysis met the inclusion and exclusion criteria and were included as the final umbrella review (Fig. 1).

Four out of the five articles included sample sizes, with a range of 61,601 to 244,940 participants in each review. Two articles used a qualitative systematic review method, two articles used a quantitative meta-analysis method, and one article used a combination of both methods. Four reviews included in this study used a cross-sectional study design. Population age ranges were from 1.5 years to 13.5 years.

All five articles included acetaminophen drug use as exposures during pregnancy and examined ADHD as outcomes that were relevant to the review. Three out of the five articles examined ASD outcomes. Only acetaminophen drug use was reviewed due to insufficient power for the other analgesic drugs of aspirin, ibuprofen, naproxen, diclofenac, and ketoprofen in the selected articles regarding ADHD and ASD

Table 2
Descriptive characteristics of included reviews.

Author (Year)	Participants	Databases	Study method	Study Type	Design	Number of studies assessed for eligibility	Final number of studies included
Hoover et al. (2015)	NS	Cochrane Library, PubMed, Embase	Qualitative	Systematic Review	Cross-sectional	NS	4
Bauer et al. (2018)	137,738	Embase	Qualitative	Systematic Review	Longitudinal	64	9
Masarwa et al. (2018)	61,601	Cochrane Library, Embase, Global Health	Quantitative, Qualitative	Meta-analysis and Systematic Review	Cross-sectional	30	7
Gou et al. (2019)	244,940	Embase, Cochrane Library, PubMed	Quantitative	Meta-analysis	Cross-sectional	16	8
Alemany et al. (2021)	73,881	PubMed	Quantitative	Meta-analysis	Cross-sectional	NS	NS

NS: Not Stated

Table 3
Methodological characteristics of included reviews.

Author (Year)	Population age range (years)	Exposures relevant to review	Outcomes relevant to review	Analysis Used	Adjusted for covariates and confounders	Additional analysis performed within review	Heterogeneity I^2 (%)	Significance of heterogeneity (p-value)
Hoover et al. (2015)	3 – 12	Acetaminophen	ADHD	Narrative Review	No	NS	NS	NS
Bauer et al. (2018)	1.5 – 12	Acetaminophen, ibuprofen	ADHD, ASD, HKD	Narrative Review	Yes	Performed in included studies	NS	NS
Masarwa et al. (2018)	3–13.5	Acetaminophen	ADHD, ASD, Hyperactivity symptoms	Narrative Review, Random Effects Models	Yes	Sensitivity analysis, moderator analysis for heterogeneity	ADHD: 72 ASD: 14Hyperactivity symptoms: 93	ADHD: .03 ASD: .31 Hyperactivity symptoms: < 0.001
Gou et al. (2019)	3 – 11	Acetaminophen	ADHD	Random Effects Models	Yes	Sensitivity analysis, subgroup analysis for heterogeneity	ADHD: 26	.22
Alemany et al. (2021)	4 – 12	Acetaminophen	ADHD, ASD	Meta-analytic Models	Yes	Sensitivity analysis, Cochran's Q test and I2 test for heterogeneity	ADHD: <1 ADHD: 2.4	ADHD: .89 ASD: .50

NS: Not Stated ADHD: diagnosis classification of Attention-Deficit Hyperactivity Disorder
Hyperactivity Symptoms: hyperactivity-impulsiveness symptoms
Hyperkinetic disorder (HKD): hyperactive behavioural phenotype

Table 4
GRADE certainty ratings (downgrading or upgrading of evidence).

Author (Year)	Risk of bias present	Publication bias present	Imprecision (based on 95% CI)	Inconsistency of effects	Indirectness of outcomes	Large effect size (RR/ OR/ HR: >3.0)	Dose-response gradient	All plausible confounding would reduce a demonstrated effect (increase confidence in estimated effects)	All possible confounding would suggest a spurious effect (for results showing no effect)	Total GRADE rating score
Hoover et al. (2015)	Yes (sampling bias)	No	NA	No	No	No	No	Yes	No	0
Bauer et al. (2018)	No	No	No	No	No	No	Yes	Yes	NA (results show some effect)	2
Masarwa et al. (2018)	Yes	NA (unable to evaluate due to limited studies)	No	No	No	No	Yes	Yes	NA (results show some effect)	1
Gou et al. (2019)	No	No	No	No	No	No	No	Yes	NA (results show some effect)	1
Alemany et al. (2021)	No	No	No	No	No	No	No	Yes	NA (results show some effect)	1

Down-ratings (yes = −1, no = 0, not applicable (NA) = 0), Up-ratings (yes = +1, no = 0, not applicable (NA) = 0)

Table 5
Findings of included reviews.

Author (Year)	Primary results	Risk Ratio for ADHD Outcomes (95% CI)	Risk Ratio for ASD Outcomes (95% CI)	AMSTAR 2 Category	GRADE certainty ratings	GRADE (decision-making)
Hoover et al. (2015)	Small associations found between prenatal acetaminophen exposure and ADHD symptoms during childhood. However, included studies in this review were limited in conclusions due to not controlling for variables such as prenatal use of acetaminophen for pain relief and fever, previously associated with negative pregnancy outcomes. Associations remained after adjustments for confounders such as maternal pyrexia or psychiatric illness.	Not stated	Not stated	Critically Low	0	Of limited importance
Bauer et al. (2018)	Associations were found between only prenatal acetaminophen drug exposure and neurodevelopmental risk outcomes, but not ibuprofen or other analgesic drugs. Review also noted that the included studies controlled for exposure across all pregnancy trimesters, indications for acetaminophen use (e.g. fever, headache/migraine, infection, pain). All included studies used prospective design and statistically controlled for confounders such as selection or recall bias.	Not stated	Not stated	High	2	Critical
Masarwa et al. (2018)	Associations were found between prenatal acetaminophen exposure and increased risk of ADHD and ASD outcomes (20–30%). As included studies controlled for covariates and confounders of both maternal and child factors, the review noted that associations were moderated by exposure duration, maternal age, and age of follow-up for the child.	1.34	1.19	High	1	Important but not critical
Gou et al. (2019)	Consistent associations were found between prenatal acetaminophen exposure and increased risk of ADHD outcomes (25%) using prospective cohort studies. Prenatal acetaminophen use was also linked to higher risk when taken in the third trimester as compared to the first and second trimester. Included studies adjusted for acetaminophen use due to infection/inflammation during pregnancy, but not other conditions such as pain relief. Some studies within this review controlled for the wide range of confounds using negative control comparison or sibling-controlled analysis.	1.28 (any exposure) 1.08 (third trimester) 1.63 ($\geq$ 28 days)	Not stated	Moderate	1	Important but not critical
Alemany et al. (2021)	Associations found between prenatal acetaminophen exposure and risk of ADHD symptoms (12.2%). Associations also found between acetaminophen exposure and Autism Spectrum Conditions (ASC) (12.9%). Slightly stronger associations were found for males for ASD and ADHD outcomes, as compared to females. A common set of confounders was used with harmonised exposure and outcome measures across all the cohort studies.	1.088 (OR=1.21; Females OR=1.18 Males OR=1.23)	1.093 (OR = 1.19; Females OR=1.06 Males OR=1.28)	Low	1	Important but not critical

NS: Not Stated

outcomes. Three articles used a narrative summary method, and four articles adjusted for covariates and confounders. Confounders include purpose of usage such as pain relief or maternal fever, of which the latter has been shown to distort observed associations and have adverse pregnancy outcomes. In addition to this, the reviews also noted that women sought relief from pain or fever also were more likely to use other medications apart from acetaminophen, which then presents a further confounding effect on mechanisms affecting the fetus. Some confounders that were adjusted for within reviewed studies from the selected articles included variables such as socioeconomic status, maternal education, nicotine and alcohol intake, psychiatric illness, infection or inflammation during pregnancy, child's birth weight, and child's gestational age. Certain residual confounding such as selection bias raised some potential concerns. To adjust for these confounding effects, authors of the primary studies used multiple methods to minimise their effects such as using prospective designs on large clinical datasets or using propensity score matching or power analysis to control for these variables.

AMSTAR 2 quality ratings were "High" for two articles (Masarwa et al., 2018; Bauer et al., 2018), "Moderate" for one article (Gou et al., 2019), "Low" for one article (Alemany et al., 2021), and "Critically Low" for one article (Hoover et al., 2015). Identified issues were failing to use a comprehensive literature search strategy (Bauer et al., 2018; Gou et al., 2019; Alemany et al., 2021; Hoover et al., 2015), to provide a list of excluded studies and justify the exclusions (Masarwa et al., 2018; Alemany et al., 2021; Hoover et al., 2015), and to use a satisfactory technique for assessing the risk of bias (Hoover et al., 2015). Only one review registered a written protocol prior to review conduct (Masarwa et al., 2018). Adhering to a predefined, well-developed methodology minimises the risk of bias in the conduct and reporting of research and prevents unnecessary duplication of work (Tawfik et al., 2020).

GRADE was used as reproducible and transparent framework to show certainty of evidence. This review showed selected articles have a score range of 0 – 2; two articles were downrated for risk of bias present, two articles were uprated for including a dose-response gradient, and all articles discussed possible confounding on estimated effects. For decision-making scores based on GRADE, one article was rated "Of limited importance", three articles were rated "Important but not critical", and one article was rated "Critical". Five out of six articles were rated as important, pointing towards recommendation for clinical decision making as per the GRADE guidelines.

Risk ratios were also calculated for ADHD and ASD outcomes in three articles. Masarwa et al. (2018) found that acetaminophen exposure showed a RR of 1.34 for ADHD outcomes (95% CI, 1.21, 1.47) and 1.19 for ASD outcomes (95% CI, 1.14, 1.25). Gou et al. (2019) found that acetaminophen exposure showed a RR of 1.26 for ADHD outcomes for

exposure in the third trimester (95% CI, 1.08, 1.47), and RR of 1.63 for ADHD outcomes if the dose exceeded 28 consecutive days (95% CI, 1.23, 2.16). Alemany et al. (2021) found that acetaminophen exposure showed a RR of 1.09 for ADHD outcomes for any exposure across 3 pregnancy trimesters (95% CI, OR = 1.21, 1.07, 1.36), and RR of 1.09 in ASD outcomes (95% CI, OR =1.19, 1.07, 1.33).

4. Narrative synthesis

Primary results from the included reviews generally showed associations between maternal prenatal acetaminophen use and ADHD outcomes. Other analgesic drugs of interest such as aspirin, ibuprofen, naproxen, diclofenac, and ketoprofen were not examined due to insufficient evidence in the selected reviews when looking at our outcomes of interest. Upon examination of the AMSTAR and GRADE categories, studies that fell within the higher categories showed similar results of prenatal acetaminophen exposure being associated with neurodevelopmental risk, particularly for ADHD outcomes. The study designs included in this umbrella review consisted of cross-sectional, longitudinal, randomised control trials, case-control studies, register-based studies, and cohort studies.

One review attempted to control for ibuprofen and aspirin use, but there was insufficient statistical power to detect associations as the usage rates were low (Bauer et al., 2018). This was reflective of limited studies examining other analgesic drugs and neurodevelopmental outcomes, possibly due to lack of drug accessibility or medical records. Some reviews did not adjust for variables such as timing of exposure, purpose, duration, or frequency of use. However, those that did, provided valuable insight into factors involved in examining maternal drug use and its effects. While effects were seen to be slightly moderated by maternal and child confounds such as age (Masarwa et al., 2018; Bauer et al., 2018; Gou et al., 2019), the direction and strength of association were largely similar across the articles. In addition, there is a possibility that the effects of acetaminophen involve a dose-dependent relationship or a trimester-based relationship where the third trimester presented the highest risk for increased ADHD outcomes (Gou et al., 2019; Alemany et al., 2021). Findings regarding differences in ADHD outcomes due to gender have been inconclusive, with one study suggesting that males are at a slightly higher risk than females (Alemany et al., 2021), while another study arguing that effects may be stronger amongst girls (Gou et al., 2019). Effect sizes for gender differences were, however, too small to draw any firm conclusions.

The selected reviews did not provide any direct evidence on the mechanisms; however, one hypothesis for potential mechanisms underlying this association is that acetaminophen directly affects physiological mechanisms (Bauer et al., 2018; Gou et al., 2019). For example, acetaminophen use indirectly activates the maternal immune system and fetal endocannabinoid system, which have been implicated in both ASD and ADHD aetiology (Alemany et al., 2021; Blecharz-Klin et al., 2017). Animal studies have also found links between exposure to acetaminophen and lower levels of brain-derived neurotrophic factor (BDNF) in the striatum in male rats, with alterations in the metabolism of dopamine identified as well (Blecharz-Klin et al., 2017). A decrease in BDNF and dopaminergic dysfunction are thought to be highly relevant in the pathogenesis of ADHD and ASD outcomes (Liew et al., 2014). Further, an imaging study by Baker et al. (2020) found that prenatal acetaminophen exposure affected frontoparietal brain connectivity in children and was associated with an increased risk of ADHD at ages 6–7 years. As the study measured prenatal acetaminophen use using meconium collected from newborns instead of maternal self-reports, these results provide a different methodological angle in supporting the findings of articles included in this review that relied on mothers' self-reports. Evidence for a trimester-based association of acetaminophen and ADHD could also be due to the processes of rapid brain growth and structural differentiation during the third trimester being disrupted (Brandlistuen et al., 2013).

4.1. Heterogeneity and potential bias

Studies selected for this review showed some evidence of heterogeneity in both study measures and outcomes. Alemany et al. (2021) found substantial between-study heterogeneity when examining exposure to acetaminophen and ASD symptoms among girls using hospital diagnosis (I^2 = 68.37%, p < .001). Masarwa et al. (2018) found evidence of significant heterogeneity between study estimates of ADHD outcomes (I^2 = 93%, p < .001) and hyperactivity symptoms (I^2 = 72%, p < .03). The study acknowledged that variability of exposure times (first 20 weeks to any point in pregnancy), and exposure duration (4–28 days, to ≥ 28 days) possibly contributed to heterogeneity of observed effects. Gou et al. (2019) found heterogeneity for estimates of ADHD outcomes (I^2 = 26%, p < .03). Study adjustments were made for previously associated maternal factors (e.g. age, psychiatric illness, intelligence, behavioural scores). Masarwa et al. (2018) also noted the possible presence of ecological fallacy for the factor of a dose-response effect, where there was possibly no link between exposure duration and outcomes on an individual level, due to the wide range of exposure duration, which may have contributed to heterogeneity. Study results were consistent with previous research (Ystrom et al., 2017) in showing observed significant associations with ADHD and ASD. Two out of the five studies (Bauer et al., 2018; Hoover et al., 2015) did not use meta-analytic methods to provide summary estimates of effects. Variability across these reviews suggests that the mechanisms behind a dose-response relationship of acetaminophen exposure and child neurodevelopment outcomes are still not fully understood.

Three out of the five studies (Masarwa et al., 2018; Gou et al., 2019; Alemany et al., 2021) used standard random-effects models to account for unexplained heterogeneity and account for study variability in outcomes (Table 3). These three studies also carried out subgroup analyses to either identify potential sources of heterogeneity or examine the contribution of relevant covariates. Acetaminophen frequency, timing, and duration of use, age of follow-up, and maternal age, were seen as significant moderators in the association between prenatal acetaminophen use and the risk of ADHD outcomes. Significant moderators in the association between prenatal acetaminophen use and the risk of ASD were identified as timing and prolonged exposure. Acetaminophen exposure during the second trimester and exposure of more than 28 days presented a marginally higher risk of ASD with HKD symptoms (Bauer et al., 2018).

4.2. Limitations

Study conclusions are limited according not only to the quantity of articles fitting the eligibility criteria, but also the comprehensiveness of data within the articles. Measures used to assess ADHD and ASD outcomes were varied, most were not based on validated instruments with specific cut-offs for clinical symptoms; instruments used included parent or teacher-based questionnaires (Bauer et al., 2018; Gou et al., 2019; Alemany et al., 2021; Hoover et al., 2015), trained psychologist assessment questionnaires (Gou et al., 2019), clinical diagnoses (Masarwa et al., 2018; Bauer et al., 2018; Hoover et al., 2015), and hospital admission registries (Gou et al., 2019; Alemany et al., 2021). This increased risk for outcome misclassification. In addition, the duration of exposure to acetaminophen, gestational week at exposure, children's age at follow-up, and maternal age varied between articles included in each review, possibly contributing the heterogeneity of observed effects. It should also be noted that the individual articles often only included participants of European descent and so results are potentially limited in generalisability. This is important because pharmaceutical research has identified ethnic differences in drug metabolism, therapeutic responses, and side effects (Peacock and Patel, 2008). This review is also limited by different methods of evaluation regarding drug exposures (such as dosage) and ASD and ADHD outcomes (such as standardised forms of diagnosis). However, most of the

included studies used the Newcastle-Ottawa Scale, a scoring system that assesses study quality and risk of bias for observational studies. In addition, this study used two quality assessments to establish stricter criteria firstly for initial inclusion of articles, followed by weighted conclusions according to the quality assessment scores. Higher scores were given more weight in the discussion.

4.3. Implications

Analgesic drugs are commonly used by pregnant women for a wide variety of reasons (Elsabbagh et al., 2012; Thomas et al., 2015; Lupattelli et al., 2014; Servey and Chang, 2014; Henry and Crowther, 2000), suggesting low hesitancy about these drugs despite not knowing long-term effects on the fetus. It has been suggested that awareness amongst health professionals about long-term risks of prenatal acetaminophen should be increased (Bauer et al., 2021). Findings of this umbrella review reinforce this and suggest that health professionals should advise women early in pregnancy to use acetaminophen only when needed. Guidelines on the appropriate use of acetaminophen should not only be available to all women, but also include information on the lowest effective dose for the shortest possible duration, while balancing out more immediate benefits of acetaminophen use such as for pain relief or fever. Pregnant women who use acetaminophen should be closely monitored across all trimesters of pregnancy, with emphasis placed on reducing excessive use due to links with risk of neurodevelopmental difficulties.

4.4. Future research

Future studies should aim to gain a better understanding of the various potentially interacting mechanisms exploring associations between acetaminophen use in pregnancy with offspring neurodevelopmental outcomes. This will provide valuable insights for proper use of acetaminophen, or possible development of alternative safer analgesics to be taken during pregnancy. Studies should record acetaminophen exposure at different time points in pregnancy and include details such as timing, duration, dose, and frequency of use. Examination of other types of analgesic drugs could also provide further insight to the mechanisms of fetal development. Outcomes could include cord or clinical biomarkers such as hair analysis directly from the fetus, which could also provide further understanding of analgesic drug exposure metabolization in the fetus. In addition, closer examination of other drugs which can possibly counteract the effects on the fetus can be studied. Measuring direct fetal exposure to acetaminophen in meconium or through cord plasma acetaminophen (APAP) metabolites will aid in accurately capturing the dose of acetaminophen that reaches the fetus and subsequently isolate unique effects on development (Bauer et al., 2018; Laue et al., 2019). Other methods such as polygenic risk scores or sibling control designs can also be used to account for genetic confounding. Due to the difficulty of conducting experimental research to understand how much analgesic drug exposure in pregnancy impacts neurodevelopmental outcomes, use of empirical designs like counterfactual statistical approaches can possibly help to rule out confounding; for example, matching based methods. Other methods to increase accuracy could also include biomarkers of analgesic drug exposure taken during pregnancy rather than retrospective self-reports from mothers. Lastly, examined outcomes can be expanded to test for associations between analgesic drugs and neurodevelopmental disorders or psychopathology onset in adulthood. This is especially important considering recent evidence that suggests that ADHD symptoms may not always manifest at a clinically significant level until later in development that is traditionally recognised (Murray et al., 2021). Therefore, caution should be given by healthcare professionals regarding the dosage and duration of acetaminophen drug use during pregnancy and its potential effects on fetal neurodevelopment.

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Ethics approval and consent to participate

No informed consent or ethical approval is required for the purpose of this review.

Authors' contributions

JK and HAH conceptualised, designed, interpreted study data, and contributed to manuscript writing. EL analysed and interpreted the data and contributed to manuscript writing. ALM and BA contributed to manuscript writing.

Competing Interests

The authors declare that they have no competing interests.

Availability of data and materials

Data available in public (institutional, general, or subject specific) repositories that issue datasets with DOIs (non-mandated deposition). Repositories include Embase, Maternity and Infant Care, PsycINFO, PsycARTICLES, PubMed, and Cochrane Library.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.neubiorev.2022.104607.

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