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Review

Educational outcomes associated with prenatal exposure to antiseizure medications: A systematic literature review and meta-Analysis

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ABSTRACT

Objective: To systematically review and meta-analyse evidence of the associations between prenatal exposure to antiseizure medications (ASMs) and educational outcomes in childhood, including educational difficulties, learning difficulties and academic performance.

Methods: We conducted a systematic review following the PICOS framework and PRISMA guidelines. MEDLINE (Ovid), CINAHL, PubMED, ERIC, and PsycINFO databases, along with Google Scholar, were searched from inception to 28 June 2024. Study quality was assessed using the Newcastle-Ottawa Scale and ROBINS-E. Relevant outcomes included record of special education needs, school-related behavioural problems, learning difficulties, and examination scores in core academic subjects. Pooled estimates were derived where appropriate and bias and heterogeneity assessed using funnel plots, Egger's tests, and I^2 tests.

Results: Seventeen studies (12 cohort, 5 case-control) were included, encompassing 854,142 participants. Pooled estimates indicated that prenatal exposure to ASMs was associated with increased educational difficulties (RR 1.3, 95 % CI 1.01–1.69, $p = 0.04$), with sodium valproate showing the strongest association (RR 2.38, 95 % CI 1.25–4.53, $p = 0.01$). Carbamazepine and other first-generation ASMs showed no significant associations. Narrative findings suggested associations between newer-generation ASMs and educational difficulties, but limited data precluded quantitative synthesis. Studies assessing academic outcomes suggested lower academic performance among children exposed to sodium valproate or ASM polytherapy but could not undergo meta-analysis due to methodological heterogeneity.

Conclusions: Prenatal exposure to first-generation ASMs, especially sodium valproate, was associated with increased educational support needs. Newer-generation ASMs appear to have a more favourable risk profile, though evidence remains limited, underscoring the need for further high-quality research to inform clinical practice.

1. Introduction

Epilepsy affects approximately 70 million people globally [1], with a prevalence of 0.3 %–0.7 % among pregnant women [2]. Despite being a chronic neurological condition that requires continuous management, treatment decisions are often not tailored to sex-specific considerations, even though many women with epilepsy are of reproductive age and may consider pregnancy [3,4]. This issue is particularly significant given that approximately 50 % of pregnancies are unplanned, emphasizing the need for anticipatory management alongside pre-conception counselling [5,6].

Studies indicate that 90 % of women of childbearing age with epilepsy receive antiseizure medication (ASM) therapy [7,8]. Whilst medication use during pregnancy generally raises concerns, continued management of epilepsy remains essential as uncontrolled seizures pose significant health risk to both the mother and foetus [9]. Clinicians should therefore provide comprehensive counselling to women of reproductive age regarding potential risks, enabling informed decision-making about treatment options. However, ASMs are often prescribed with limited evidence regarding their safety and efficacy during pregnancy [7].

Pregnancy can worsen the frequency and severity of epileptic

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seizures [10], sometimes necessitating medication adjustments. Recent reports from worldwide pregnancy registries show that pregnant women with epilepsy, particularly those prescribed newer ASMs, frequently receive a combination of ASMs (polytherapy) [1]. This increases foetal exposure to different medications, as well as exposing them to potential drug interactions. Polytherapy has previously been associated with an increase in adverse child outcomes compared to monotherapy [11,12].

The effects of prenatal ASM exposure have been extensively studied for birth outcomes, congenital anomalies, and early neurodevelopmental outcomes. Epilepsy and the use of ASMs during pregnancy have been associated with increased risk of pregnancy-related hypertension, preeclampsia, and unexplained stillbirth [13]. In-utero exposure to ASMs has been associated with lower birth weight, being born small for gestational age, and lower Apgar score [13,14]. Pregnancy registries suggest higher risk of congenital malformations among prenatally exposed children, with risk varying by drug type and dose [15–17].

Neurodevelopmental outcomes have also received substantial attention. Studies have reported a ten-fold higher prevalence of autism spectrum disorder among children exposed to sodium valproate prenatally [18]. Parental reports indicate increased autism symptoms and clinical diagnoses of emotional and behavioural disorders among children exposed to newer generation ASMs, like lamotrigine (Lamictal) and gabapentin (Neurontin) [19]. However, other commonly prescribed ASMs, such as levetiracetam, have shown little or no association with adverse neurodevelopmental outcomes [19,20].

Educational outcomes represent a critical domain for assessing the long-term impact of prenatal ASM exposure, yet findings in this area remain inconsistent. Some studies suggest that children born to mothers with epilepsy require more educational support than their peers [21–23]. However, evidence regarding specific ASMs varies considerably. While some research found no evidence of poorer educational outcomes following prenatal ASM exposure [24,25], other studies demonstrate increased likelihood of special education needs after prenatal exposure to sodium valproate [22,23], and higher risk of learning difficulties following exposure to newer generation ASMs, such as topiramate (Topamax tablets) and levetiracetam [22].

Given these inconsistencies and the importance of educational outcomes for long-term life prospects, a comprehensive synthesis of the available evidence is needed to guide clinical decision-making and patient counselling. Therefore, this study aims to systematically review and meta-analyse the existing evidence on associations between prenatal exposure to ASMs and educational outcomes in children.

2. Methods

2.1. Search strategy

The research questions and search strategy were developed using the PICOS (Population, Intervention, Comparison, Outcome, Study design) framework [26] and the review was conducted in accordance with the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines [27]. The databases searched were MEDLINE (Ovid), CINAHL, PubMED, ERIC, PsycINFO, and the first ten pages of Google Scholar. An initial search was conducted on January 24, 2024, and updated on June 28, 2024. Search terms for pregnancy, children, epilepsy and educational outcomes, were combined and are listed in Supplementary Table 1.

2.2. Selection criteria and screening process

Inclusion was restricted to peer-reviewed, original studies, conducted on humans, with an abstract available in English. Eligible studies investigated exposure to antiseizure medication monotherapy or polytherapy at any point during pregnancy. Outcomes in the offspring, up to 18 years of age, included special education needs, learning difficulties in the classroom, school-related behaviour problems, and academic performance. Studies were excluded if they reported cognitive tests or neurodevelopmental outcomes without reporting their impact on educational needs or academic performance.

The screening process comprised two steps. First all returned titles and abstracts were independently assessed to confirm eligibility for inclusion by two reviewers (A.K., L.S.). The same process was conducted for the subsequent full-text screening. In both steps the reviewers used a priori selection criteria (Table 1). Conflicts were resolved at the end of each stage through discussion.

2.3. Data extraction and quality assessment

The data extracted from eligible studies included: publication year; country; study design; sample size and demographics; comparison/control group, definition and measurement of the exposure and outcomes, and adjustment for potential confounders. The methodological quality of the included studies was evaluated using the Newcastle-Ottawa Scale (NOS) [28] for non-randomised studies as it allowed comparison with previous systematic reviews. For case-control studies, the evaluation criteria covered adequacy of definition, representativeness of cases, selection and definition of controls, comparability of cases and controls, ascertainment of exposure, method of ascertainment, and non-response rate. For cohort studies, the evaluation criteria assessed whether the participants were representative, selection of the non-exposed group, ascertainment of exposure, if the outcome of interest was present at the start of the study, comparability of cohorts, assessment of the outcome, and consideration of the timing and adequacy of follow-up. Studies were classified as high quality (overall score 7–9), moderate quality (4–6) or low quality (0–3).

Risk of bias was assessed using the Risk of Bias in Non-Randomized Studies - of Exposures (ROBINS-E) tool [29]. The ROBINS-E tool provides a comprehensive assessment across seven domains; confounding, exposure measurement, participant selection, post-exposure interventions, missing data, outcome measurement, and reported result selection. For each domain possible judgements were 'low risk of bias', 'some concerns', 'high risk of bias', and 'very high risk of bias'. After

Table 1
Inclusion and exclusion criteria for study selection in the systematic review.

Criteria	Inclusion	Exclusion
Population	Pregnant women with epilepsy that commenced prior to or during pregnancy.	Studies of women who are not pregnant and/or do not have epilepsy.
Intervention	Exposure to first- or newer-generation antiseizure medication during pregnancy.	Studies not investigating exposure to antiepileptic drugs during pregnancy.
Outcomes	Educational or functional school-related outcomes (e.g., SEN, ASN, attainment, academic achievement, classroom difficulties, school-related behavioural/social outcomes).	Outcomes focused solely on cognitive (IQ, executive function, or neurological development) and neurodevelopmental (e.g. diagnoses of ASD or ADHD) or parent-reported behavioural/social outcomes.
Study Design	Prospective, retrospective, registry studies, and RCTs.	Non-peer-reviewed studies, grey literature, or case studies with fewer than 9 participants.
Setting	Study samples recruited from the general population, or an educational or health setting with outcomes ascertained in an educational setting.	Outcomes not obtained in an educational setting or outcomes unrelated to school performance.
Age Range	Children aged 0–18 years.	Studies reporting outcomes only ascertained in adults.

Abbreviations: SEN= Special education needs; ASN= Additional support needs; RCT= Randomized-controlled trial; ASD= Autism spectrum disorder; ADHD= Attention deficit hyperactivity disorder.

completing all seven bias domains, an overall risk of bias judgement was made of the predicted direction of bias and its potential threat to conclusions.

2.4. Meta-analyses

Meta-analyses were conducted using Stata 18 (StataCorp, College Station, TX) using the "meta" command. Effect sizes were log-transformed to ensure normality, and standard errors were derived from the log-transformed confidence intervals (CI). To take account of potential between-study variability, random-effects meta-analyses were conducted to derive pooled effect size estimates, applying inverse variance weighting. Risk ratios (RR) with 95 % CI were used to estimate the differences in dichotomous outcomes between exposed and unexposed children. Between-study heterogeneity in outcome was assessed using the Cochran's *Q* statistic and quantified with the I^2 statistic, to estimate the percentage of total variation due to heterogeneity rather than chance. Publication bias and small study effects were assessed using Egger's regression asymmetry test and visualized using funnel plots. Sensitivity analyses, including leave-one-out analyses, were performed to examine the robustness of pooled estimates and to identify any influential studies.

To assess whether the pooled effect sizes differed by study-level characteristics (ASM type, polytherapy versus monotherapy, study design, and country), meta-regression models and sub-group analyses were conducted. Random-effects meta-regression was initially performed using the DerSimonian and Laird (DL) estimator to account for residual between-study variability. Given the small number of included studies, and the presence of heterogeneity, sensitivity analyses were also conducted using the Sidik-Jonkman estimator to provide a more robust inference.

3. Results

The electronic search identified 5763 individual studies, of which 17 satisfied the inclusion criteria (Fig. 1). The eligible studies were published between 1988 and 2023. Their sample sizes ranged from 26 to 477,811 (median 396), with a total of 854,142 mother-child pairs across all the studies. Twelve (71 %) studies were retrospective cohort studies and in 11 (65 %) the comparison group was pregnant women with epilepsy who did not receive ASMs. All included studies measured educational outcomes typically measured between 5 and 17 years of age, with two studies extending follow-up into young adulthood (ages 23–39 year), offering valuable long-term insights. The average age at which outcomes were measured was 10.6 years. The most commonly studied medications were sodium valproate, carbamazepine, and phenytoin.

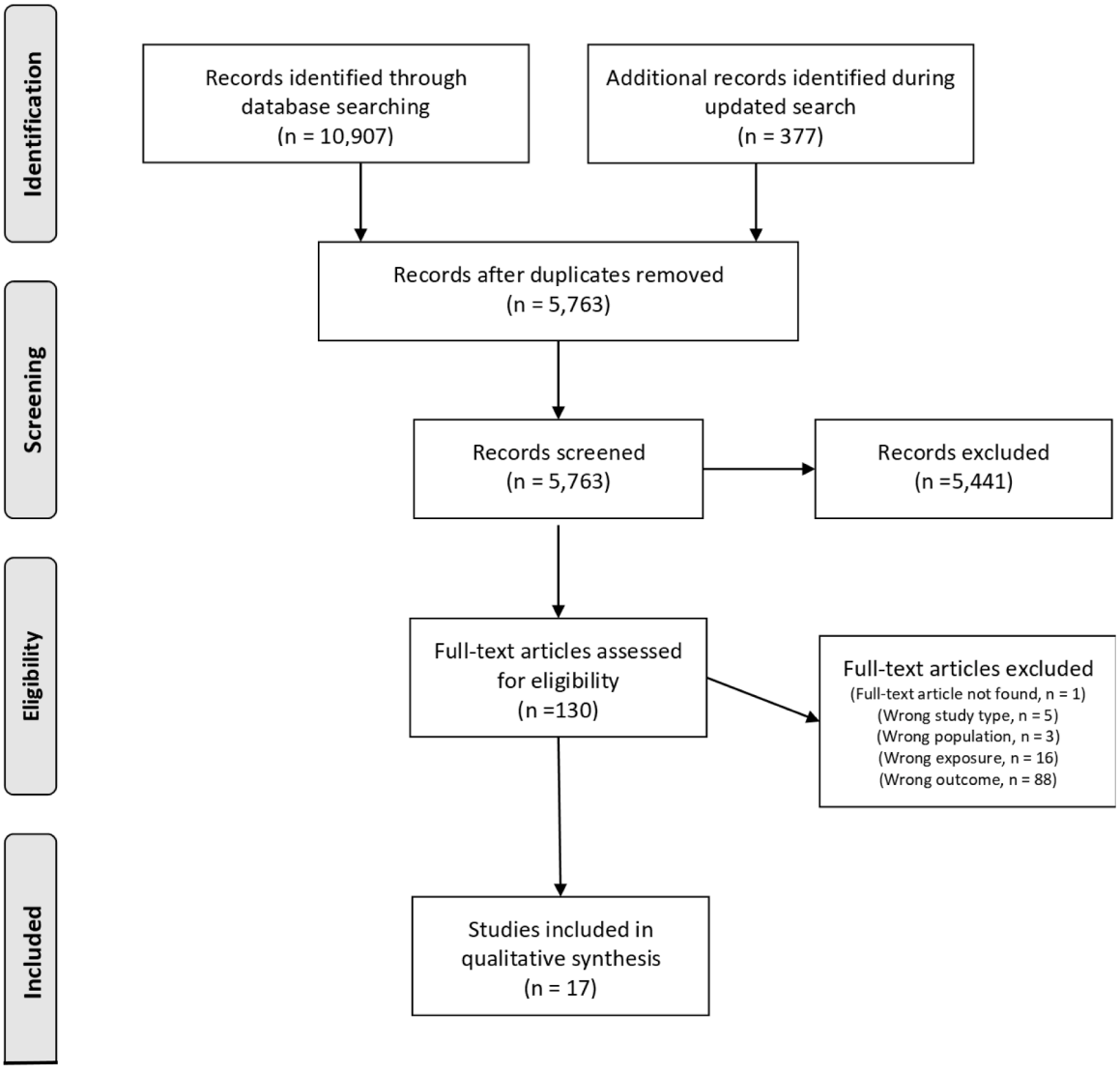

Fig. 1. PRISMA flow diagram of the systematic literature review.

Some studies also investigated newer generation ASMs, such as lamotrigine (Lamictal), topiramate (Topamax tablets), and oxcarbazepine. Outcomes were categorized into two broad themes: educational difficulties (special education needs, learning difficulties, and school behaviour) and academic performance (general or subject-specific examination performance). Ten studies examined educational difficulties, six studies focused on academic performance, and one study investigated both. Details of the included studies are shown in Table 2 and Supplementary Table 2.

3.1. Quality assessment and risk of bias of the included studies

The five case-control studies scored between 6 and 8, out of a possible 9 points, indicating moderate to high quality (Supplementary Table 3). Common strengths included the selection and definition of controls, while some studies were limited by less rigorous methods of measuring and reporting response rate. The majority of the 12 cohort studies exhibited high quality, with scores ranging from 7 to 9 points. These studies were particularly strong in terms of the representativeness of exposed participants and adequacy of follow-up, although a few studies had limited control for confounding factors.

Most of the case-control studies were rated as having moderate to high risk of bias using the ROBINS-E tool (Fig. 4). Key concerns included outcome measurement and potential recall bias due to a reliance on self-reported data. The 12 cohort studies generally exhibited low to moderate risk of bias, with strengths including adjustment for confounders and use of reliable outcome measures. However, four studies had a high risk of bias mostly due to missing data and selective reporting.

Table 2
Summary characteristics of studies included in the systematic review.

Study/Participant Characteristic	n	%
Year of publication		
1988–2009	8	47.06
2010–2017	3	17.65
2018–2023	6	35.29
Study location		
Europe (UK)	7 (6)	41.18 (35.29)
North America	2	11.76
Asia	2	11.76
Study design		
Cohort	12	70.59
Case-control	5	29.41
Sample Size		
0–299	7	41.18
300–999	6	35.29
≥1000	4	23.53
Outcomes		
Special educational needs	6	35.29
Learning difficulties/classroom support	2	11.76
School-related behaviour	2	11.76
Academic performance	6	35.29
Comparison group		
Yes (no treatment)	11	64.71
Yes (other treatment)	2	11.76
No/Not reported	4	23.53
Mean maternal age (years)		
24–29	7	41.18
≥30	3	17.65
Not reported	7	41.18
Number of ASMs		
1–2	5	29.41
3–4	5	29.41
5+	7	41.18
Type of ASMs		
First-generation only	9	52.94
Both first and new generation	8	47.06
Measurement of dosage		
Yes	10	58.82
No/Not reported	7	41.18

N number; UK United Kingdom; ASM anti-seizure medication.

3.2. Educational difficulties

Five of the 11 studies examined special education needs in children with prenatal exposure to ASMs [21,36–39]. Three studies reported a significant association between exposure to a first-generation ASM and increased likelihood of requiring special education support - sodium valproate, carbamazepine, phenobarbital, or phenytoin - though not all findings were statistically significant, and two other studies reported no significant associations for other ASMs, such as lamotrigine (Lamictal; Supplementary Table 2) [36–39]. Phenobarbital and phenytoin exposure was also found to be associated with persistence of special education needs into adulthood [39].

Four studies investigated the impact of prenatal ASM exposure on learning difficulties [22,24,34,40], with mixed findings (Supplementary Table 2). Two reported an increased likelihood of learning difficulties, particularly for sodium valproate and phenytoin [34,40]. Some newer-generation ASMs, such as topiramate (Topamax tablets) and levetiracetam, were narratively reported to be associated with learning difficulties, whereas lamotrigine (Lamictal) did not show the same association; meanwhile, ASM polytherapy was associated with a higher risk of adverse educational outcomes [22]. One study found no significant differences in learning difficulties between children exposed to any ASM in utero and the general population [24].

Behavioural problems in school after prenatal exposure to first-generation ASMs were examined in three studies [34,41,42], showing mixed findings (Supplementary Table 2). One study reported a higher prevalence of behavioural difficulties in children exposed to sodium valproate monotherapy, and ASM polytherapy compared to their peers [34], while a small study found increased classroom behavioural issues in children exposed to sodium valproate but not in those exposed to carbamazepine [41]. However, one study reported no significant differences in school behaviour between exposed and unexposed children [42].

Of the 11 studies investigating educational difficulties, two were excluded from the meta-analysis as they lacked comparison groups [24, 34]. Another study was excluded because it was a pilot study, and its findings were superseded by those of the subsequent main study, which was included in the meta-analysis [36]. Of the eight studies included in the meta-analysis, four contributed data on sodium valproate, four on carbamazepine, and four on phenobarbital or phenytoin. The pooled effect estimate for the association between prenatal exposure to any ASM and educational difficulties was RR 1.30 (95 % CI 1.01 to 1.69, $p = 0.040$; Fig. 2). Between-study heterogeneity was high ($I^2 = 83.69$ %, $Q = 39.74$, $p < 0.001$). When stratified by ASM type, children exposed to sodium valproate prenatally had more than double the risk of educational difficulties RR 2.38 (95 % CI 1.25 to 4.53, $p = 0.010$; $I^2 = 80.86$ %, $Q = 12.55$, $p = 0.010$). Visual inspection of the funnel plot and Egger's test ($p = 0.67$) suggested no significant publication or small study bias (Fig. 3). In contrast, there was no significant association with carbamazepine and other first-generation ASMs (Table 3; Fig. 2). Leave one out sensitivity analyses confirmed the robustness of results for sodium valproate exposure, with no single study significantly altering the pooled effect estimate. Meta-regression analysis suggested that the pooled effect estimates were not significantly associated with study design, investigation of monotherapy versus polytherapy, or country (Table 4).

3.3. Academic performance

Seven studies investigated academic performance - either including general academic performance or subject-specific exam scores - but these could not be meta-analysed due to substantial variability in the definitions and measurements used across studies [25,30–33,35,42]. Three studies that examined general academic performance found that children exposed in-utero to ASMs, tended to have lower school examination scores or higher dropout and absenteeism rates, compared to

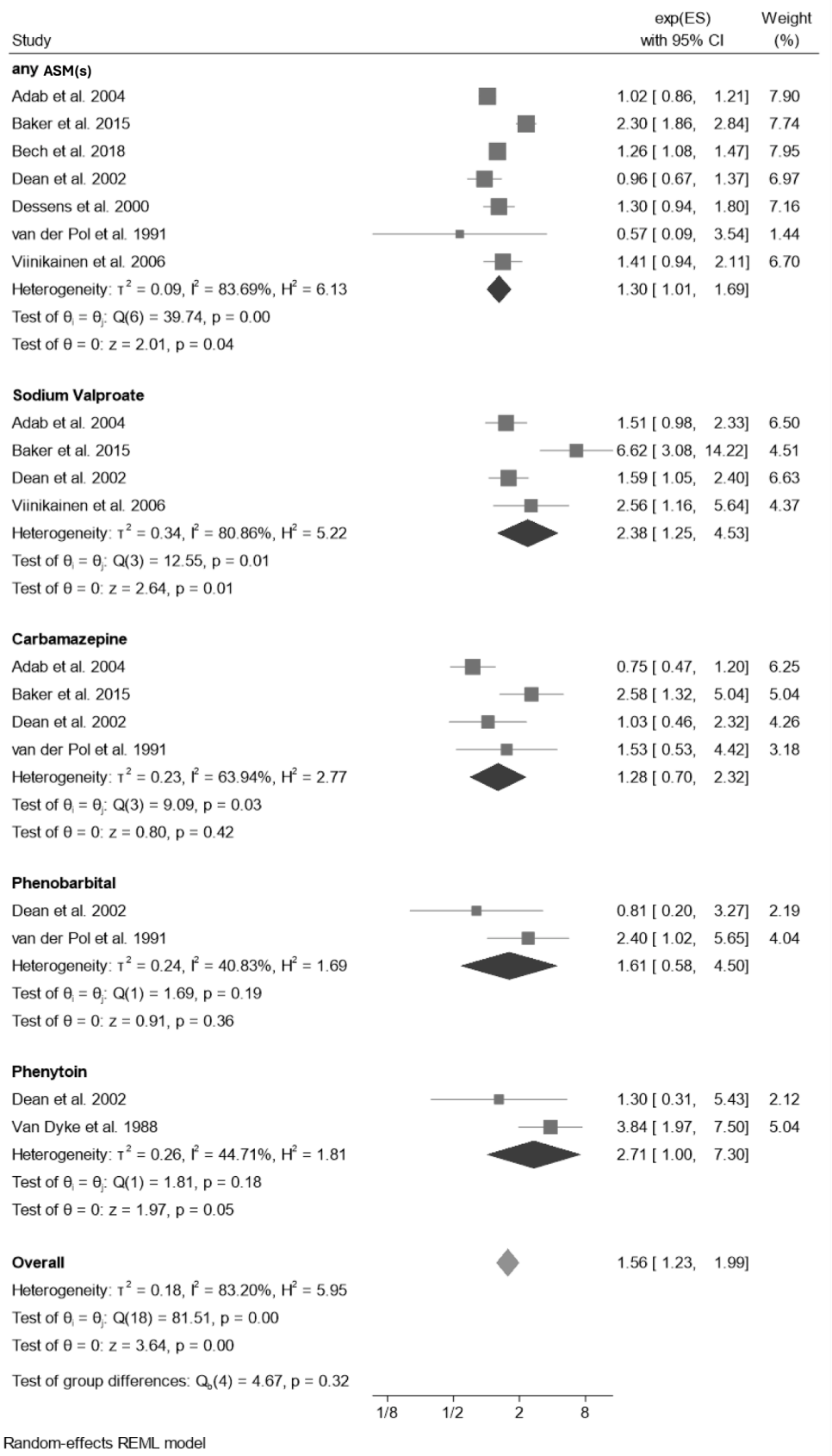

Fig. 2. Forest plots of the pooled effect estimates of prenatal exposure to anti-epileptic drugs and educational outcomes, stratified by ASM type.

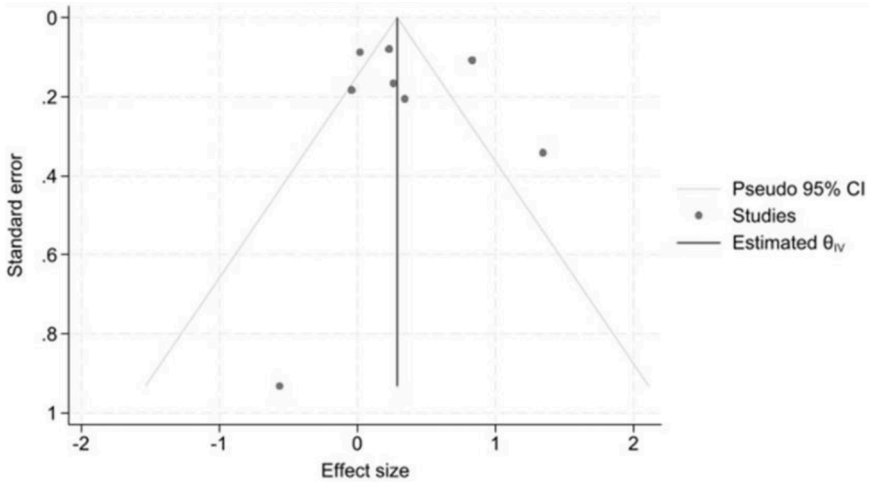

Fig. 3. Funnel plot of studies included in the meta-analysis.

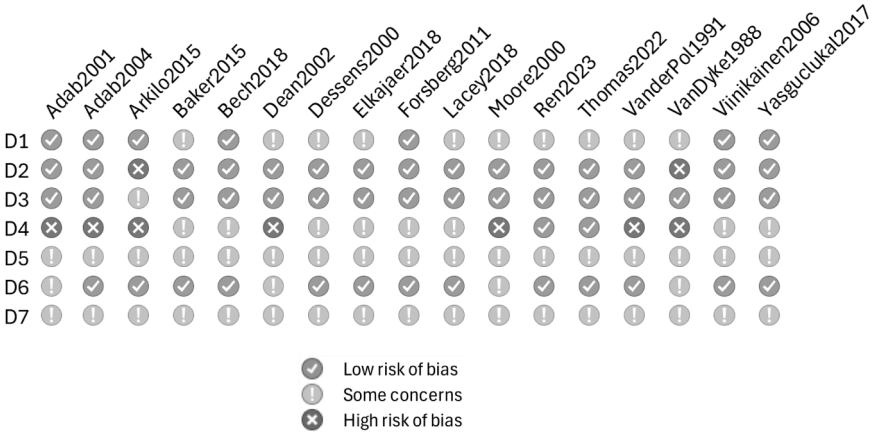

Fig. 4. Risk of bias (ROBINS-E) results of included studies. D1: Confounding, D2: Exposure measurement, D3: Participant selection, D4: Post-exposure interventions, D5: Missing data, D6: Outcome measurement, D7: Result selection.

Table 3
Antiseizure Medication Exposure Counts and Risk Ratios for Educational Needs.

ASM	N exposed	N control	RR	95 % CI	p-value
Carbamazepine	238	413	1.28	0.70, 2.32	0.423
Phenobarbital	74	99	1.61	0.58, 4.50	0.361
Phenytoin	202	145	1.82	0.72, 4.6	0.207
Sodium Valproate	173	324	2.38	1.25, 4.53	0.008

RR= Risk Ratio; CI = confidence interval; ASM = antiseizure medication.

their unexposed peers [30,32,35; Supplementary Table 2]. Sodium valproate monotherapy was consistently associated with poorer academic performance, even after adjusting for maternal education and socioeconomic factors [30,32]. ASM polytherapy was also associated with lower academic performance compared to monotherapy or no exposure [32]. Additionally, one study reported that those exposed to both first and new-generation ASMs had lower university enrolment rates and experienced career difficulties in young adulthood [35].

Among the studies examining subject-specific exam performance, five reported that children prenatally exposed to ASMs had lower achievement in key academic areas [25,30,31,33,42; Supplementary Table 2]. Exposure to first-generation ASMs, including sodium valproate and carbamazepine, was associated with lower examination grades in maths and language [25,30,31,33]. In contrast, children exposed to lamotrigine (Lamictal) had similar academic performance to their peers [30,33]. Two studies reported that the offspring of mothers who took

Table 4
Meta-Regression Results.

	RR	95 % CI	p-value	I^2 (%)	Cochrane's Q (p)	Wald chi^2 (p)
Meta-Regression[#]						
Polytherapy	0.983	0.267, 3.625	0.979			
Study design	1.184	0.455, 3.079	0.730			
ASM type	1.386	0.918, 2.093	0.121			
Country	0.929	0.319, 2.708	0.893			
Overall Residual				84.59	19.47 (<0.001)	3.83 (0.429)

[#] The model was adjusted for ASM investigated: any, sodium valproate, carbamazepine, phenobarbital or phenytoin
RR= Risk Ratio; CI = confidence interval; ASM = anti-seizure medication.

ASMs during pregnancy were less likely to participate in sports activities [25,31].

4. Discussion

Although most women with epilepsy are of reproductive age [43], only 17 studies were identified that had investigated the association between prenatal ASM exposure and educational outcomes. The pooled estimates obtained from eight of these studies demonstrated worse educational outcomes among children with prenatal ASM exposure and specifically with exposure to sodium valproate. Notably, the risk of special education needs and learning difficulties was increased even at low doses of sodium valproate.

Our findings were consistent with a previous systematic review that demonstrated impaired cognitive development and learning difficulties associated with prenatal exposure to sodium valproate [44]. Behavioural problems and lower academic performance, particularly in subjects such as maths and language, have been observed more frequently among children exposed to sodium valproate [45,46]. However, long-term cognitive skills have generally not been found to be significantly affected by prenatal ASM exposure, except in cases involving high doses of sodium valproate [47–49]. Similarly, the behavioural and social functioning of children prenatally exposed to ASMs has been reported to be comparable to that of their peers [44]. The observed variability in findings may be attributed to differences in study design, particularly the inclusion of research specifically examining educational outcomes and school-related behaviours, which provide more detailed insights into the effects of ASM exposure.

Similarly, children exposed to carbamazepine, phenytoin, and phenobarbital were more likely to have a record of special education need or poorer academic performance compared to their unexposed peers. A previously published meta-analysis reported that children exposed to carbamazepine during pregnancy were more likely to have lower scores in performance abilities, such as problem-solving, compared to their peers [50]. Additionally, some studies have suggested that in utero exposure to phenytoin and phenobarbital may be associated with poorer language abilities, though findings have been inconsistent [50]. This would suggest a subsequent need for additional learning support among children with prenatal exposure to ASMs. However, our meta-analysis did not support this finding for these ASMs. The very limited evidence available to date does not demonstrate any significant developmental [47,48] or educational differences among children exposed to carbamazepine, phenytoin, or phenobarbital in utero but the limited data available precludes the drawing of concrete conclusions.

Most of the studies of prenatal exposure to newer generation ASMs have concentrated on teratogenic effects [48], pregnancy outcomes [48, 51] and neurodevelopmental effects [48,49], while long-term educational and academic outcomes in children have received less attention. The studies that have been conducted on educational and academic outcomes suggest that, in contrast to first-generation ASMs, there is no evidence that newer generation ASMs such as lamotrigine (Lamictal) are associated with increased risk of special education needs or poorer academic performance compared to unexposed children. However, this could not be confirmed in our meta-analysis due to the limited number of studies, specifically studies examining lamotrigine (Lamictal) monotherapy exposure. A recent meta-analysis of lamotrigine (Lamictal) monotherapy exposure in utero showed no statistical association with neurodevelopmental disorders including delays in language in school-age children [49]. This suggests this specific ASM may be a safer treatment option for managing epilepsy during pregnancy. Nevertheless, studies with extended follow-up periods focusing on newer-generation ASM monotherapy are required to draw more robust conclusions regarding specific educational needs and academic outcomes. Of note, among the studies that included newer ASMs in the systematic review, topiramate (Topamax tablets) and levetiracetam were still associated with a higher risk of learning difficulties. However, this risk appeared to be less pronounced compared to that observed with first generation ASMs. Both topiramate (Topamax tablets) and levetiracetam exposure in-utero have been previously linked to a higher risk of specific behavioural issues [52,53], with topiramate (Topamax tablets) also being associated with an increased risk of learning disabilities [54]. Hence, although the findings indicate that newer generation medications carry a lower risk than first generation medications, their effects on adverse educational outcomes differ by medication, with some newer ASMs still presenting potential risks, highlighting the need for future research.

To the best of our knowledge, this is the first systematic review to specifically explore the educational and academic outcomes of children who were exposed to ASMs in utero. This review is novel in terms of the outcomes investigated, and the methodology was robust and undertaken in accordance with current guidelines [26,27]. While not all studies could be included in the meta-analysis due to substantial variation in the outcome measures, several studies were incorporated, thereby strengthening the conclusions drawn from the narrative review. The findings support the conclusion of the Medicines & Healthcare Products Regulatory Agency, that newer-generation medications, such as lamotrigine (Lamictal) and levetiracetam, appear to be safer options for the treatment of pregnant women [55]. However, further research is necessary to corroborate these findings due to the limited number of publications.

Several limitations should also be acknowledged. Due to incomplete reporting in some studies, relative risk ratios had to be calculated, and adjustments for confounding variables were not possible in these studies. Failure of many studies to report results stratified by, for example polypharmacy, limited our ability to determine whether effect modifiers existed. Evidence on newer-generation ASMs was sparse and drawn from small samples, precluding meta-analysis and limiting the robustness of these findings. Additionally, only a few studies reported drug dosages, requiring the assumption that different dosages of the same ASM had equivalent effects on outcomes. However, teratogenic effects are known to be dose dependent [1]. This along with the lack of other important factors, such as maternal education, highlights the need for future prospective studies employing therapeutic drug monitoring to better understand dose-dependent effects. Future studies should also consider investigating the timing of exposure, as certain trimesters are critical periods for foetal brain development [48]. Moreover, the severity of epilepsy and the type of epileptic disorder may impact adverse child outcomes [21], thus these confounding factors should be closely examined in future research. Although strict inclusion and exclusion criteria ensured consistency and specificity in outcomes, they may have led to the exclusion of germane studies, potentially limiting the breadth of findings included in this review. Future reviews with a narrower focus on individual antiseizure medications (ASMs) may allow inclusion of a broader range of relevant studies, potentially recovering additional useful data. Furthermore, all included studies were observational in nature and therefore inherently susceptible to selection bias.

This review underscores the significant clinical implications and the critical need for epilepsy services to deliver comprehensive information and counselling on ASM treatments during the reproductive years. Previous studies have identified gaps in preconception counselling and noted challenges related to insufficient or unclear guidelines [56,57]. Alarmingly, recent evidence highlights persistent inconsistencies in how healthcare professionals discuss ASMs and supplements with women with epilepsy [58]. Many clinicians report limited familiarity with current research and attribute conflicting recommendations from different providers as barriers to effective counselling. In alignment with recent clinical guidelines [2] and evidence-based practices, it is imperative that women with epilepsy receive comprehensive pre-pregnancy counselling to support informed decisions about ASMs, pregnancy planning, and associated risks. Moving forward, this review highlights the need for more extensive research into lesser-studied ASMs and their

potential impacts on child development, with the goal of refining prescribing practices and improving counselling by equipping women with reliable, evidence-based information on potential risks.

5. Conclusions

The use of antiseizure medications (ASMs) in women with epilepsy is essential, as untreated epilepsy can result in significantly increased morbidity and mortality rates [59–61]. This systematic review and meta-analysis underscore the higher risks of adverse educational and academic outcomes in school-aged children who had prenatal exposure to first-generation ASMs, particularly sodium valproate. In contrast, newer-generation ASMs, such as lamotrigine (Lamictal), appear to present a lower risk, though the evidence remains limited and influenced by methodological constraints. These findings highlight the critical need for high-quality, prospective longitudinal studies to further elucidate the effects of ASMs on offspring outcomes. Future research should prioritize understanding of the long-term impacts of newer-generation ASMs and the factors influencing their prescription to guide clinical practice and optimize care for women with epilepsy and their children.

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Alexia Karain: Methodology, Investigation, Data curation, Validation, Formal analysis, Writing – original draft, Writing – review & editing. **Lama A. Shakhshir:** Investigation. **Jill P. Pell:** Supervision, Writing – review & editing. **Daniel F. Mackay:** Supervision, Writing – review & editing. **Scott M Nelson:** Writing – review & editing. **Sarjit Singh:** Writing – review & editing. **Michael Fleming:** Conceptualization, Funding acquisition, Supervision, Writing – review & editing.

Declaration of competing interest

All authors declare no competing interests.

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Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.seizure.2025.08.016.

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