Scientific Research Publishing

Open Journal of Psychiatry, 2023, 13, 106-121
https://www.scirp.org/journal/ojpsych
ISSN Online: 2161-7333
ISSN Print: 2161-7325

Risk of Autism Spectrum Disorder According to the Dose and Trimester of Exposure to Antiseizure Medications: A Systematic Review and Meta-Analysis

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How to cite this paper: Mohamed, Z.A., Thokerunga, E., Jimale, A.O., Liu, Z.C. and Fan, J.Y. (2023) Risk of Autism Spectrum Disorder According to the Dose and Trimester of Exposure to Antiseizure Medications: A Systematic Review and Meta-Analysis. *Open Journal of Psychiatry*, **13**, 106-121.
https://doi.org/10.4236/ojpsych.2023.132011

Received: March 17, 2023
Accepted: April 22, 2023
Published: April 25, 2023

Abstract

Background: The association between prenatal exposure to antiseizure medications (ASM) and autism spectrum disorder has been documented. This study sought to examine and synthesize evidence from studies that have evaluated these associations, with particular focus on the trimester of pregnancy and dosage of exposure. **Methodology:** PubMed, Embase, and PsycINFO databases were searched following strict inclusion/exclusion criteria. 10 studies were recruited involving children born to mothers with epilepsy who took ASM during pregnancy as cases, and those with epilepsy who did not take any ASM in pregnancy. **Results:** The relative risk of developing ASD among children exposed to valproic acid (RR, 3.90 [95% CI: 2.36 - 6.44], $p < 0.006$), was twice higher than that of carbamazepine (RR, 1.65 [95% CI: 0.62 - 4.37], $p < 0.0001$), or lamotrigine (RR, 1.60 [95% CI: 0.77 - 3.32], $p = 0.006$). The trimester of exposure and dosage of ASM administered were not significant. **Conclusion:** In summary, prenatal exposure to ASM increased the risk of developing ASD in children. The relative risk was twice as high in those exposed to valproic acid compared to those exposed to carbamazepine or lamotrigine. Trimester of pregnancy and dosage of ASM used by the mothers were not significant.

Keywords

Autism, Anti-Seizure, Anticonvulsants, Anti-Epileptic, Fetal, Prenatal

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1. Introduction

World over, an estimated 3 to 7 per every 1000 pregnancies are affected by epilepsy [1]. Having uncontrolled epilepsy while pregnant increases both maternal and fetal risks of pregnancy-related complications such as decreased oxygen supply to the fetus, slowdown of fetal heart rate, and premature delivery [2]. Clinicians are thus encouraged to treat epilepsy during pregnancy, given the treatment benefits to both the mother and the fetus. The primary treatment for epilepsy is pharmacotherapy with antiseizure medications (ASM) [3]. Commonly prescribed antiseizure drugs include: valproic acid/sodium valproate, lamotrigine, carbamazepine, levetiracetam, oxcarbazepine, and phenytoin [4]. Concerns about the safety of ASM during pregnancy have been raised due to evidence indicating risks of unfavorable birth outcomes [5], putting physicians in a position of having to weigh the benefits derived from the ASM against potentials for teratogenic effects, before deciding to prescribe or not.

Autism spectrum disorder (ASD), is a childhood neurological disorder characterized by repetitive behaviors and limited interest in the affected children, coupled with social and communication difficulties. Key diagnostic characteristics include: impaired social interactions, stereotyped patterns of behavior and impaired communication ability. In order for a diagnosis to be established, one of these key characteristics must occur before the age of 3 [6]. This disorder results from the interactions among genetic and environmental risk factors [7]. In this context, prenatal exposure to antiseizure medications is a modifiable environmental risk factor.

Studies, both in animal models and humans have demonstrated that exposure to ASM in utero carries an increased risk for the development of ASD [8]-[13]. However, critical analysis of the relative risk of ASD from exposure to the different ASM, which trimester of exposure or dosage presents the highest risk among women with epilepsy is still unclear. [10] [13] [14] [15] This systematic review and meta-analysis thus sought to examine and synthesize evidence from all relevant studies that have characterized and evaluated the association between fetal exposures to ASM in women with epilepsy, with particular attention to the relative risk of ASD among children exposed to the different ASM in utero, and which trimester of pregnancy and/or dosage of exposure carries the most increased risk.

2. Methodology

2.1. Search Strategies

The systematic review was registered with the International Prospective Register of Systematic Reviews (PROSPERO); Reg no: CRD42021254001. The review was conducted according to the PRISMA guidelines [16]. A literature search was performed on PubMed, Embase, and PsycINFO databases to identify relevant studies. The search algorithm was generated as follows: ("pregnancy" [MeSH Terms]) *OR (*"prenatal" [All Fields]) OR ("prenatal" [Title/Abstract]) OR ("fetal

exposer" [All Fields]) OR ("fetal exposure" [Title/Abstract]) AND ("antiseizure*" [Title/Abstract]) OR ("anti-seizure*" [All Fields]) OR ("antiseizure*" [All Fields]) OR ("anti-epileptic" [Title/Abstract]) OR ("anticonvulsant*" [MeSH Terms]) OR ("anticonvulsant*" [Title/Abstract]) AND ("autism spectrum disorder" [MeSH Terms]) OR ("spectrum disorders autism" [Title/Abstract]) OR ("autism spectrum disorder" [Title/Abstract]) OR ("ASD" [Title/Abstract]) OR ("Autistic disorder" [Title/Abstract]). Databases were searched in March 2021 and updated in January 2023 for published literature containing the search terms within titles or abstracts. Reviewers ZAM and ET conducted independent searches to identify studies reporting the association between prenatal antiseizure medications exposure and the risk of developing autism spectrum disorder.

2.2. Inclusion and Exclusion Criteria

Studies evaluating the association between fetal antiseizure medication exposure and ASD were examined and subsequently selected if they fulfilled the following inclusion criteria: 1) Were written and published in English; 2) design was observational cohort or case-control; 3) population was children born to women with epilepsy who took antiseizure medications during pregnancy and the control groups were children born to women with epilepsy who did not take antiseizure medications during pregnancy. Studies were excluded if they were case reports or case series, reviews or meta-analyses, conference abstracts, or assessed autistic traits rather than ASD diagnosis.

2.3. Data Extraction and Quality Assessment of the Studies

According to the search strategy, two investigators (ZAM and ET), independently evaluated the methodological quality in each study and extracted all relevant data using a standardized data extraction form. The two reviewers independently evaluated the quality of all included studies using the Newcastle Ottawa Scale (NOS) [17], a standard tool designed to evaluate the quality of non-randomized studies. Each study received a maximum of nine stars based on the following criteria: Group selection (four stars); group comparability (two stars); and ascertainment of the desired outcome (three stars). Scores of 0 - 3, 4 - 6, and 7 - 9 were assigned to each study to indicate low, moderate, or high quality. Disagreements between the two investigators were resolved by discussions and consensus. The following data were independently extracted from each included study by ZAM and ET: Name of first author, publication year, country of origin, study design, total children exposed to ASM, type of antiseizure drug, trimester of exposure, ASD diagnosis criteria used, information about study quality and confounding factors.

2.4. Statistical Analysis

Data were analyzed using the Cochrane Collaboration Review Manager Software (RevMan version 5.3). All the outcomes were regarded as dichotomous variables,

thus, were expressed as risk ratio (RR) with 95% confidence intervals (95% CIs). A random-effect model, which takes into account between-study heterogeneity, if present, was used. Chi-square test and I^2 were used to determine heterogeneity. $I^2 > 50\%$ was considered to have significant heterogeneity. Meta-analysis was conducted separately for each drug exposed and the risk of autism. Funnel plot was not produced since the meta-analyses had less than ten studies. $P < 0.05$ was considered to be statistically significant.

3. Results

3.1. Study Identification and Selection

The initial search yielded 309 records. No additional records were identified from other sources. Of the 309 studies included, 153 were from PubMed, 127 were from EMBASE, and 29 were from PsycINFO. 76 references were duplicates. After screening the title/abstracts and full-text information, 196 and 27 studies were excluded, respectively. Finally, 10 studies that met the inclusion criteria were included [9]-[15] [18] [19] [20]. The study selection flow chart is shown in Figure 1.

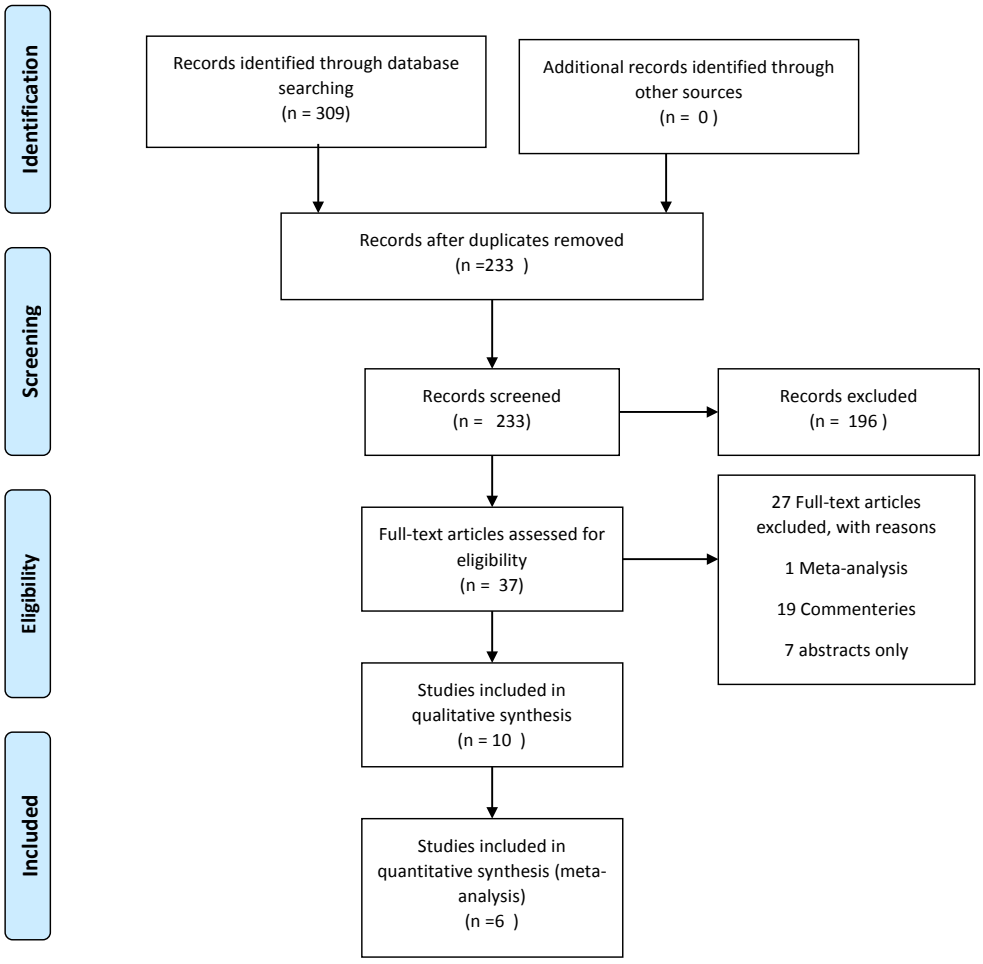

Figure 1. PRISMA flow chart for study selection.

3.2. Study Characteristics and Quality

These studies were published between 2008 and 2022. They had a combined sample size of 5,272,413 children, ranging from 47 to 4,494,926 children among individual studies. 9 of the studies were cohorts, and 1, a case control. The median Newcastle Ottawa Scale (NOS) score for the quality of the included studies was 7 (ranging from 5 to 9). The two studies by Veiby *et al.* [20] and Bjørk *et al.* [18]. both used the same database with similar patients. We thus decided to drop Bjørk *et al.* [18]. since it lacked specific data on lamotrigine and carbamazepine, and continued with Veiby *et al.* for meta-analysis. Similarly, Bromley *et al.* 2013 [19] and 2008 [9] were conducted in the same population, hence we removed Bromley *et al.* 2008 from the meta-analysis as it was the older reference. Moreover, the two studies Wood *et al.* [13] and Rasalam *et al.,* [14] did not report clearly the unexposed control, and so we simply added them for qualitative analysis. The major characteristics of the included studies are presented in **Table 1** and Appendix **Table A1** & **Table A2**. The major confounding factors assessed in this study were (maternal age, paternal age, maternal epilepsy, parental psychiatric history, gestational age, birth weight, child sex, congenital malformations, parity, and smoking history). All the studies included evaluated the impact of maternal history of epilepsy and maternal age at conception except Rasalam *et al.* [14]. Most of the studies assessed gestational age, child sex, and history of smoking. Adjustment of parental psychiatric history was limited. The major confounding factors assessed in this study are presented in Appendix **Table A3**.

3.3. Systematic Review

3.3.1. Prenatal Exposure to Antiseizure Medications and the Risk of ASD in Children

The studies by Wiggs *et al.,* [12] and Bromley *et al.,* [19] comprehensively focused on 3 major ASM: Valproic acid, lamotrigine, and carbamazepine. Wiggs *et al.*, had a relatively robust result because it had a large sample size (14,614 children), accounted for various possible confounders (e.g., bipolar disorders, psychiatric diagnoses, maternal use of other additional medications, etc.), and used high-quality data source; the Swedish register data. In their study, children born to mothers who used valproic acid during pregnancy had a 2.3-fold increase in the risk of ASD (hazard ratio [HR] 2.3, [95% CI: 1.53 - 3.47]) compared to those whose mothers reported no use of ASM. Carbamazepine usage had a weak non statistically significant association, while Lamotrigine was not associated with increased risk of ASD after adjusting for all possible confounders. Since all three drugs are also used to treat mood swings, the study ensured that bipolar disorder and maternal psychiatric diagnoses as confounders were accounted for. It however did not assess exposure by trimester of pregnancy or dosage of the drugs administered. Similarly, Bromley *et al.*, observed that monotherapy with valproic acid had a significantly increased risk for ASD, 12.0% (OR: 6.05 [95% CI: 1.65% - 24.53%]) compared to the control children (1.87%). A weak non statistically significant association was noted between the increase in dosage of valproic acid

and ASD, however, the study had a very low sample size which could have greatly affected its power to determine such associations. Again, no increased risk for ASD was seen among those that used lamotrigine or carbamazepine monotherapy, while exposure by trimester of pregnancy was not assessed.

Table 1. Characteristics of the included studies.

Studies	Study design	Country	Children exposed to ASM	Type of Antiseizure medication	ASD Diagnostic criteria of	Trimester of Exposure	NOS Quality
Bromley, *et al.* 2008 [9]	Population-based cohort study	UK	249 children	Valproic acid, lamotrigine and phenytoin	DSM-IV criteria	During pregnancy	8
Christensen *et al.* 2013 [10]	Population-based cohort study	Denmark	508 children	valproic acid	ICD-10 criteria	During pregnancy	9
Stadelmaier *et al.* 2017 [11]	Population-based Case-control study	USA	47 children	Valproic acid	ADI-R, ADOS and SCQ	First trimester	7
Wiggs *et al.* 2020 [12]	Population-based cohort study	Sweden	3316 children	valproic acid, lamotrigine, carbamazepine and any AEDs	ICD-10 criteria	First trimester	8
Wood *et al.* 2015 [13]	Population-based cohort study	Australia	105 children	valproic acid, carbamazepine and lamotrigine	DSM-IV criteria	During pregnancy	5
Rasalam *et al.* 2017 [14]	Population-based cohort study	Scotland	260 children	Valproic acid, Carbamazepine	DSM-IV criteria	During pregnancy	6
Bjork, *et al.* 2022 [15]	Population-based cohort study	Denmark Finland Norway and Sweden	24,825 children	Lamotrigine, Carbamazepine Valproate, Pregabalin, Gabapentin, Oxcarbazepine, Clonazepam, Levetiracetam, topiramate and Phenobarbital	ICD-10 criteria	During pregnancy	9
Bjork, *et al.* 2018 [18]	Population-based cohort study	Norway	335 children	valproate, oxcarbazepine, primidone, levetiracetam, gabapentin, Carbamazepine, clonazepam, phenobarbital, phenytoin, clobazam	M-CHAT And SCQ Criteria	First trimester	9
Bromley, *et al.* 2013 [19]	Population-based cohort study	UK	201 children	Valproate, lamotrigine Carbamazepine	N/A	During pregnancy	9
Veiby, *et al.* 2013 [20]	Population-based cohort study	Norway	333 children	Lamotrigine, valproate, oxcarbazepine, primidone, levetiracetam, gabapentin Carbamazepine, clonazepam, phenobarbital, phenytoin, clobazam	MCHAT and ESAT	During pregnancy	8

The other studies that looked at a combination of ASM were Rasalam *et al.*, [14], the Nordic countries cohort by Bjørk *et al.* [15] and the Norwegian mother and Baby cohorts by Veiby *et al.*, [20] and Bjørk *et al.,* [18]. In all these studies, in utero exposure to ASM, in general, showed an increased risk of ASD. Unlike other studies, Bjørk *et al.* [15] found topiramate-exposed children of epileptic mothers have a higher risk of developing ASD than valproate-exposed children with HRs of 2.8 (95% CI, 1.4 - 5.7) and 2.4 (95% CI, 1.7 - 3.3). in their study a weak association HR, 1.3; [95% CI, 1.1 - 1.5], was also observed for lamotrigine exposure and no increased risk for levetiracetam, gabapentin, pregabalin, or phenobarbital. Meanwhile, Veiby *et al.* [20], reported that exposure to lamotrigine and not valproate had the highest risk of ASD, however, the sample size for exposure to valproate (n = 19), was much lower than that for lamotrigine (n = 44) exposure, which could explain the difference. They further analyzed children whose fathers used ASM prior to the conception of the baby and found that these children were more likely to show neurodevelopmental delays than the controls, but this was not specific for ASD. It is thought that having epilepsy, these fathers could possess inheritable traits that predispose their babies to neurodevelopmental delays just like epileptic mothers. It would be interesting to know the risk of ASD in children from non-epileptic fathers exposed to ASM prior to conception.

Two studies, Christensen *et al.*, [10] and Stadelmaier *et al.*, [11] looked at the risk of exposure to Valproic acid as monotherapy in detail. Christensen *et al.* assessed a very large number of children including (508, mean age 8.84 years) exposed to Valproic acid in utero from 1996 to 2006. The study reported that the absolute risk of developing ASD in children exposed to Valproic acid in utero was 4.42% [95% CI: 2.59% - 7.46%], for autism spectrum disorder and 2.50% [95% CI: 1.30% - 4.81%] for childhood autism, compared to 2.44% [95% CI: 1.88% - 3.16%] and 1.02% [95% CI: 0.70% - 1.49%] for autism spectrum disorder and childhood autism respectively in those not exposed to valproic acid. This result indicates that in utero exposure to valproic acid increases the risk of developing ASD by 2-folds. A similar finding was observed in the study by Stadelmaier *et al.* where out of 47 children exposed to valproic acid in utero, 13 were diagnosed with autism spectrum disorder, significantly higher than the unexposed children. These results are generally consistent with findings from other studies that valproic acid use in pregnancy is indeed a risk factor for autism [21].

3.3.2. Risk of ASD According to Trimester of Exposure to ASM

According to Bjørk *et al.,* [18], Wood *et al.* [13], Stadelmaier *et al.* [11] and *Wiggs et al.* [12], exposure to antiseizure medications (especially valproic acid) in utero in the first trimester of pregnancy appeared to present relatively higher risks for developing ASD compared to second and third trimesters. However, Christensen *et al.* [10], found that the risk of autism spectrum disorder among children whose mothers were exposed to valproic acid in the first trimester (ad-

justed HR, 2.9 [95% CI, 1.6 - 5.1]) were relatively lower compared to the risk in those exposed in the second and third trimesters, [3.1 (95% CI, 0.8 - 12.2)]. However, the confidence intervals of the second and third trimester exposures varies widely, probably due to the smaller sample size used (67 children), and so was not powered enough to detect a meaningful association. The findings of Christensen was supported by Bjørk *et al.* [15] who found that exposure to valproate during the second and third trimesters without exposure during the first trimester was still associated with an increased risk of ASD with a HR of 1.94 (1.04 - 3.60). Bjørk *et al.* [18], and Wood *et al.* [13] studied the usefulness of folic acid supplements in the first trimester in preventing ASD, so the supposed increase in the risk of ASD in first-trimester exposure to ASM is extrapolated from the fact that women who did not take folic acid early in pregnancy had increased risks of producing autistic children. Given the observed benefits of folic acid supplements in decreasing ASD, it may not be possible on ethical grounds to conduct a study purely comparing exposure to ASM in the first trimester of pregnancy and the risk of ASD.

3.3.3. Risk of ASD According to Dosage of ASM Administered

The Nordic countries cohort study by Bjork *et al.* [15], assessed the relationship between dosage of ASM used and the risk of ASD and noticed positive associations. In their study they found HR of 1.7 (95% CI, 1.0 - 2.8) for those exposed to topiramate doses less than 100 mg per day, and HR of 2.9 (95% CI, 1.3 - 6.7) for doses greater than 100 mg per day. Meanwhile, the HR for those exposed to less than 750 mg per day of valproate was found to be 2.3 (95% CI, 1.9 - 2.8) and 5.6 (95% CI, 4.7 - 6.8) for those exposed to more than 750 mg per day. Two studies, Wood *et al.* [13], and Bromley *et al.* [19] also found positive associations. However, the associations were not statistically significant probably because of the small sample sizes in each study. In contrast, Bjork *et al.* [16] revealed that there is no significant association between ASM doses and the risk of ASD. This is supported by Christensen *et al.* (Christensen & Gr, n.d.) who assessed a large number of women and found that those that used a high dosage of Valproic acid (VPA) did not have a significantly different risk for producing autistic children (adjusted HR, 2.5 [95% CI, 1.03 - 6.1] and 3.2 [95% CI, 1.4 - 13.4] for high and low dose VPA respectively). The question of what dose of ASM (especially VPA) is safe for pregnant women with epilepsy is very important because if a safe dose exists, then women whose epilepsy can only be controlled by VPA will not have to discontinue its use in case they decide to get pregnant. It is therefore important that further studies are pursued in this direction.

3.4. Meta-Analysis

According to our inclusion criteria, meta-analysis was conducted for six studies that looked at the association between valproic acid and the risk of ASD. These included: [10] [11] [12] [15] [19] [20]. Furthermore, data for the association between carbamazepine and lamotrigine and the risk of ASD were extracted

from studies by Wiggs *et al.* [12], Bjørk *et al.* [15], Bromley *et al.* [19], and Veiby [20] for meta-analysis.

Meta-analysis showed that the relative risk for developing ASD was higher in children exposed to valproic acid monotherapy compared to carbamazepine and lamotrigine. The risk of ASD for VPA was (RR, 3.90 [95% CI: 2.36 - 6.44], $p < 0.006$) Figure 2, while those for carbamazepine and lamotrigine were: (RR, 1.65 [95% CI: 0.62 - 4.37], $p < 0.0001$), and (RR, 1.60 [95% CI: 0.77 - 3.32], $p = 0.006$) respectively Figure 3 & Figure 4.

4. Discussion

Our meta-analysis found that prenatal exposure to antiseizure medications is associated with an increased risk of ASD in children, with valproic acid presenting the highest risk as a monotherapy. Carbamazepine and lamotrigine exposures showed an association with ASD, but not as strongly as valproic acid. This drug has also been associated with other neurodevelopmental disorders such as attention deficit hyperactivity syndrome (ADHD) [22] and major congenital

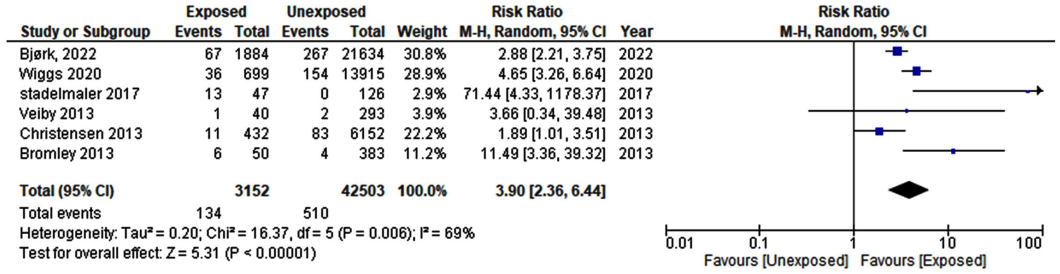

Figure 2. Forest plot showing the association between prenatal Valproic acid exposure and risk of autism spectrum disorder in children.

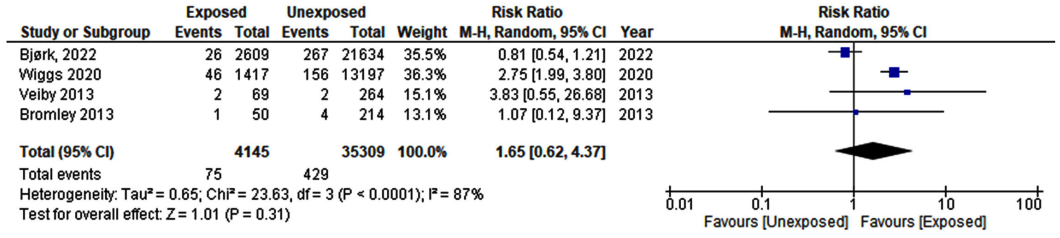

Figure 3. Forest plot showing the association between prenatal Carbamazepine exposure and risk of autism spectrum disorder in children.

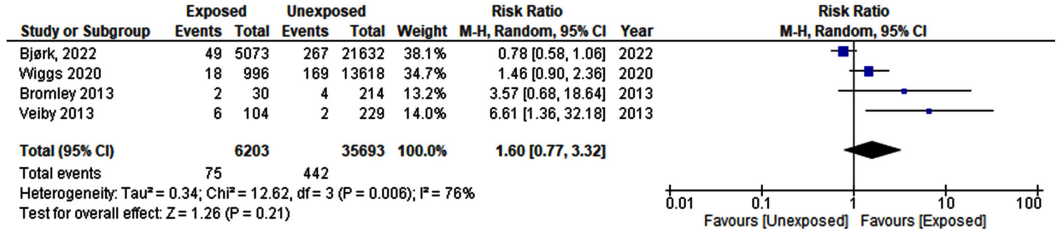

Figure 4. Forest plot showing the association between prenatal Lamotrigine exposure and risk of autism spectrum disorder in children.

malformations [23]-[28]. This finding thus supports the hypothesis that not all antiseizure medications are associated with greater risk to ASD, and so women with epilepsy wishing to get pregnant should be counseled to make an informed decision on what antiseizure medications to use.

According to the dose of ASM and risk of ASD, the analysis was not statistically significant. There is, however, a positive association between the mean dose of exposure to valproic acid in pregnancy and neurodevelopmental disorders [29]. Other adverse outcomes associated with the use of valproic acid are birth defects and neurocognitive impairments [30] [31] [32] [33] [34]. The higher the dose, the worse the outcome. According to a prospective cohort study by Adab *et al.* [35] from the United Kingdom, the cognitive and verbal skills of children exposed to low-dose valproic acid during pregnancy seemed to be compromised, raising further queries about the safe use of valproic acid in pregnancy. It is thus imperative that women in whom valproic acid is the only effective seizure control medicine be assessed to see if a safe dose exists, that ensures seizures are controlled without causing harm to the baby.

When assessed by trimester of exposure, Bjørk *et al.* [18], Wood *et al.* [13], Stadelmaier *et al.* [11], and *Wiggs et al.* [12] all reported that exposure to ASM (specially valproate) during first trimester increased the risk of ASD. However, they did not objectively compare the odds across all the three trimesters. On the other hand, Christensen *et al.* [10], objectively compared the three trimesters and found a HR of 2.9 [95% CI: 1.6 - 5.1] in first trimester and 3.1 [95% CI: 0.8 - 12.2] in second and third trimesters, although the confidence intervals of the second and third trimester exposures vary widely, probably because the sample size used was small (67 children), and so did not have enough power to detect a meaningful association. The findings of Christensen *et al.* are supported by Coste *et al.,* who examined a large cohort of French children exposed to ASM in utero, and discovered that exposures in the second and third trimesters were instead more associated with neurodevelopmental disorders [36]. Moreover, Bjørk *et al.* [15] further found that exposure to valproate in the second and third trimesters without first trimester exposure were still associated with an increased risk of autism in children with a HR 1.94 (1.04 - 3.60). Furthermore, Mezzacappa *et al.,* reported that the risk of ASD in children exposed to antidepressant drugs (some of which are ASM), in utero has no statistical significance by trimester of exposure [37]. A child's brain development occurs across all the three trimesters of pregnancy; neural tubes divide and form the basic region of the brain in the first semester [38], more complex synaptic connection occurs in the second trimester [39], while myelin—a sheath that ensures efficient cell-cell communication—is formed in the third trimester [40]. Exposure to teratogenic antiseizure medications at any of these stages of the brain could have an effect on brain development at that level, hence presenting a risk for ASD. It is therefore plausible to say that the trimester of exposure does not have a significant risk for developing ASD.

Our study had a few limitations that could affect the interpretation of the findings: 1) There could have been a possibility of publication bias, however we could not draw a funnel plot due to the small number of studies analyzed, because, in general, funnel plot asymmetry should only be tested in meta-analyses with at least 10 studies included [41]. 2) Heterogeneity among the combined studies was high (I^2 = 87%). This could also be seen by a simple eyeballing of the forest plot, **Figure 3**. The most probable causes of heterogeneity could be the fact that majority of the studies did not use classic cohort or case-control designs, but rather used population registries in a retrospective approach. Also, the different studies used different methods of ASD diagnosis. Despite the existence of relatively standard tools for ASD diagnosis, much of the assessment questions in these tools are answered based on the assessor's clinical judgment and not a definite laboratory or radiological exam. This scenario creates assessor bias that results in misdiagnosis of cases, hence variability among studies. For instance, Stadelmaier *et al.* [11] discovered 3 false-positive ASD diagnoses by rescreening children using a different diagnostic tool, and wood *et al.* [13] reported the possibility of including children with an intellectual disability who are not necessarily autistic as ASD since their clinical presentations tend to mimic ASD. The use of electroencephalogram (EEG) has been evaluated and shown to be promising for ASD diagnosis [42] [43], while expression of SHANK 3; a genetic biomarker has shown a very strong association with ASD [44] [45] [46] Furthermore, big data analysis of the gut microbiome has shown an association between the composition of the gut microbiome and ASD [47] [48]. Studies along these lines should be accelerated to ensure a more non-subjective diagnosistic tool for ASD.

5. Conclusion

In summary, this study found out that prenatal exposure to antiseizure medications significantly increased the risk of developing ASD in children. The relative risk (RR) of developing ASD in children born to women with epilepsy exposed to valproic acid monotherapy during pregnancy was twice higher than that of carbamazepine and lamotrigine. Though many studies reported an increased risk for ASD from ASM exposure in the first trimester of pregnancy, the quality of evidence was not robust enough to make an independent conclusion. Similarly, there was no statistically significant association between the dosage of ASM used and the risk of ASD. It is therefore important to prescribe antiseizure medications that have been proven to have a low risk of ASD, and consider counseling women with epilepsy intending to get pregnant in order to customize for them the safest regimen available.

Declarations

Authors' Contribution

The author's Z.A.M and E.T conducted literature search, data extraction, data analysis and manuscript drafting. A.O.J and Z.L conducted data analysis and re-

viewed the manuscript. J.F conceived the study and supervised the entire process of the study. All authors have read and agreed to the published version of the manuscript.

Data Availability

The data used to support the findings of this study are included within the article.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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Appendix

Table A1. Critical appraisal of the included cohort studies using the Newcastle-Ottawa Quality Assessment Scale.

	Selection				Comparability	Outcome					
Study	Representativeness of the exposed cohort	Selection of the non-exposed cohort	Ascertainment of exposure	Demonstration that outcome of interest was not present at start of study	Comparability of cohorts on the basis	Assessment of outcome	Was follow-up long enough for outcomes to occur	Adequacy of follow up of cohorts	Total score	Agreement (%)	Risk of Bias
Bromley, *et al.* 2008 [9]	*	*	*	*	**	*		*	8	90%	Low
Christensen *et al.* 2013 [10]	*	*	*	*	*	*	*	*	9	100%	Low
Wiggs *et al.* 2020 [12]	*	*	*	*	**	*		*	8	100%	Low
Wood *et al.* 2015 [13]	*		*			*	*	*	5	70%	Medium
Rasalam *et al.* 2017 [14]	*		*	*		*	*	*	6	75%	Medium
Bjork, *et al.* 2022 [15]	*	*	*	*	**	*	*	*	9	90%	Low
Bjork, *et al.* 2018 [18]	*	*	*	*	**	*	*	*	9	90%	Low
Bromley, *et al.* 2013 [19]	*	*	*	*	**	*	*	*	9	90%	Low
Veiby, *et al.* 2013 [20]	*	*	*	*	*	*	*	*	8	100%	Low

Table A2. Critical appraisal of the included case control studies using the Newcastle-Ottawa Quality Assessment Scale.

	Selection				Comparability	Exposure					
Study	Is the case definition adequate?	Representativeness of the cases	Selection of Controls	Definition of Controls	Comparability of cases and controls based on the design or analysis	Ascertainment of exposure	Same method of ascertainment for cases and controls	Non-Response rate	**Total score**	**Agreement (%)**	**Risk of Bias**
Stadelmaier *et al.* 2017 [11]	*	*	*	*	*	*		*	7	85%	Low

Thresholds for converting the Newcastle-Ottawa scales to AHRQ standards (good, fair, and poor): **Good quality:** 3 or 4 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; **Fair quality:** 2 stars in selection domain AND 1 or 2 stars in comparability domain AND 2 or 3 stars in outcome/exposure domain; **Poor quality:** 0 or 1 star in selection domain OR 0 stars in comparability domain OR 0 or 1 stars in outcome/exposure domain IRR; **Risk of Bias regarded as the following:** High when agreement is below 50%; medium when agreement is between 51% - 80% and low when agreement is greater than 80%.

Table A3. Potential confounders and risk factors evaluated in studies of maternal antiseizure medications use and risk of ASD in offspring.

Potential confounder	Bromley, *et al.* 2008 [9]	Christensen *et al.* 2013 [10]	Stadelmaier *et al.* 2017 [11]	Wiggs *et al.* 2020 [12]	Wood *et al.* 2015 [13]	Rasalam, *et al.* 2017 [14]	Bjork *et al.* 2022 [15]	Bjork, *et al.* 2018 [18]	Bromley, *et al.* 2013 [19]	Veiby, *et al.* 2013 [20]
Maternal age at conception,	Y	Y	Y	Y	Y	_	Y	Y	Y	Y
Paternal age at conception,	Y	Y	_	Y	_	_	_	_	_	_
Maternal epilepsy	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Parental psychiatric history	_	Y	_	Y	_	_	_	_	_	_
Gestational age	_	Y	_	Y	Y	Y	Y	_	_	Y
Birth weight	_	Y	Y	_	_	_	Y	_	_	Y
Child sex	_	Y	_	Y	Y	Y	Y	_	Y	_
Congenital malformations	_	Y	Y	_	_	_	_	_	Y	Y
Parity	_	Y	_	_	_	_	Y	Y	_	Y
Smoking	Y	_	_	Y	Y	_	Y	Y	Y	Y