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Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability

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IMPORTANCE Women with epilepsy frequently need antiseizure medication (ASM) to prevent seizures in pregnancy. Risk of neurodevelopmental disorders after prenatal exposure to AMSs is uncertain.

OBJECTIVE To determine whether children exposed prenatally to ASMs in monotherapy and duotherapy have increased risk of neurodevelopmental disorders.

DESIGN, SETTING, AND PARTICIPANTS The Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) is a population-based cohort study using health register and social register data from Denmark, Finland, Iceland, Norway, and Sweden (1996-2017; analysis performed February 2022). From 4 702 774 alive-born children with available mother-child identities and maternal prescription data, this study included 4 494 926 participants. Children from a multiple pregnancy or with chromosomal disorders or uncertain pregnancy length were excluded (n = 207 848).

EXPOSURES Prenatal exposure to ASM determined from maternal prescription fills between last menstrual period and birth.

MAIN OUTCOMES AND MEASURES We estimated cumulative incidence at age 8 years in exposed and unexposed children. Cox regression adjusted for potential confounders yielded adjusted hazard ratios (aHRs) with 95% CIs for autism spectrum disorder (ASD), intellectual disability (ID), or any neurodevelopmental disorder (ASD and/or ID).

RESULTS A total of 4 494 926 children were included; 2 306 993 (51.3%) were male, and the median (IQR) age at end of follow-up was 8 (4.0-12.1) years. Among 21 634 unexposed children of mothers with epilepsy, 1.5% had a diagnosis of ASD and 0.8% (numerators were not available because of personal data regulations in Denmark) of ID by age 8 years. In same-aged children of mothers with epilepsy exposed to topiramate and valproate monotherapy, 4.3% and 2.7%, respectively, had ASD, and 3.1% and 2.4% had ID. The aHRs for ASD and ID after topiramate exposure were 2.8 (95% CI, 1.4-5.7) and 3.5 (95% CI, 1.4-8.6), respectively, and after valproate exposure were 2.4 (95% CI, 1.7-3.3) and 2.5 (95% CI, 1.7-3.7). The aHRs were elevated with higher ASM doses compared with children from the general population. The duotherapies levetiracetam with carbamazepine and lamotrigine with topiramate were associated with increased risks of neurodevelopmental disorders in children of women with epilepsy: levetiracetam with carbamazepine: 8-year cumulative incidence, 5.7%; aHR, 3.5; 95% CI, 1.5-8.2; lamotrigine with topiramate: 8-year cumulative incidence, 7.5%; aHR, 2.4; 95% CI, 1.1-4.9. No increased risk was associated with levetiracetam with lamotrigine (8-year cumulative incidence, 1.6%; aHR, 0.9; 95% CI, 0.3-2.5). No consistently increased risks were observed for neurodevelopmental disorders after prenatal exposure to monotherapy with lamotrigine, levetiracetam, carbamazepin, oxcarbazepine, gapapentin, pregabalin, clonazepam, or phenobarbital.

CONCLUSIONS AND RELEVANCE In this cohort study, prenatal exposure to topiramate, valproate, and several duotherapies were associated with increased risks of neurodevelopmental disorders.

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Women with epilepsy frequently require antiseizure medication (ASM) during pregnancy, and precise knowledge is needed about the safety for the exposed child.[1] Five in 1000 pregnant women use ASMs, and this use is increasing.[1,2] Discontinuation before or during pregnancy is associated with uncontrolled seizures and increased maternal mortality.[3,4] This places the patient and physician in a difficult position because some ASMs are teratogenic and may increase the risk of neurodevelopmental disorders.[5,6] Previous studies have shown a 3- to 5-fold increased risk of autism spectrum disorder (ASD) and intellectual disability (ID) in children after prenatal exposure to valproate.[7-10] However, for most other ASMs, the risk of neurodevelopmental disorders after prenatal exposure remains uncertain despite their frequent use.[5,7-15] The risk is unknown for commonly used combination therapies, but in some patients, seizure control can only be achieved by combining different ASMs.[16]

The objective of the Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) study is to fill knowledge gaps for women needing ASMs during pregnancy. Using the Nordic register infrastructure, we obtained data on 4.5 million mother-child pairs to estimate the risks of ASD and ID after prenatal exposure to the 10 most frequently used ASM monotherapies and the 5 most used duotherapies accounting for ASM dose and potential confounders.

Key Points

Question Is there an association between prenatal exposure to antiseizure medications and neurodevelopmental disorders?

Findings In this cohort study including 25 000 children prenatally exposed to antiseizure medications, of which 16 000 were born to mothers with epilepsy, topiramate and valproate in monotherapy were associated with a 2- to 4-fold increased risk of autism spectrum disorders and intellectual disability. Prenatal exposure to duotherapy with levetiracetam with carbamazepine and lamotrigine with topiramate, but not levetiracetam with lamotrigine, were also associated with child neurodevelopmental disorders within the same range as for valproate exposure.

Meaning In this study, prenatal exposure to valproate, topiramate, and several duotherapies were associated with increased risk of child neurodevelopmental disorders.

Methods

Ethical and Regulatory Considerations

We followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines and Reporting of Studies Conducted Using Observational Routinely-Collected Data (RECORD) reporting guidelines. The relevant ethical and/or data protection authorities in all countries approved the project and granted a waiver of informed consent (eTable 4 in the Supplement).[17] Data are available on application to the relevant authorities.[17]

Data Sources, Design, and Study Cohort

The Nordic countries have a government-funded health care system with universal coverage, and reporting to social and health registers is mandated by law.[17] A personal identification number assigned to each resident at birth or immigration enables individual-level data linkage across registers. We conducted a cohort study including all live-born infants in Denmark (1997-2017), Finland (1996-2016), Iceland (2004-2017), Norway (2005-2017), and Sweden (2006-2017). We identified mother-child pairs, pregnancy characteristics, prescription fills, mother and child diagnoses, and demographic and socioeconomic information from the national health and social registers in each country.[17] We harmonized variable definitions across the 5 countries according to a common data model[18] (eTables 1 and 2 in the Supplement).

To avoid misclassification of the pregnancy period, we excluded births with a recorded gestational length of 154 days or less or 314 days or more, implausible combinations of birth weight and pregnancy length, or missing information on these variables. We also excluded twins and triplets for statistical reasons and children with chromosomal disorders diagnosed before end of follow-up (eFigure 1 in the Supplement).[19]

Maternal Epilepsy and ASM Exposure

We defined maternal epilepsy as any diagnosis of epilepsy during the available time period of the cohort and before birth of the child (eTables 1 and 2 in the Supplement). Epilepsy diagnoses in health registries have moderate to high validity.[20] We identified ASM prescriptions through national prescription registers[17] according to Anatomical Therapeutic Chemical classification[21] codes N03, N05BA09, and S01EC01. We defined prenatal exposure as the mother filling at least 1 ASM prescription from her last menstrual period until birth. We defined monotherapy as filled prescriptions for 1 type of ASM and no other ASM during the exposure period and duotherapy as filled prescriptions for 2 different ASMs within the same trimester. We present results for the 10 most common monotherapies and the 5 most common duotherapies. We calculated the mean daily cumulative dose as the sum of the defined daily doses (DDD)[22] from all prescriptions filled from 90 days before last menstrual period to birth, divided by number of days in the same period. We converted mean DDDs per day to milligrams per day[22] and applied cutoffs based on 50% of DDD. Observations with extreme values defined as doses above the 98% percentile or below the 2% percentile were excluded.

Neurodevelopmental Outcomes

Severe neurodevelopmental disorders are diagnosed by child psychiatrists and psychologists in specialist health care in the Nordic countries and recorded with *International Statistical Classification of Diseases and Related Health Problems, Tenth Revision* (*ICD-10*) codes.[23] We considered children to have ASD if they had at least 1 occurrence of a diagnosis of childhood autism (F84.0), atypical autism (F84.1), and Asperger syndrome (F84.5), and children with at least 1 occurrence of a diagnosis of mild ID (F70), moderate ID (F71), severe ID (F72), and profound ID (F73). The diagnoses were not mutually exclusive. We defined a composite neurodevelopmental outcome—any neurodevelopmental disorder, as any of the diagnoses above, plus other childhood disintegrative disorder

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(F84.3), disorder of mental retardation and stereotyped movements (F84.4), other pervasive developmental disorder (F84.8), unspecified pervasive developmental disorder (F84.9), or unspecified ID (F79). The positive predictive values of the ASD diagnosis in the Nordic health registers is 86% to 90%.[24,25] ID diagnoses have not been validated.[8]

Statistical Analysis

Data were stored at Statistics Denmark and analyzed using Stata (version 16.1; Stata Corp) and RStudio (version 16.1; R). We assessed the distributions of sociodemographic and medical characteristics among the exposed and unexposed groups (eTable 2 and in eTable 5 in the Supplement). We calculated crude incidence rates by dividing the total number of cases of neurodevelopmental disorders by the sum of the person-time in each exposure group. Crude cumulative incidence by age 8 years was calculated using Kaplan-Meier failure functions (eMethods in the Supplement). Using adjusted hazard ratios (aHRs) and 95% CIs with nonclustered standard errors, we measured the risk of ASD, ID, and any neurodevelopmental disorder in children exposed to ASMs as monotherapy or duotherapy and in different monotherapy dose categories. The comparison group comprised children of women with epilepsy and children from the general population who had not been exposed to ASMs from 90 days preceding the last menstrual period to birth. We calculated aHRs using Cox proportional hazard regression with children's age as the time scale until a diagnosis of ASD, ID, any neurodevelopmental disorder, death, emigration, or end of follow-up (December 31, 2017). Based on previous literature,[7-11,14,26] the child's sex, birth year, and maternal characteristics (birth country, age, parity, marital status, education, concurrent antidepressant and opioid use, depression, anxiety, personality disorders, number of somatic diagnoses, and hospitalizations in the year preceding pregnancy) were included as covariates in all analyses.[26] Birth country and birth year violated the proportional hazard assumption and were applied as strata variables in all models. We imputed missing data for maternal education, marital/cohabitation status, and parity with multiple imputation by chained equations (MICE; eMethods in the Supplement).[27]

Sensitivity Analyses

We performed several sensitivity analyses. We repeated the analyses with an extended exposure interval including women who filled prescriptions from 90 days before the last menstrual period. To estimate the association with unmeasured confounding, we established a new reference group of children born to women who used ASMs in the 2 years preceding pregnancy but discontinued all ASMs prior to 90 days before the last menstrual period. To investigate the importance of exposure timing, we analyzed the risk in children of women who filled an ASM prescription in the second or third trimester only. To investigate association with genetic risk for neurodevelopmental disorders, we adjusted for maternal ASD and ID and examined the association between childhood epilepsy as a time-varying covariate and neurodevelopmental disorders using an interaction term. We repeated the dose analyses using an alternative algorithm for dose calculations to capture the dose in the beginning of pregnancy. Serum concentrations of many ASMs decline during pregnancy, frequently leading to increased dose[28] without subsequent increase in prenatal exposure. We repeated the analysis requiring at least 2 diagnoses of ASD, ID, or any neurodevelopmental disorder to increase diagnostic specificity. Estimates were further adjusted for covariates with incomplete data (ie, smoking and body mass index). We repeated the primary analyses using fine-strata propensity score weighting to estimate the hazard ratio for the average treatment effect among the treated[29] (eMethods, eFigure 2a and 2b in the Supplement).

Results

We observed 4 494 926 children (2 306 993 [51.3% male]), including 24 825 children (0.6%) who were prenatally exposed to ASMs, 16 170 of whom born to mothers with epilepsy (eTable 5, eFigure 1 in the Supplement). The median (IQR) age at the end of follow-up was 8 (4.0-12.1) years. Children's mean age at diagnosis was between 6.1 and 7.9 years across all countries (eTable 3 in the Supplement). Among unexposed children of mothers with epilepsy, the 8-year cumulative incidence of ASD and ID was 1.5% and 0.8%, respectively, while in children of mothers with epilepsy exposed to topiramate, it was 4.3% and 3.1% (numerators were not available because of personal data regulations in Denmark). The aHRs were 2.8 (95% CI, 1.4-5.7) and 3.5 (95% CI, 1.4-8.6), respectively (**Table 1** and **2** and **Figure 1**). Among children of mothers with epilepsy exposed to valproate, the 8-year-cumulative incidence of ASD and ID was 2.7% and 2.4%, respectively. The aHRs were 2.4 (95% CI, 1.7-3.3) and 2.5 (95% CI, 1.7-3.7), respectively. The aHR of any neurodevelopmental disorder was 2.1 (95% CI, 1.1-4.0) for children exposed to topiramate and 2.4 (95% CI, 1.9-3.1) for children exposed to valproate (**Figure 2**). In children of mothers with epilepsy exposed to other ASMs in monotherapy, the risk for neurodevelopmental disorders was not increased. When comparing risks among children from the total population, the aHRs were moderately increased after exposure to oxcarbazepine (aHR, 1.5; 95% CI, 1.2-2.0), carbamazepine (aHR, 1.6; 95% CI, 1.3-1.9) and clonazepam (aHR, 1.4; 95% CI, 1.1-1.9) (Tables 1 and 2, Figure 2). We found weak associations between lamotrigine exposure and any neurodevelopmental disorder (aHR, 1.3; 95% CI, 1.1-1.5), but no increased risks were identified for levetiracetam, gabapentin, pregabalin, or phenobarbital (Table 1, Figure 2). Extending the exposure interval to 90 days before pregnancy attenuated associations slightly (eTables 6A and 6B in the Supplement). When comparing monotherapy-exposed children with children whose mothers filled a prescription for the same ASM in the 2 years preceding pregnancy, but not from 90 days before the last menstrual period to birth, the aHR was 2.0 (95% CI, 1.3-3.0) for any neurodevelopmental disorder after prenatal exposure to valproate and 2.3 (95% CI, 1.1-4.8) for topiramate, but no increased risks were observed for other ASMs (eTable 7 in the Supplement).

The aHR was 1.9 (95% CI, 1.0-3.6) for any neurodevelopmental disorder in children whose mothers filled prescrip-

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Table 1. Risk of Autism Spectrum Disorder (ASD) After Prenatal Exposure to Antiseizure Medication (ASM) Monotherapy[a]

Characteristic	Exposed, No.	With ASD, No.	Incidence rate per 1000 person-years (95% CI)	Cumulative risk by age 8 y, % (95% CI)	Hazard ratio (95% CI)	
					Basic adjustment[b]	Full adjustment[c]
Children of women with epilepsy						
No ASM	21 634	267	1.85 (1.64-2.09)	1.5 (1.3-1.7)	1 [Reference]	1 [Reference]
Any ASM	16 170	274	2.08 (1.85-2.34)	1.7 (1.5-1.9)	1.30 (1.08-1.56)	1.29 (1.07-1.55)
Lamotrigine	5073	49	1.49 (1.13-1.97)	1.0 (0.7-1.5)	0.81 (0.59-1.11)	0.81 (0.59-1.11)
Carbamazepine	2609	26	0.98 (0.66-1.43)	0.9 (0.6-1.4)	0.94 (0.60-1.47)	0.94 (0.60-1.46)
Valproate	1884	67	3.45 (2.72-4.39)	2.7 (2.0-3.6)	2.37 (1.72-3.26)	2.40 (1.73-3.30)
Pregabalin	91	<5	NA[d]	NA[d]	NA[d]	NA[d]
Gabapentin	110	<5	NA[d]	NA[d]	NA[d]	NA[d]
Oxcarbazepine	1429	NA[e]	1.75 (1.18-2.59)	1.2 (0.8-2.1)	1.33 (0.83-2.12)	1.33 (0.83-2.13)
Clonazepam	318	9	2.61 (1.36-5.01)	2.2 (1.0-4.9)	1.32 (0.66-2.61)	1.23 (0.62-2.45)
Levetiracetam	1004	7	1.62 (0.77-3.39)	1.5 (0.7-3.5)	1.03 (0.48-2.22)	1.06 (0.49-2.30)
Topiramate	246	NA[e]	4.76 (2.38-9.51)	4.3 (2.0-8.8)	2.73 (1.34-5.57)	2.77 (1.35-5.65)
Phenobarbital	45	<5	NA[d]	NA[d]	NA[d]	NA[d]
Children from the total population						
No ASM	4 463 879	38 437	1.00 (0.99-1.01)	0.8 (0.8-0.8)	1 [Reference]	1 [Reference]
Any ASM	24 825	399	2.09 (1.89-2.30)	1.8 (1.6-2.0)	1.90 (1.72-2.10)	1.61 (1.46-1.78)
Lamotrigine	7950	82	1.80 (1.45-2.23)	1.4 (1.1-1.9)	1.34 (1.08-1.67)	1.13 (0.91-1.40)
Carbamazepine	3256	41	1.13 (0.83-1.54)	1.1 (0.7-1.5)	1.44 (1.06-1.96)	1.36 (1.00-1.85)
Valproate	2421	82	3.22 (2.59-4.00)	2.5 (1.9-3.3)	3.71 (2.98-4.60)	3.44 (2.77-4.28)
Pregabalin	1666	16	1.93 (1.18-3.15)	1.7 (0.9-3.1)	1.55 (0.95-2.54)	1.01 (0.62-1.66)
Gabapentin	965	8	1.73 (0.87-3.46)	1.3 (0.6-2.7)	1.25 (0.63-2.51)	0.94 (0.47-1.88)
Oxcarbazepine	1539	27	1.69 (1.16-2.46)	1.2 (0.7-1.9)	1.97 (1.35-2.88)	1.88 (1.29-2.73)
Clonazepam	1182	25	2.12 (1.43-3.13)	2.0 (1.3-3.1)	1.93 (1.30-2.86)	1.43 (0.96-2.12)
Levetiracetam	1017	7	1.60 (0.76-3.37)	1.5 (0.7-3.5)	1.65 (0.79-3.46)	1.59 (0.76-3.33)
Topiramate	471	12	3.99 (2.26-7.02)	3.3 (1.8-6.1)	3.27 (1.85-5.75)	2.64 (1.50-4.65)
Phenobarbital	175	5	2.24 (0.93-5.38)	2.0 (0.7-6.1)	1.61 (0.67-3.89)	1.40 (0.58-3.37)

Abbreviation: NA, not applicable.

[a] ASM exposure defined as prescription fills of 1 ASM type (only) between last menstrual period and birth. Exposed children were compared with children born to mothers with epilepsy and with children from the general population not filling ASM prescriptions between 90 days before last menstrual period and birth.

[b] Adjusted for maternal age, education and marital status, parity, child's birth year, sex, and country of birth. Missing values on education, marital status, and parity were imputed using multiple imputation by chained equations. All the models were run with separate strata for country and year as these variables violated the proportional hazard assumption.

[c] Adjusted for basic adjustment plus maternal use of antidepressants or opioids, depression, anxiety, personality disorders, number of chronic somatic diseases, and number of hospitalizations the year before last menstrual period.

[d] NA, owing to personal data protection restrictions on publishing cell counts less than 5.

[e] NA, owing to personal data protection restrictions on publishing tables where the difference between upper and lower panel of the table is less than 5.

tions for valproate in monotherapy only after the first trimester compared with children not exposed to ASMs (eTable 8 in the Supplement). Late pregnancy exposure to carbamazepine and lamotrigine was not associated with increased risk of neurodevelopmental disorders, and there were too few exposed cases to estimate aHRs for other ASMs.

The risk associated with exposure to duotherapy was only assessed for the combined outcome any neurodevelopmental disorder because of too few cases when considering only ASD and ID. Increased risks were associated with all duotherapies except levetiracetam with lamotrigine (Figure 2).

The aHR was 1.7 (95% CI, 1.0-2.8) for any neurodevelopmental disorder associated with topiramate doses less than 100 mg per day and 2.9 (95% CI, 1.3-6.7) for doses 100 mg per day or more compared with children from the general population. For valproate, the aHR was 2.3 (95% CI, 1.9-2.8) with doses less than 750 mg per day and 5.6 (95% CI, 4.7-6.8) with doses of 750 mg or more per day. For the other ASMs, we observed minimal or no dose-related associations (**Table 3**). The dose-association patterns were reproduced using the alternative dose calculation algorithm (eTable 9 in the Supplement). Requiring 2 diagnoses in the child strengthened the associations for valproate and topiramate (eTable 10 in the Supplement).

Repeating the primary analyses after adjusting for maternal neurodevelopmental disorders, body mass index, and smoking did not change the estimates for prenatal exposure to valproate and topiramate (eTables 11 and 12 in the Supplement). Propensity score–weighted analyses did not change these results either (eTable 13 in the Supplement). In models investigating the association between ASM exposure, childhood epilepsy, and neurodevelopmental disorders, there was a significant interaction and the association between ASM exposure and neurodevelopmental disorders decreased among children with epilepsy (eTable 14 in the Supplement).

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Table 2. Risk of Intellectual Disability (ID) After Prenatal Exposure to Antiseizure Medication (ASM) Monotherapy[a]

Characteristic	Exposed, No.	With ID, No.	Incidence rate per 1000 person-years (95% CI)	Cumulative risk by age 8 y, % (95% CI)	Hazard ratio (95% CI)	
					Basic adjustment[b]	Full adjustment[c]
Children of women with epilepsy						
No ASM	21 634	139	0.97 (0.81-1.14)	0.8 (0.6-1.0)	1 [Reference]	1 [Reference]
Any ASM	16 170	187	1.42 (1.23-1.64)	1.2 (1.0-1.4)	1.31 (1.03-1.67)	1.32 (1.04-1.68)
Lamotrigine	5073	21	0.64 (0.42-0.98)	0.6 (0.3-1.0)	0.73 (0.46-1.16)	0.73 (0.46-1.16)
Carbamazepine	2609	20	0.75 (0.48-1.16)	0.4 (0.2-0.8)	0.82 (0.48-1.40)	0.83 (0.49-1.42)
Valproate	1884	56	2.89 (2.23-3.76)	2.4 (1.8-3.3)	2.43 (1.65-3.57)	2.50 (1.70-3.69)
Pregabalin	91	<5	NA[d]	NA[d]	NA[d]	NA[d]
Gabapentin	110	<5	NA[d]	NA[d]	NA[d]	NA[d]
Oxcarbazepine	1429	NA[e]	1.05 (0.63-1.73)	0.6 (0.3-1.3)	0.87 (0.48-1.57)	0.87 (0.48-1.58)
Clonazepam	318	5	1.44 (0.60-3.46)	1.1 (0.4-3.5)	0.96 (0.38-2.38)	0.83 (0.33-2.08)
Levetiracetam	1004	<5	NA[d]	NA[d]	NA[d]	NA[d]
Topiramate	246	NA[e]	2.95 (1.23-7.08)	3.1 (1.2-8.2)	3.53 (1.42-8.74)	3.47 (1.40-8.63)
Phenobarbital	45	<5	NA[d]	NA[d]	NA[d]	NA[d]
Children from the total population						
No ASM	4463 879	16 384	0.42 (0.42-0.43)	0.3 (0.3-0.3)	1 [Reference]	1 [Reference]
Any ASM	24 825	247	1.29 (1.14-1.46)	1.0 (0.9-1.2)	2.74 (2.42-3.11)	2.52 (2.22-2.86)
Lamotrigine	7950	27	0.59 (0.40-0.86)	0.6 (0.4-0.9)	1.50 (1.03-2.19)	1.34 (0.92-1.95)
Carbamazepine	3256	36	0.99 (0.71-1.37)	0.5 (0.3-0.8)	2.08 (1.50-2.89)	2.01 (1.45-2.79)
Valproate	2421	64	2.52 (1.97-3.21)	2.1 (1.6-2.9)	5.03 (3.94-6.43)	4.77 (3.73-6.10)
Pregabalin	1666	5	0.60 (0.25-1.45)	0.5 (0.2-1.5)	1.31 (0.54-3.14)	1.01 (0.42-2.43)
Gabapentin	965	<5	NA[d]	NA[d]	NA[d]	NA[d]
Oxcarbazepine	1539	16	1.00 (0.61-1.63)	0.5 (0.2-1.2)	2.01 (1.23-3.28)	1.95 (1.19-3.18)
Clonazepam	1182	15	1.27 (0.76-2.10)	1.0 (0.5-1.9)	2.14 (1.29-3.55)	1.76 (1.06-2.92)
Levetiracetam	1017	<5	NA[d]	NA[d]	NA[d]	NA[d]
Topiramate	471	6	1.97 (0.89-4.39)	2.0 (0.8-4.9)	4.45 (2.00-9.92)	3.92 (1.76-8.74)
Phenobarbital	175	<5	NA[d]	NA[d]	NA[d]	NA[d]

Abbreviation: NA, not applicable.

[a] ASM exposure defined as prescription fills of 1 ASM type (only) between last menstrual period and birth. Exposed children were compared with children born to mothers with epilepsy and with children from the general population not filling ASM prescriptions between 90 days before last menstrual period and birth.

[b] Adjusted for maternal age, education and marital status, parity, child's birth year, sex, and country of birth. Missing values on education, marital status, and parity were imputed using multiple imputation by chained equations. All the models were run with separate strata for country and year as these variables violated the proportional hazard assumption.

[c] Adjusted for basic adjustment plus maternal use of antidepressants or opioids, depression, anxiety, personality disorders, number of chronic somatic diseases, and number of hospitalizations the year before last menstrual period.

[d] NA, owing to personal data protection restrictions on publishing cell counts less than 5.

[e] NA, owing to personal data protection restrictions on publishing tables where the difference between upper and lower panel of the table is less than 5.

Discussion

In this population-based cohort including 4.5 million mother-child pairs, the most important findings were robust and dose-dependent associations between prenatal topiramate and valproate exposure and neurodevelopmental disorders. These associations persisted after accounting for potential confounding factors. Our results further demonstrated that prenatal exposure to several common ASM duotherapies was associated with an increased risk of neurodevelopmental disorders within the same range as prenatal topiramate and valproate exposure, even without these ASMs being one of the drugs used.

We found a clear risk of adverse neurodevelopment in children exposed to topiramate, particularly at doses of 100 mg or more per day. Prenatal topiramate exposure is associated with an increased risk of being born small for gestational age, and with an increased risk of congenital malformations.[28,30-32] High risks for congenital malformations have been associated with daily doses more than 100 mg.[31] Few studies have assessed cognitive and behavioral child outcomes after prenatal topiramate exposure.[9,33-36] Two clinical studies with 27 topiramate-exposed children[33] and 9 topiramate-exposed children[34] came to opposite conclusions regarding cognitive function. In 2 studies identifying prenatal topiramate exposure from health register data, one found a more than 5-fold increased risk of learning disability,[36] whereas the other identified no abnormal neurodevelopment.[9] However, in the latter study, 75% of the included mothers only filled topiramate prescriptions before or very early in the pregnancy.[9] This pattern of early topiramate discontinuation has been observed previously in the Nordic countries, US, and Australia,[1] and may attenuate estimates of adverse effects associated with topiramate exposure during the whole pregnancy.

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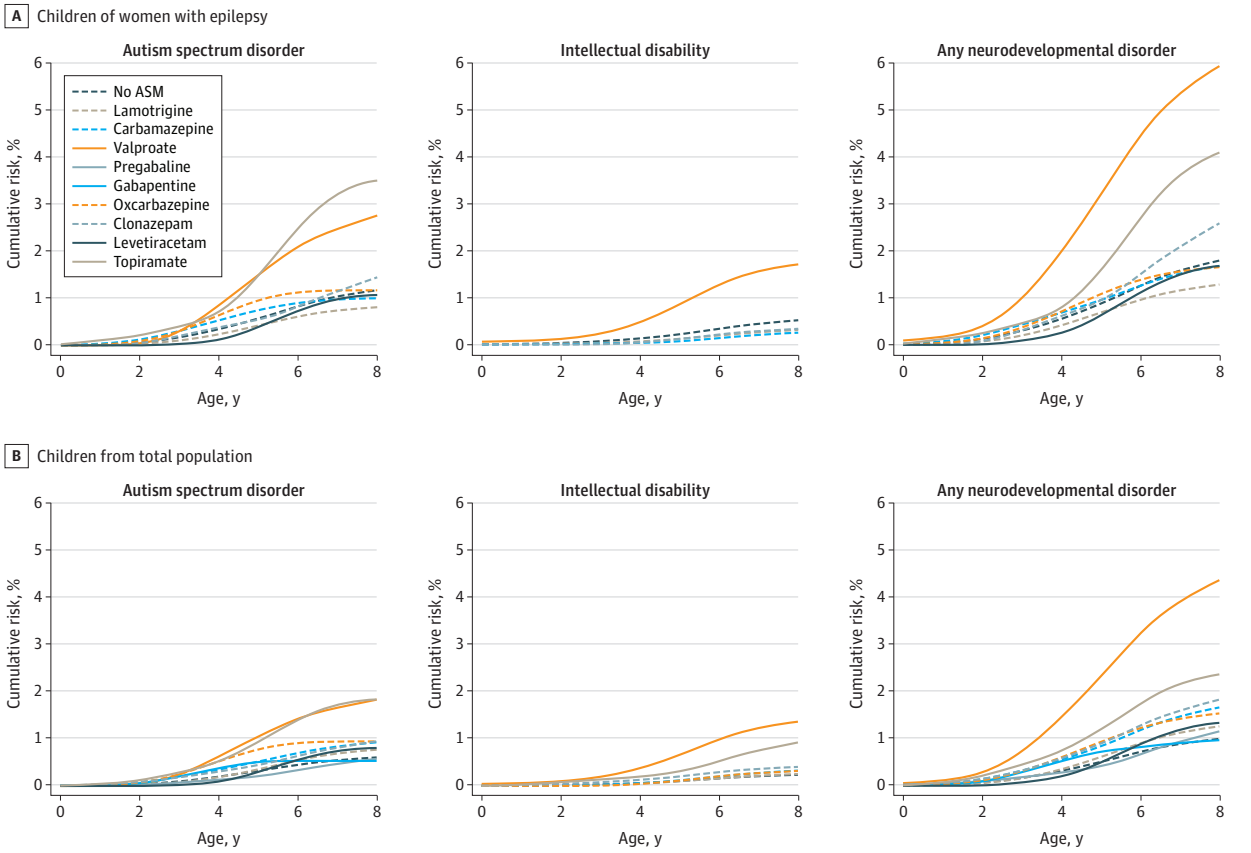
Figure 1. Cumulative Incidence of Neurodevelopmental Disorders After Prenatal Exposure to Antiseizure Medication (ASM)



A, Children of women with epilepsy. B, Children from total population. The graphs are shown for exposures with sufficient numbers for the estimation.

Our data show a 2.4- to 5-fold increased risk of ASD and ID in children with prenatal exposure to valproate. Furthermore, exposure to valproate in the second and third trimester only, without first-trimester exposure, was still associated with an increased risk of neurodevelopmental disorders. Epidemiological,[7-10] clinical,[2,11,14] and preclinical[37] studies support our results. Previous nationwide register studies have shown similar strength associations between valproate use during pregnancy and ASD and ID.[7-10] In clinical prospective cohort studies controlling for maternal IQ, children with prenatal exposure to valproate have IQ scores approximately 10 points lower than unexposed peers,[2,14,38] and present with more autistic traits.[11] In our study, the risk of neurodevelopmental disorders after exposure to valproate doses more than 750 mg per day was increased more than 5-fold. Strong associations between valproate doses more than 750 to 800 mg per day and a risk of congenital malformations[39] and cognitive performance[33] have been identified in clinical studies.

Children exposed to lamotrigine and levetiracetam, as either monotherapy or duotherapy, had similar risks for neurodevelopmental disorders as unexposed children when comparing risks among children of mothers with epilepsy. Published studies support our findings[15,40] but, despite its wide use in pregnancy, previous safety data on levetiracetam monotherapy and lamotrigine with levetiracetam duotherapy are sparse.

We found no associations between prenatal exposure to gabapentin and pregabalin and the risk of ASD or ID. These medications are mainly used for nonepilepsy indications. Their use is increasing in pregnant women,[1] but few reports are available on neurodevelopment after prenatal exposure.[40] Most,[15] but not all,[9] studies have found normal neurodevelopment after prenatal exposure.

Children exposed prenatally to clonazepam, carbamazepine, or oxcarbazepine had an increased risk of ASD and ID compared with unexposed children in the general population. However, these findings were likely biased by underlying maternal indication, as the associations with neurodevelopmental disorders disappeared when restricting the analyses to children of women with epilepsy.

With regulatory warnings cautioning against valproate use in women of childbearing potential, safety data are urgently needed for alternative treatment options. Similar to valproate, topiramate is indicated for focal and generalized seizures and migraine prevention.[41] Topiramate is also used off-label as a mood stabilizer[42] and for body weight reduction.[42] However, our results do not suggest that topiramate is a safe alternative to valproate. Women of reproductive age who are

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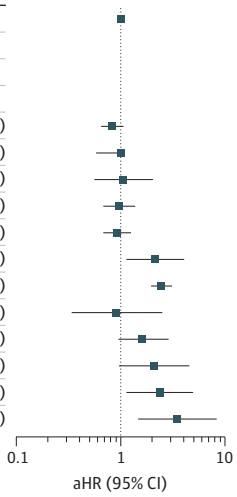
Figure 2. Association Between Prenatal Antiseizure Medication (ASM) Exposure and Child Neurodevelopmental Disorder (ND)

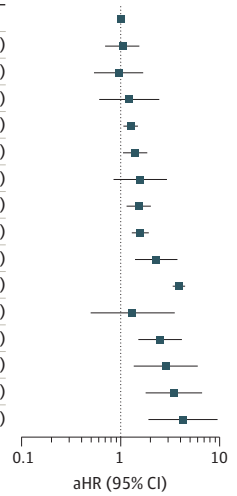
A Children of women with epilepsy

Exposure	8-y Incidence, %	No. with ND	aHR (95% CI)
Unexposed, n = 21 634	2.4	443	1 [Reference]
Pregabalin, n = 91	NA	<5	NA
Gabapentin, n = 110	NA	<5	NA
Phenobarbital, n = 45	NA	<5	NA
Lamotrigine, n = 5073	1.8	81	0.83 (0.65-1.06)
Clonazepam, n = 318	4.5	15	1.00 (0.58-1.04)
Levetiracetam, n = 1004	2.1	10	1.06 (0.56-2.02)
Oxcarbazepine, n = 1429	2.0	[a]	0.97 (0.68-1.37)
Carbamazepine, n = 2609	1.9	65	0.92 (0.68-1.25)
Topiramate, n = 246	5.1	10	2.13 (1.13-4.01)
Valproate, n = 1884	6.5	152	2.44 (1.94-3.07)
Lamotrigine + levetiracetam, n = [a]	1.6	[a]	0.91 (0.34-2.48)
Valproate + lamotrigine, n = 312	5.5	[a]	1.65 (0.95-2.85)
Lamotrigine + oxcarbazepine, n = [a]	4.3	[a]	2.07 (0.96-4.49)
Lamotrigine + topiramate, n = 123	7.5	[a]	2.35 (1.13-4.87)
Levetiracetam + carbamazepine, n = [a]	5.7	[a]	3.46 (1.46-8.18)



B Total cohort

Exposure	8-y Incidence, %	No. with ND	aHR (95% CI)
Unexposed, n = 4 463 879	1.3	68 295	1 [Reference]
Pregabalin, n = 1666	2.9	25	1.05 (0.71-1.55)
Gabapentin, n = 965	2.4	12	0.96 (0.54-1.69)
Phenobarbital, n = 175	2.6	8	1.23 (0.61-2.46)
Lamotrigine, n = 7950	2.4	133	1.27 (1.07-1.50)
Clonazepam, n = 1182	3.9	48	1.40 (1.06-1.86)
Levetiracetam, n = 1017	2.1	10	1.58 (0.85-2.94)
Oxcarbazepine, n = 1539	2.0	48	1.53 (1.15-2.02)
Carbamazepine, n = 3256	2.0	99	1.59 (1.30-1.93)
Topiramate, n = 471	4.0	16	2.29 (1.40-3.74)
Valproate, n = 2421	5.9	190	3.87 (3.36-4.47)
Lamotrigine + levetiracetam, n = 414	1.6	<5	1.32 (0.50-3.52)
Valproate + lamotrigine, n = 363	5.3	15	2.50 (1.51-4.15)
Lamotrigine + oxcarbazepine, n = 130	4.2	7	2.86 (1.36-6.01)
Lamotrigine + topiramate, n = 148	7.8	9	3.45 (1.79-6.63)
Levetiracetam + carbamazepine, n = 136	5.7	6	4.26 (1.91-9.50)



A, Children of women with epilepsy. B, Children from total population. ASM exposure was defined as filled prescriptions between last menstrual period and birth. Monotherapy was assumed if a prescription was filled for only 1 ASM during the exposure period. Duotherapy was assumed if prescriptions were filled for 2 types of ASMs within the same trimester. Owing to low numbers in subgroups, only results for the composite outcome any ND (a diagnosis of autism, intellectual disability, or global developmental delay) are shown. For numbers less than 5, the number cannot be given owing to personal data restrictions. Adjusted hazard ratios (aHRs) and 95% CIs are adjusted for birth year and sex of child, country of birth, maternal age, parity, education, marital status, use of antidepressants or opioids, depression, anxiety, personality disorders, number of chronic somatic diseases, and number of hospitalizations the year before last menstrual period. Missing data imputed with multiple imputation by chained equation. The median (IQR) follow-up time in years for each ASM was as follows: lamotrigine, 5.1 (2.4-8.5); carbamazepine, 10.5 (6.4-16.6); valproate, 9.9 (6.0-14.3); pregabalin, 5.2 (2.7-7.5); gabapentin, 3.5 (1.7-6.7); oxcarbazepine, 10.5 (5.5-15.5); clonazepam, 9.5 (5.5-13.9); levetiracetam, 3.6 (1.8-6.5); topiramate, 5.7 (2.9-9.1); and phenobarbital, 14.7 (8.3-18.8). For duotherapy: lamotrigine with levetiracetam, 4.0 (1.7-6.8); valproate with lamotrigine, 7.5 (3.7-11.2); lamotrigine with oxcarbazepine, 10.5 (6.5-14.5); lamotrigine with topiramate, 6.5 (3.5-9.7); and levetiracetam with carbamazepine, 5.6 (3.0-9.4). NA indicates not applicable; 8-y Incidence, 8-year cumulative incidence.

[a] Number cannot be given owing to personal data protection restrictions.

prescribed topiramate should be informed of the potential risks, and these should be weighed against the benefits and available treatment options.[43]

ASM duotherapy is common in women with epilepsy who are not free of seizures when taking monotherapy. In our data, children exposed to duotherapy with lamotrigine with val-

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proate, lamotrigine with topiramate, levetiracetam with carbamazepine, or lamotrigine with oxcarbazepine had an increased risk of neurodevelopmental disorders within the same range as children exposed to valproate. Thus, these duotherapies do not appear to be alternatives to valproate to reduce the risk of neurodevelopmental disorders in children. However, the combination of levetiracetam and lamotrigine was not associated with adverse neurodevelopment and should be investigated further for safety and efficacy during pregnancy.

Strengths and Limitations

To our knowledge, this is the largest study of neurodevelopmental outcomes following prenatal ASM exposure to date. High-quality, unselected nationwide data[17] from 5 countries provided a sample size large enough to investigate the associations of prenatal exposure to 15 monotherapies and duotherapies with rare and severe neurodevelopmental disorders. Neurodevelopmental disorders are associated with epilepsy.[44] We conducted analyses restricted to maternal epilepsy to account for shared factors between maternal epilepsy and offspring neurodevelopmental outcomes. We also accounted for a range of other potential confounders. Nonetheless, unmeasured confounding may still influence our effect estimates. Selecting live births may mask fetal deaths caused by toxic effects. We did not account for whether the mother had generalized or focal epilepsy. However, maternal epilepsy type has not been related to child neurodevelopmental outcomes in previous studies.[11,14] As we recorded lifetime diagnosis of epilepsy, some women in the untreated group probably had epilepsy in remission, but the psychosocial background factors were balanced between groups. We were unable to account for paternal and other family history of neurodevelopmental disorders. As in all studies relying on filled prescriptions, we cannot know if the women consumed the dispensed medication or used medication outside of the period of interest.[45] As the diagnoses were given as part of routine clinical care, the person evaluating the child could have been aware of the prenatal exposure possibly affecting the diagnostic process. Diagnostic data cannot inform on children with subdiagnostic level symptoms that may still have an effect on daily functioning. Thus, the risks identified by this study are likely an underrepresentation of the risks associated with these exposures.[15]

The median follow-up after childbirth varied from 4 to 6 years for gabapentin, pregabalin, levetiracetam, topiramate, and lamotrigine, and from 10 to 15 years for valproate, oxcarbazepine, carbamazepine, clonazepam, and phenobarbital. The mean age at diagnosis was between 6.1 to 7.9 years. As Cox regression compares incidence rates according to age, and estimates were adjusted for year of birth, this did not affect the effect sizes, but it may affect the sensitivity for detecting neurodevelopmental disorders.

Table 3. Risk of Any Neurodevelopment Disorder (ND)[a] After Prenatal Antiseizure Medication (ASM)[b] Exposure by Dose Compared With Unexposed Children

Mean daily dose[c]	Total, No.	With ND, No.	Adjusted hazard ratio (95% CI)[d]
No ASM	4 462 418	68 295	1 [Reference]
Lamotrigine, mg[b]			
<150	4933	108	1.46 (1.20-1.76)
≥150	4267	51	1.01 (0.76-1.32)
Carbamazepine, mg[b]			
<500	2012	71	1.74 (1.38-2.20)
≥500	1492	42	1.48 (1.09-2.00)
Valproate, mg[b]			
<750	1982	97	2.27 (1.86-2.77)
≥750	945	103	5.64 (4.65-6.84)
Oxcarbazepine, mg[b]			
<500	396	16	1.54 (0.95-2.52)
≥500	1169	36	1.64 (1.19-2.28)
Topiramate, mg[b]			
<100	717	16	1.71 (1.04-2.79)
≥100	129	6	2.93 (1.32-6.55)

[a] ND defined as any diagnosis of autism, intellectual disability, or global developmental delay. Owing to low numbers in outcome subgroups, only results for this composite outcome are shown. There were too few observations in each cell to include estimates for levetiracetam, gabapentin, pregabalin, clonazepam, and phenobarbital.

[b] ASM exposure defined as prescription fills of 1 ASM type (only) in the exposure period (extended to 90 days before last menstrual period). Exposed children were compared with children born to mothers from the general population not filling ASM prescriptions between 90 days before last menstrual period and birth,

[c] Dose is calculated by dividing the cumulative sum of all defined daily doses[22] prescribed between 90 days before last menstrual period to birth and then dividing by the number of days between in the same period. Cutoff is 50% defined daily doses apart from for topiramate where one-third of defined daily doses is used as cutoff as very few (n = 82) used doses less than 50% of defined daily doses.[7]

[d] Hazards ratios with 95% CI adjusted for birth year and sex of child, country of birth, maternal age, parity, education, marital status, use of antidepressants or opioids, depression, anxiety, personality disorders, number of chronic somatic diseases, and number of hospitalizations the year before last menstrual period. Missing data imputed with multiple imputation by chained equations. All the models were run with separate strata for country and year as these variables violated the proportional hazard assumption.

Conclusions

In conclusion, prenatal exposure to topiramate and valproate was associated with a risk of ASD and ID, which increased with higher doses. ASM duotherapies, except lamotrigine with levetiracetam, were similarly associated with neurodevelopmental disorders.

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Correction: This article was corrected on July 1, 2022, to fix a typographical error.

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Author Contributions: Drs Bjørk and Igland had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Bjørk, Zoega, Cohen, Dreier, Gilhus, Gissler, Igland, Tomson, Christensen.
Acquisition, analysis, or interpretation of data: All authors.
Drafting of the manuscript: Bjørk, Zoega, Christensen.
Critical revision of the manuscript for important intellectual content: All authors.
Statistical analysis: Igland, Christensen.
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Supervision: Bjørk, Zoega, Dreier, Gilhus, Tomson, Christensen.

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