



Prenatal exposure to Antiseizure Medications for all indications and the risk of neurodevelopmental disorders in offspring: a nationwide population-based cohort study in South Korea

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ABSTRACT

Purpose: Antiseizure medications (ASMs) are used during pregnancy for both epilepsy and non-epilepsy indications, yet the neurodevelopmental safety of prenatal ASM exposure remains uncertain, particularly in Asian populations. We evaluated the risk of neurodevelopmental disorders (NDDs) following in utero ASM exposure using a nationwide Korean database.

Methods: This population-based cohort study (2009–2021) used the Korea National Health Insurance Database to identify 3663,052 mother–infant pairs. ASM exposure was defined as ≥ 1 prescription between the last menstrual period and delivery. Using 1:5 propensity score matching to balance baseline covariates, we estimated adjusted hazard ratios (aHRs) for autism spectrum disorder (ASD) and intellectual disability (ID).

Results: After matching, 9587 ASM-exposed and 47,935 unexposed mother–infant pairs were included; among ASM users, 48.2% had epilepsy. Prenatal ASM exposure was associated with significantly increased risks of ASD (aHR 1.57; 95% CI 1.15–2.15) and ID (aHR 2.40; 95% CI 1.80–3.19). A dose–response pattern was observed, with higher risks for duotherapy (ID: aHR 3.23; 95% CI 1.79–5.83) than for monotherapy (ID: aHR 1.74; 95% CI 1.24–2.45). Prolonged exposure and later pregnancy recognition were associated with the highest risks. Among single-trimester exposures, first-trimester-only exposure showed the strongest association with composite outcomes.

Conclusion: In this nationwide Korean cohort, prenatal ASM exposure was associated with dose-dependent risks of ASD and ID. These findings underscore the importance of preconception counseling and early pregnancy management for all women receiving ASMs, beyond those with epilepsy.

1. Introduction

Antiseizure medications (ASMs) were originally developed for the management of epilepsy, which affects approximately 50 million individuals worldwide [1], and effectively control seizures in

approximately two-thirds of patients with epilepsy [2]. However, the clinical use of ASMs has expanded considerably to encompass several non-epilepsy conditions, including neuropathic pain, psychiatric disorders such as bipolar disorder, and migraine prophylaxis [3–5]. In Europe, ASM prescribing has shifted from older to newer agents, with

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lamotrigine and levetiracetam frequently prescribed in women of childbearing potential, while valproate use has declined following regulatory restrictions due to its teratogenic and neurodevelopmental risks [6]. ASM prescribing in South Korea shares broad similarities with European trends, although valproate continues to be prescribed in approximately 30% of women of childbearing age with epilepsy [1,7].

A growing body of evidence suggests that prenatal exposure to specific ASMs may increase the risk of neurodevelopmental disorders (NDDs) in offspring [8,9]. NDDs, including autism spectrum disorder (ASD) and intellectual disability (ID), are characterized by neurodevelopmental impairments that can lead to lifelong cognitive and behavioral deficits [10]. Previous research using Nordic registry data indicated that monotherapy with valproate or topiramate during pregnancy was associated with a two- to four-fold increased risk of ASD and ID [8]. In contrast, a recent large-scale US cohort study found no significant association between topiramate monotherapy and ASD [11], highlighting ongoing uncertainty regarding the long-term safety of specific ASM regimens.

The association between in utero ASM exposure and NDD risk thus remains inconclusive. In addition, because ASM exposure in real-world populations does not reflect maternal epilepsy alone, the relevant target population for safety assessment extends well beyond women with epilepsy. Existing evidence, however, is predominantly derived from Western registries, with a notable scarcity of large-scale studies in Asian populations, where distinct genetic backgrounds, environmental factors, and healthcare systems may alter risk profiles. To address this knowledge gap, we conducted a nationwide, population-based cohort study using the Korea National Health Insurance Service mother–child linkage database. Findings from this study may inform evidence-based guidance for optimized ASM prescribing and safer pregnancy management for

women in Asia.

2. Methods

2.1. . Study data

We used the National Health Insurance Database provided by the Korea National Health Insurance Service (NHIS). This database includes pseudonymized data on eligibility, healthcare utilization, prescription drugs, and health check-ups for all individuals covered by the NHIS [12]. To identify pregnant individuals, we linked the Pregnancy and Childbirth Medical Expenses dataset, which contains specific information related to pregnancy including the date of pregnancy confirmation by a healthcare professional [13]. Additionally, to identify their offspring, we used the NHIS Family Tree database [14]. This study was approved by the Institutional Review Board of the National Institute of Food and Drug Safety Evaluation (approval no. 3078, Office of Cardiovascular and Neurological Products; approved on 14 November 2022).

2.2. . Study population

The selection process for the study population is illustrated in Fig. 1. We included all women who had a live birth between January 2009 and April 2022, had available information on the last menstrual period (LMP) and the date of delivery ($N = 3829,177$). We excluded women who delivered before age 19 or after age 46, those with gestational ages outside the normal range (<154 days or >314 days), mothers of multiples, and women who had prescribed ASM within 90 days before the LMP but no ASM prescription during pregnancy to minimize the potential for carry-over effects. In addition, we excluded children

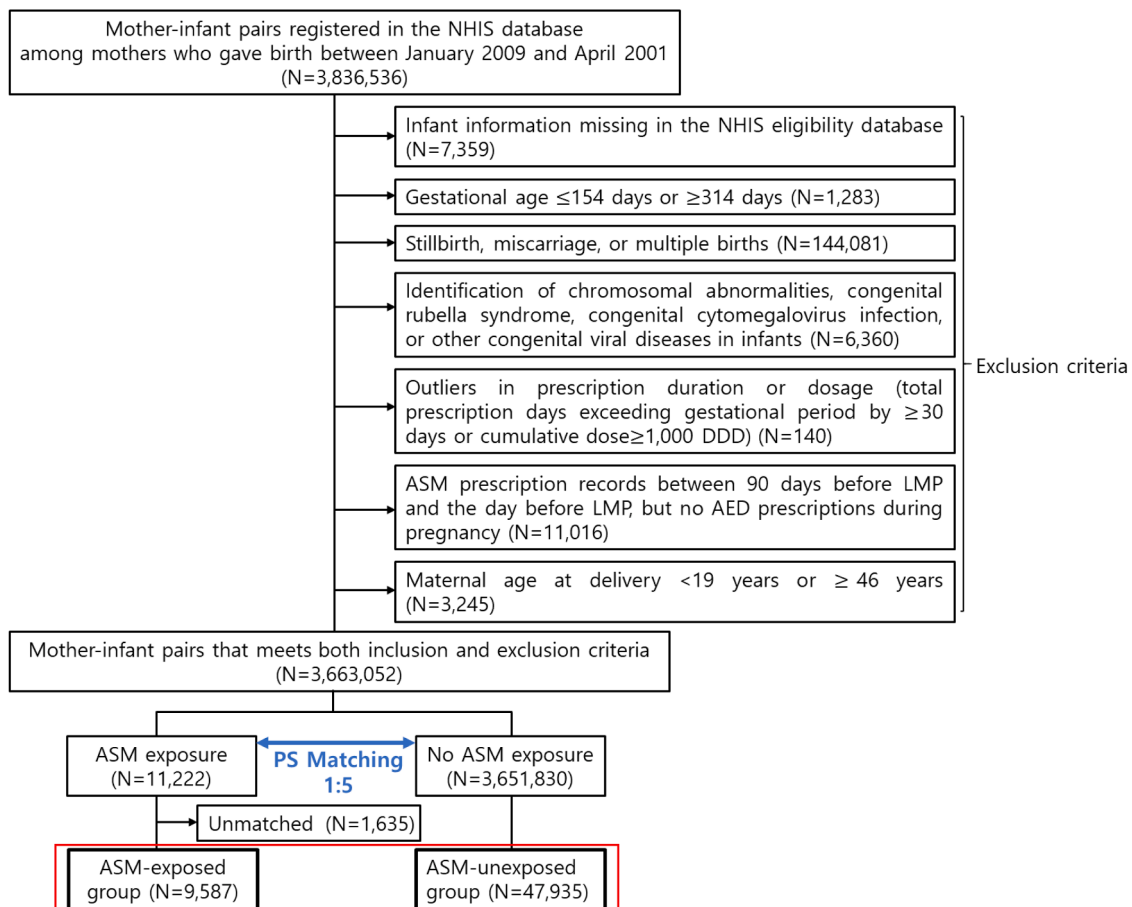


Fig. 1. Flowchart of study population selection.

diagnosed with chromosomal disorders before the end of follow-up.

2.3. . Exposure

ASMs identified in this study were: acetazolamide, carbamazepine, clobazam, clonazepam, divalproex sodium, ethosuximide, fosphenytoin sodium, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, primidone, rufinamide, topiramate, valproic acid, vigabatrin, and zonisamide. Women who were prescribed at least one dose of any ASMs between the LMP and the birth date were classified as ASM users, while those who were not prescribed any ASMs during pregnancy were classified as non-users. Monotherapy was defined as the use of a single ASM type during pregnancy without the addition of other ASMs. Duotherapy was defined as the concurrent prescription of two different ASMs within the same trimester. To account for varying potencies, the mean daily dose was calculated using the WHO-defined daily dose (DDD) [15]. The cumulative dose was calculated as follows for all prescriptions during the gestational period:

$$\text{Cumulative dose} = \sum_{i=\text{prescription}} \left(\sum_{j=\text{ingredient}} \frac{\text{Dose}_{ij} \times \text{Number of prescription days}_{ij}}{\text{Defined Daily Dose (DDD)}_j} \right)$$

2.4. . Outcome

Neurodevelopmental outcomes were identified as at least one diagnosis of one of the following codes: [1] ASD, including autism (F84.0), atypical autism (F84.1), and Asperger syndrome (F84.5); and [2] ID, including mild (F70), moderate (F71), severe (F72), and profound ID (F73). We also considered two composite neurodevelopmental outcomes: Composite Outcome 1 included any of the above diagnoses, as well as unspecified ID (F79), other childhood disintegrative disorder (F84.3), disorder of mental retardation with stereotyped movements (F84.4), other pervasive developmental disorders (F84.8), unspecified pervasive developmental disorder (F84.9), and other psychological developmental disorders (F88). Composite Outcome 2 comprised specific developmental disorders of speech and language (F80), specific developmental disorders of scholastic skills (F81), specific developmental disorder of motor function (F82), unspecified in addition to all diagnoses in Composite Outcome 1. All infants were followed from birth to the earliest date of the first NDD diagnosis, death, or the end of study period (April 2023).

2.5. . Statistical analysis

Descriptive statistics were used to summarize the baseline characteristics of the study population. Categorical variables are present as numbers and percentages, while continuous variables are expressed as means (standard deviations, SD). We calculated crude incidence rates by dividing the total number of cases by the total person-time in each exposure group. Missing data was regarded as missing.

To address potential selection bias and confounding by indication, we performed 1:5 propensity score matching (PSM) to balance the ASM-exposed and unexposed cohorts. Covariates included delivery-related characteristics (delivery year, mode of delivery, prior delivery history, history of pregnancy-related complications), maternal characteristics (age, income level, lifestyle factors, medical history, including autism spectrum disorder and intellectual disability diagnosed before delivery, and medication exposure from 90 days before the last menstrual period to delivery, including opioids, antipsychotics, anxiolytics, sedative-hypnotics, and antidepressants), and child-related characteristics (sex, medical history, health status at birth) [8,16]. Covariates that remained imbalanced after PSM were additionally adjusted for in the Cox proportional hazards model.

We employed Cox proportional hazards models to estimate adjusted

hazard ratios (aHRs) and 95% confidence intervals (CIs). To account for the typical age of NDD diagnosis, sensitivity analyses were conducted by limiting the cohort to children diagnosed at ≥ 36 months (for ASD, ID, and Composite 1) and ≥ 72 months (for Composite 2). Additional subgroup analyses were conducted based on ASM dosage and duration by categorizing the level of exposure as low ($<$ median) or high ($\geq$ median), timing (trimester) at pregnancy confirmation, and by history of maternal epilepsy.

3. Results

From 2009 to 2021, 3836,536 mother-infant pairs were screened, with 3663,052 meeting eligibility criteria. Following propensity score matching, the final cohort comprised 57,522 pairs (9587 ASM-exposed; 47,935 unexposed) (Fig. 1, Table A.1). The mean maternal age was 32.5 years (Table 1). Epilepsy was documented in 10% of the total matched cohort, though the prevalence was markedly higher among ASM users (48.2%) compared to non-users (2.3%). The indication profile varied substantially across individual ASMs, with gabapentin, pregabalin, and clonazepam predominantly prescribed in women without maternal epilepsy, whereas levetiracetam, lamotrigine, and oxcarbazepine were predominantly prescribed in women with maternal epilepsy (Table A.2). While several comorbidities—including depression, diabetes, and hypertension—were more prevalent in the exposed group initially ($p < 0.001$), propensity score matching achieved a robust balance across all baseline covariates (Table 1).

The most frequently prescribed ASMs were gabapentin (18.62%), clonazepam (17.89%), and lamotrigine (16.54%) (Table A.2). Monotherapy was the predominant treatment strategy (83.52%) (Table 2). Over half of the users (51.49%) were exposed only during the first trimester, reflecting a high rate of early-pregnancy exposure (Table A.3).

Prenatal ASM exposure was associated with a significantly increased risk of ASD (aHR 1.57; 95% CI 1.15–2.15) and ID (aHR 2.40; 95% CI 1.80–3.19) (Table 3). These associations remained consistent in sensitivity analyses restricted by age at diagnosis (36 or 72 months) (Table A.4). A clear dose–response relationship was observed, with risks increasing in correlation with higher daily doses and longer exposure durations (Tables A.5, A.6).

While the association between monotherapy and ASD did not reach statistical significance (aHR 1.34; 95% CI 0.93–1.91), it significantly increased the risk of ID (aHR 1.74; 95% CI 1.24–2.45). Notably, duotherapy carried a markedly higher risk, particularly for ID (aHR 3.23; 95% CI 1.79–5.83) (Table 3).

The timing of pregnancy confirmation significantly influenced NDD risk; women who confirmed pregnancy after the first trimester exhibited higher risks of adverse outcomes compared to those with early confirmation (Table 4). Furthermore, among single-trimester exposures, first-trimester-only exposure showed the strongest association with Composite Outcome 2 (Table A.7). After stratification by maternal history of epilepsy, incidence rates of composite neurodevelopmental outcomes were highest in ASM-exposed mothers with epilepsy, followed by ASM-unexposed mothers with epilepsy, ASM-exposed mothers without epilepsy, and ASM-unexposed mothers without epilepsy (Table A.8).

4. Discussion

This nationwide retrospective cohort study provides robust evidence regarding the neurodevelopmental safety of ASM exposure in a cohort of 57,522 mother-child pairs in Korea. Our findings demonstrate that children exposed to ASMs in utero have a significantly higher risk of being diagnosed with a neurodevelopmental outcome, with adjusted hazard ratios of 1.57 for ASD, and 2.40 for ID compared to the general population, in a cohort that included both epilepsy and non-epilepsy mothers. These results are particularly salient when considering the dose-response relationships and the heightened risk associated with

Table 1

Baseline characteristics of participants following propensity score matching according to anti-seizure medication use.

Characteristics	Total		Non-users		Users		P
	N	%	N	%	N	%	
Total	57,522	100	47,935	83.33	9587	16.67	
Year of Delivery							
2009	4138	7.19	3459	7.22	679	7.08	0.989
2010	4407	7.66	3669	7.65	738	7.7	
2011	4327	7.52	3604	7.52	723	7.54	
2012	4339	7.54	3631	7.57	708	7.39	
2013	4677	8.13	3911	8.16	766	7.99	
2014	4565	7.94	3789	7.9	776	8.09	
2015	4461	7.76	3707	7.73	754	7.86	
2016	4541	7.89	3793	7.91	748	7.8	
2017	4834	8.40	4028	8.4	806	8.41	
2018	5147	8.95	4306	8.98	841	8.77	
2019	4879	8.48	4063	8.48	816	8.51	
2020	5028	8.74	4181	8.72	847	8.83	
2021	2179	3.79	1794	3.74	385	4.02	
Mode of Delivery							
Cesarean section	25,718	44.71	20,823	43.44	4895	51.06	<0.001
Induced labor	13,703	23.82	11,634	24.27	2069	21.58	
Spontaneous vaginal delivery	18,101	31.47	15,478	32.29	2623	27.36	
Parity							
Primipara	31,471	54.71	26,258	54.78	5213	54.38	0.47
Multipara	26,051	45.29	21,677	45.22	4374	45.62	
Pregnancy-related Complications							
Malnutrition	21	0.04	17	0.04	4	0.04	0.77
Small for Gestational Age	73	0.13	51	0.11	22	0.23	0.002
Fetal distress	270	0.47	212	0.44	58	0.6	0.033
Placental abruption	227	0.39	186	0.39	41	0.43	0.572
Premature Rupture of Membranes	11,879	20.65	10,067	21	1812	18.9	<0.001
Polyhydramnios / Oligohydramnios	3689	6.41	3061	6.39	628	6.55	0.547
Infection during pregnancy	590	1.03	484	1.01	106	1.11	0.395
Gestational hypertension	1091	1.90	905	1.89	186	1.94	0.732
Gestational diabetes	20,531	35.69	17,055	35.58	3476	36.26	0.205
Preeclampsia / Eclampsia	806	1.40	621	1.3	185	1.93	<0.001
<i>Maternal Characteristics</i>							
Age, mean (SD)	32.50 (4.21)		32.50 (4.20)		32.53 (4.25)		0.487
Insurance Type							
Medical Aid	325	0.57	5374	11.21	1114	11.62	0.676
Self-employed, Income Quintile 1–2	6488	11.28	5191	10.83	1036	10.81	
Self-employed, Income Quintile 3–5	6227	10.83	14,663	30.59	2894	30.19	
Employee-insured, Income Quintile 1–2	17,557	30.52	16,016	33.41	3175	33.12	
Employee-insured, Income Quintile 3–5	19,191	33.36	6427	13.41	1307	13.63	
Missing	7734	13.45	264	0.55	61	0.64	
Disability Status, Yes	252	0.44	201	0.42	51	0.53	0.127
Smoking	907	1.58	733	1.53	174	1.81	0.05
Alcohol consumption	4774	8.30	3918	8.17	856	8.93	0.01
Total comorbidities, mean (SD)	0.63 (1.51)		0.60 (1.46)		0.74 (1.78)		<0.001
Asthma	6622	11.51	5434	11.34	1188	12.39	0.003
Hypertension	1493	2.60	1123	2.34	370	3.86	<0.001
Renal disease	42	0.07	32	0.07	10	0.1	0.214
Rheumatoid arthritis	715	1.24	538	1.12	177	1.85	<0.001
Thyroid disease	13,467	23.41	11,208	23.38	2259	23.56	0.701
Heart disease	1745	3.03	1360	2.84	385	4.02	<0.001
Diabetes	2646	4.60	2026	4.23	620	6.47	<0.001
Depression	6741	11.72	5009	10.45	1732	18.07	<0.001
Anxiety disorder	14,962	26.01	12,480	26.04	2482	25.89	0.766
Personality disorder	132	0.23	85	0.18	47	0.49	<0.001
Autism Spectrum Disorder	15	0.03	6	0.01	9	0.09	<0.001
Intellectual disability	159	0.28	122	0.25	37	0.39	0.025
Obesity	146	0.25	120	0.25	26	0.27	0.711
Mental/Behavioral disorders due to substance use	13	0.02	7	0.01	6	0.06	<0.004
Poisoning by drugs or biological substances	40	0.07	26	0.05	14	0.15	0.002
Total pre-pregnancy hospitalizations, mean (SD)	0.51 (0.91)		0.50 (0.88)		0.56 (1.03)		<0.001
Medications							
Opioids	8305	14.44	7177	14.97	1128	11.77	<0.001
Antipsychotics	1043	1.81	439	0.92	604	6.3	<0.001
Anxiolytics	8415	14.63	6835	14.26	1580	16.48	<0.001
Hypnotics and Sedatives	2491	4.33	1942	4.05	549	5.73	<0.001
Antidepressants	3430	5.96	2133	4.45	1297	13.53	<0.001
<i>Neonatal Characteristics</i>							
Sex							
Male	29,536	51.35	24,548	51.21	4988	52.03	0.144
Female	27,986	48.65	23,387	48.79	4599	47.97	
Epilepsy	2003	3.48	1515	3.16	488	5.09	<0.001
Preterm/Low Birth Weight	2439	4.24	1973	4.12	466	4.86	0.001

Table 2

Specific anti-seizure medications prescribed during pregnancy.

Category	N	%
Total	9587	100
Monotherapy	8007	83.52
Gabapentin	1693	17.66
Clonazepam	1486	15.50
Lamotrigine	986	10.28
Carbamazepine	871	9.09
Levetiracetam	681	7.10
Pregabalin	576	6.01
Topiramate	538	5.61
Oxcarbazepine	332	3.46
Valproic acid	260	2.71
Phenobarbital	179	1.87
Clobazam	173	1.80
Divalproex sodium	82	0.86
Acetazolamide	68	0.71
Zonisamide	50	0.52
Phenytoin	30	0.31
Duotherapy*	868	9.05
Lamotrigine + Oxcarbazepine	112	1.17
Levetiracetam + Oxcarbazepine	80	0.83
Lamotrigine + Topiramate	62	0.65
Levetiracetam + Carbamazepine	61	0.64
Levetiracetam + Topiramate	59	0.62
Carbamazepine + Topiramate	51	0.53
Lamotrigine + Carbamazepine	35	0.37
Others	712	7.42
Two ingredients in different trimesters	301	3.14
Three or more ingredients	411	4.28

Cells with $N < 30$ are not displayed. * Used 2 ingredients in the same trimester.

polytherapy. Notably, our data revealed that the timing of pregnancy awareness is a critical determinant of NDD risk.

These findings contribute to the ongoing global debate regarding ASM safety. The overall magnitude of increased risk observed in our study is consistent with the Nordic registry study by Bjørk et al., which reported up to 1.6- and 2.5-fold increases in the risk of ASD and ID, respectively [8]. A subtle distinction lies in the prescribing patterns unique to Korea, with a high prevalence of gabapentin and clonazepam use, agents frequently prescribed not only for epilepsy but for neuropathic pain and anxiety disorders [17]. The findings suggest that the neurodevelopmental risks identified here may extend beyond classical

teratogenic ASMs to medications commonly used in broader psychiatric and primary care settings, necessitating a shift in how we counsel patients of childbearing potential, regardless of their primary diagnosis.

To further examine whether the observed associations could be attributed to maternal epilepsy itself rather than to ASM exposure, we performed an additional subgroup analysis stratified by maternal history of epilepsy before pregnancy. Incidence rates of neurodevelopmental outcomes were the highest among ASM-exposed mothers with epilepsy, followed by ASM-unexposed mothers with epilepsy, ASM-exposed mothers without epilepsy, and lowest in ASM-unexposed mothers without epilepsy. These descriptive comparisons should be interpreted with caution as they were not formally evaluated through inferential statistics. This observed trend suggests that both ASM exposure and maternal epilepsy may each contribute to offspring neurodevelopmental risk, consistent with previous findings by Bjørk et al. and Hernandez-Diaz et al [8,11].

Our analysis revealed a clear dose-response relationship, where high-dose exposure ($\geq$ median DDD) significantly increased the hazard for ID (aHR 2.14), thereby strengthening the biological plausibility of the association between NDD and ASM exposure. Previous studies have suggested that ASMs may interfere with critical neuro-migratory processes or neurotransmitter signaling in the fetus in a concentration-dependent manner [18,19]. Furthermore, the synergistic escalation of risk observed with duotherapy (ID aHR 3.23) underscores the clinical imperative to simplify regimens to monotherapy—ideally with safer alternatives like lamotrigine or levetiracetam—well before conception [9,20].

Another notable finding was that children born to mothers who confirmed pregnancy during the second trimester faced a 3.11-fold higher risk for ASD. This significantly higher risk compared to the first-trimester confirmation group (aHR 1.53) likely reflects a missed window for medication adjustment or folate supplementation during the most vulnerable period of organogenesis [20]. Our single-trimester analysis further confirmed that the first trimester carried the highest risk for composite neurodevelopmental outcomes. These findings underscore the importance of proactive preconception care and early pregnancy detection to minimize unintended exposure during pregnancy. Optimizing ASM regimens by switching to safer alternatives and initiating folic acid supplementation before conception may improve both short- and long-term pregnancy outcomes [21].

The primary strength of this study is the use of the Pregnancy and Childbirth Medical Expenses dataset to precisely identify the pregnancy

Table 3

Association between anti-seizure medication use and risk of neurodevelopmental disorders.

Category	Cases		Incidence Rate (per 10,000 P-Y)			HR (95% CI)		aHR (95% CI)	
	n	%	P-Y	IR	95% CI	HR	95% CI	HR	95% CI
Autism Spectrum Disorder									
Non-users ($N = 47,935$)	159	0.33	331,539	4.80	3.99–5.60	1	-	1	-
Users ($N = 9587$)	60	0.63	65,949.7	9.10	6.94–11.71	1.90*	1.41–2.55	1.57*	1.15–2.15
Monotherapy ($N = 8007$)	51	0.54	54,553.6	7.70	5.55–10.41	1.61*	1.15–2.26	1.34	0.93–1.91
Duotherapy ($N = 868$)	5	0.67	6522.7	12.26	5.30–24.17	2.55	1.26–5.20	2.05	0.99–4.23
Intellectual Disability									
Non-users ($N = 47,935$)	150	0.31	331,537	4.52	3.74–5.31	1	-	1	-
Users ($N = 9587$)	92	0.96	65,821.42	13.98	11.27–17.14	3.10*	2.38–4.02	2.40*	1.80–3.19
Monotherapy ($N = 8007$)	73	0.77	54,508.5	10.27	7.76–13.34	2.28*	1.68–3.11	1.74*	1.24–2.45
Duotherapy ($N = 868$)	12	1.60	6489.9	26.19	15.26–41.94	5.57	3.38–9.20	3.23*	1.79–5.83
Composite Outcome 1									
Non-users ($N = 47,935$)	439	0.92	331,350	13.25	12.04–14.55	1	-	1	-
Users ($N = 9587$)	212	2.21	65,739.6	32.25	28.05–36.89	2.81*	2.23–3.54	2.16*	1.68–2.77
Monotherapy ($N = 8007$)	183	1.94	54,446.3	27.37	23.15–32.13	2.18*	1.67–2.86	1.67*	1.25–2.24
Duotherapy ($N = 868$)	25	3.34	6483.6	50.90	35.04–71.48	4.32	2.67–6.99	2.54*	1.45–4.44
Composite Outcome 2									
Non-users ($N = 47,935$)	1645	3.43	325,711	50.50	48.00–53.01	1	-	1	-
Users ($N = 9587$)	691	7.21	63,480.1	108.85	100.89–117.28	2.17*	1.97–2.38	1.90*	1.72–2.10
Monotherapy ($N = 8007$)	651	6.91	52,739.0	98.98	90.67–107.84	1.97*	1.78–2.19	1.72*	1.55–1.92
Duotherapy ($N = 868$)	69	9.22	6175.2	137.65	109.95–170.2	2.70	2.17–3.36	2.27*	1.78–2.88

* $p < 0.05$.

Table 4

Association between anti-seizure medication use and risk of neurodevelopmental disorders by the timing of pregnancy confirmation.

Category	Cases		Incidence Rate (per 10,000 P-Y)			Unadjusted HR (95% CI)		Adjusted HR (95% CI)	
	n	%	P-Y	IR	95% CI	HR	95% CI	HR	95% CI
Autism Spectrum Disorder									
<i>1st-trimester</i>									
Non-users (N = 44,594)	141	0.32	29,662.3	4.75	3.90–5.61	1	-	1	-
Users (N = 8784)	51	1.61	57,913.6	8.81	6.56–11.58	1.85*	1.35–2.55	1.53*	1.09–2.16
<i>2nd-trimester</i>									
Non-users (N = 2431)	11	0.45	24,982.7	4.40	0.93–7.88	1	-	1	-
Users (N = 605)	8	1.32	5927.4	13.50	5.88–26.59	3.04*	1.22–7.55	3.11*	1.23–7.88
<i>3rd-trimester</i>									
Non-users (N = 910)	7	0.77	9935.2	7.05	0–14.52	1	-	1	-
Users (N = 198)	1	0.51	2108.6	4.74	0.12–26.42	1.62	0.96–2.72	0.46	0.04–5.62
Intellectual Disability									
<i>1st-trimester</i>									
Non-users (N = 44,594)	134	0.3	29,659.7	4.52	3.69–5.35	1	-	1	-
Users (N = 8784)	76	1.53	57,810.5	13.15	10.36–16.45	2.92*	2.20–3.87	2.26*	1.65–3.10
<i>2nd-trimester</i>									
Non-users (N = 2431)	11	0.45	24,995.3	4.40	0.93–7.87	1	-	1	-
Users (N = 605)	12	1.98	5918.7	20.27	10.48–35.42	4.65*	2.05–10.54	3.61*	1.40–9.37
<i>3rd-trimester</i>									
Non-users (N = 910)	5	0.55	9949.7	5.03	0–11.73	1	-	1	-
Users (N = 198)	4	2.02	2092.1	19.12	5.21–48.95	3.82*	1.03–14.25	2.20	0.28–17.5
Composite Outcome 1									
<i>1st-trimester</i>									
Non-users (N = 44,594)	388	0.87	296,500	13.09	11.72–14.46	1	-	1	-
Users (N = 8784)	183	4.42	57,740.91	31.69	27.27–36.63	2.86*	2.23–3.68	2.19*	1.66–2.88
<i>2nd-trimester</i>									
Non-users (N = 2431)	32	1.32	24,931.0	12.84	7.55–18.12	1	-	1	-
Users (N = 605)	21	3.47	5910.7	35.53	21.99–54.31	2.62*	1.31–5.23	2.37*	1.16–4.85
<i>3rd-trimester</i>									
Non-users (N = 910)	19	2.09	9919.0	19.16	8.40–29.91	1	-	1	-
Users (N = 198)	8	4.04	2087.9	38.31	16.54–75.49	2.15	0.75–6.20	1.02	0.22–4.65
Composite Outcome 2									
<i>1st-trimester</i>									
Non-users (N = 44,594)	1460	3.27	291,685.1	50.05	47.42–52.69	1	-	1	-
Users (N = 8784)	593	16.62	55,890.8	106.10	97.73–114.99	2.13*	1.94–2.34	1.87*	1.68–2.08
<i>2nd-trimester</i>									
Non-users (N = 2431)	128	5.27	24,372.9	52.52	42.59–62.44	1	-	1	-
Users (N = 605)	79	13.06	5596.4	141.16	111.76–175.93	2.71*	2.05–3.59	2.50*	1.85–3.37
<i>3rd-trimester</i>									
Non-users (N = 910)	57	6.26	9652.9	59.05	41.59–76.51	1	-	1	-
Users (N = 198)	19	9.6	1992.8	95.34	57.40–148.89	1.62	0.96–2.72	1.23	0.67–2.24

* $p < 0.05$.

confirmation date. Also, we used the NHIS-Family Tree database, which allowed for a nearly exhaustive inclusion of mother-child pairs in South Korea over a 12-year period [13]. Furthermore, this research addresses a major knowledge gap by providing large-scale evidence in an Asian population, where ethnic-specific pharmacokinetic profiles—such as the lower clearance of lamotrigine in Asians—make Western data potentially less applicable [22].

Several limitations warrant consideration when interpreting these results. First, because our cohort included all ASM users—including those prescribed these medications for non-neurological indications such as psychiatric disorders—residual confounding by indication may persist. While we employed propensity score matching to balance maternal comorbidities, the severity of the underlying maternal condition remains difficult to fully quantify in claims data. Furthermore, residual confounding by the underlying maternal condition and unmeasured shared genetic factors between mothers and offspring cannot be entirely excluded. Second, the substantially lower rate of ASD diagnosis observed in our Korean cohort (0.63%) compared to Nordic populations (1.61%) suggests that cultural stigma may have led to under-reporting or delayed diagnoses [23,24]. Nevertheless, our longitudinal follow-up period provides a substantial window for capturing the majority of primary neurodevelopmental diagnoses. Third, as a claims-based study, we could not verify actual medication adherence. In addition, detailed clinical data relevant to treatment management during pregnancy—including the reasons for treatment cessation and

information on drug level monitoring for specific ASMs—were not available. This limitation may have affected our ability to capture individual variations in seizure control during pregnancy. Finally, due to sample size constraints for certain specific agents, individual ASM-level analyses and sibling-matched analyses were not performed; sibling-matched designs would have further addressed unmeasured confounding by shared family-level factors. Also, in mothers with epilepsy only, the lack of statistically significant associations likely reflects limited statistical power, given the small number of unexposed women in this subgroup.

5. Conclusions

In this nationwide Korean cohort, prenatal ASM exposure was associated with an increased risk of ASD and ID in offspring. The heightened risk associated with delayed pregnancy confirmation emphasizes a critical need for proactive preconception counseling. Because ASM use during pregnancy extends beyond women with epilepsy, indication-aware preconception planning is essential for all women of childbearing potential receiving ASMs, with ASM regimens optimized to the lowest effective dose before the critical first trimester. These findings should not discourage necessary treatment for epilepsy or other indications, but rather facilitate shared decision-making to improve long-term outcomes for both mother and child.

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Conflict of interest

None.

Data availability

The linked datasets analyzed in this study are not publicly available due to local regulations but can be accessed upon reasonable request to the corresponding author.

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Declarations of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at [doi:10.1016/j.seizure.2026.05.030](https://doi.org/10.1016/j.seizure.2026.05.030).

References

- [1] Kang KW, Lee H, Shin JY, Moon HJ, Lee SY. Trends in prescribing of antiseizure medications in South Korea: real-world evidence for treated patients with epilepsy. *J Clin Neurol* 2022;18(2):179. <https://doi.org/10.3988/jcn.2022.18.2.179>.
- [2] Kwan P, Brodie MJ. Early identification of refractory epilepsy. *N Engl J Med* 2000;342(5):314–9. <https://doi.org/10.1056/NEJM200002033420503>.
- [3] Jeong JH, Bahk WM, Woo YS, Yoon BH, Lee JG, Kim W, et al. Korean medication algorithm project for Bipolar disorder 2022: comparisons with other treatment guidelines. *Clin Psychopharmacol Neurosci* 2023;21(1):32–48. <https://doi.org/10.9758/cpn.2023.21.1.32>.
- [4] Ornello R, Caponnetto V, Ahmed F, Al-Khazali HM, Ambrosini A, Ashina S, et al. Evidence-based guidelines for the pharmacological treatment of migraine, summary version. *Cephalalgia* 2025;45(4):3331024251321500. <https://doi.org/10.1177/03331024251321500>.
- [5] Sohn E. Treatment of neuropathic pain. *J Korean Med Assoc/Taehan Uisa Hyophoe Chi* 2021;64(7).
- [6] Chan AY, Yuen ASC, Hsia Y, Lau WCY, Cross JH, Walker MC, et al. Antiseizure medications consumption in 73 countries and regions from 2012 to 2022: a longitudinal trend study. *EClinicalMedicine* 2025;89:103558. <https://doi.org/10.1016/j.eclinm.2025.103558>.
- [7] Han SH, Lee H, Shin JY, Moon HJ, Lee SY. Real-world prescribing trends of valproate in women with epilepsy in Korea. *Epilepsy Behav* 2021;115:107700. <https://doi.org/10.1016/j.yebeh.2020.107700>.
- [8] Bjork MH, Zoega H, Leinonen MK, Cohen JM, Dreier JW, Furu K, et al. Association of prenatal exposure to antiseizure medication with risk of autism and intellectual disability. *JAMA Neurol* 2022;79(7):672. <https://doi.org/10.1001/jamaneurol.2022.1269>.
- [9] Blotiere PO, Miranda S, Weill A, Mikaeloff Y, Peyre H, Ramus F, et al. Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study. *BMJ Open* 2020;10(6):e034829. <https://doi.org/10.1136/bmjopen-2019-034829>.
- [10] Cattane N, Richetto J, Cattaneo A. Prenatal exposure to environmental insults and enhanced risk of developing schizophrenia and autism spectrum disorder: focus on biological pathways and epigenetic mechanisms. *Neurosci Biobehav Rev* 2020;117:253–78. <https://doi.org/10.1016/j.neubiorev.2018.07.001>.
- [11] Hernandez-Diaz S, Straub L, Bateman BT, Zhu Y, Mogun H, Wisner KL, et al. Risk of autism after prenatal topiramate, Valproate, or lamotrigine exposure. *N Engl J Med* 2024;390(12):1069–79. <https://doi.org/10.1056/NEJMoa2309359>.
- [12] Cheol Seong S, Kim YY, Khang YH, Heon Park J, Kang HJ, Lee H, et al. Data resource profile: the national health information database of the national health insurance service in South Korea. *Int J Epidemiol* 2017;46(3):dyw253. <https://doi.org/10.1093/ije/dyw253>.
- [13] Welfare MoHa. (2026). Pregnancy and childbirth medical expense support program [Available from: <https://www.mohw.go.kr/menu.es?mid=a10705020100/>].
- [14] Kim YY, Hong HY, Cho KD, Park JH. Family tree database of the national health information database in Korea. *Epidemiol Health* 2019;41:e2019040. <https://doi.org/10.4178/epih.e2019040>.
- [15] Methodology WCCfDS. ATC/DDD index [Available from: https://atcddd.fhi.no/atcddd_index/]; 2025.
- [16] Meador KJ, Baker GA, Browning N, Cohen MJ, Bromley RL, Clayton-Smith J, et al. Fetal antiepileptic drug exposure and cognitive outcomes at age 6 years (NEAD study): a prospective observational study. *Lancet Neurol* 2013;12(3):244–52. [https://doi.org/10.1016/S1474-4422\(12\)70323-X](https://doi.org/10.1016/S1474-4422(12)70323-X).
- [17] Fujii H, Goel A, Bernard N, Pistelli A, Yates LM, Stephens S, et al. Pregnancy outcomes following gabapentin use: results of a prospective comparative cohort study. *Neurology* 2013;80(17):1565–70. <https://doi.org/10.1212/WNL.0b013e31828f18c1>.
- [18] Blaszczyk B, Miziak B, Pluta R, Czuczwar SJ. Epilepsy in pregnancy-management principles and focus on valproate. *Int J Mol Sci* 2022;23(3):1369. <https://doi.org/10.3390/ijms23031369>.
- [19] Ornoy A, Echeffu B, Becker M. Valproic acid in pregnancy revisited: neurobehavioral, biochemical and molecular changes affecting the embryo and fetus in humans and in animals: a narrative review. *Int J Mol Sci* 2023;25(1):390. <https://doi.org/10.3390/ijms25010390>.
- [20] Pack AM, Oskoui M, Williams Roberson S, Donley DK, French J, Gerard EE, et al. Fetal antiepileptic drug exposure and neurodevelopmental outcomes after In utero exposure to antiseizure medication: practice guideline from the AAN, AES, and SMFM. *Neurology* 2024;102(11):e209279. <https://doi.org/10.1212/WNL.0000000000209279>.
- [21] Pack AM, Oskoui M, Roberson SW, Donley DK, French J, Gerard EE, et al. Teratogenesis, perinatal, and neurodevelopmental outcomes after In utero exposure to antiseizure medication. *Epilepsy Curr* 2026;26(1):64–84. <https://doi.org/10.1177/15357597241258514>.
- [22] Zhou Y, Wang X, Li H, Zhang J, Chen Z, Xie W, et al. Polymorphisms of ABCG2, ABCB1 and HNF4alpha are associated with Lamotrigine trough concentrations in epilepsy patients. *Drug Metab Pharmacokinet* 2015;30(4):282–7. <https://doi.org/10.1016/j.dmpk.2015.05.002>.
- [23] Bahn GH. The role of pediatric psychiatrists in the National health screening Program for infants and children in Korea. *J Korean Neuropsychiatr Assoc* 2020;59(3):176.
- [24] Kim YS, Leventhal BL, Koh YJ, Fombonne E, Laska E, Lim EC, et al. Prevalence of autism spectrum disorders in a total population sample. *Am J Psychiatry* 2011;168(9):904–12. <https://doi.org/10.1176/appi.ajp.2011.10101532>.