RESEARCH ARTICLE

Prenatal Exposure to Antiseizure Medications and the Risk of Congenital Anomalies

A Nationwide Population-Based Study in South Korea

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Abstract

Background and Objectives

Valproate has a well-documented teratogenic risk, whereas lamotrigine and levetiracetam seem relatively safe. However, evidence for other antiseizure medications (ASMs) and specific congenital anomalies remains limited and inconsistent. We aimed to assess the risk of overall and specific congenital anomalies associated with prenatal exposure to individual ASMs.

Methods

We conducted a retrospective cohort study using the Korean National Health Insurance Service mother-child linkage database from 2013 to 2021. Pregnant women aged 20–45 years with live births were included. Exposure was defined as the prescription of any ASM during the first trimester. The primary outcome was congenital anomalies in offspring identified by diagnostic codes within 1 year of birth. We estimated the odds ratios (ORs) for overall congenital anomalies, organ system anomalies, and specific congenital anomalies associated with prenatal exposure to ASMs compared with those in the unexposed group. Propensity score fine stratification was used to adjust for potential confounders.

Results

Among 2,494,958 pregnancies, 5,880 (0.24%) were exposed to ASMs during the first trimester. The mean maternal age at delivery was 32.9 years in the exposed group and 32.4 years in the unexposed group. ASM exposure was associated with an increased risk of overall congenital anomalies (OR 1.26, 95% CI 1.11–1.43). Among monotherapies, valproate had the highest risk (OR 1.46, 95% CI 1.11–1.91), showing a dose-dependent relationship (OR 1.57, 95% CI 1.12–2.19 at ≥500 mg/d). Polytherapy, including valproate, had a higher risk (OR 2.06, 95% CI 1.32–3.20), whereas polytherapy without valproate was not significantly associated with an increased risk (OR 1.26, 95% CI 0.92–1.71). Specific congenital anomalies associated with individual ASMs included congenital hydrocephalus (carbamazepine), atrial septal defects (oxcarbazepine), cleft palate (valproate), hypospadias (levetiracetam), and tetralogy of Fallot and talipes equinovarus (topiramate).

Discussion

This study revealed that prenatal exposure to valproate increased the risk of congenital anomalies. Although other ASMs, even in polytherapy, did not significantly increase the overall risk of congenital anomalies, carbamazepine, levetiracetam, oxcarbazepine, and topiramate were associated with specific types of congenital anomalies. Given the limited number of cases, these findings warrant further investigation in other populations.

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Supplementary Material

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Glossary

aSD = absolute standardized difference; **ASM** = antiseizure medication; **EUROCAT** = European Concerted Action on Congenital Anomalies and Twins; **ICD-10** = International Classification of Diseases, 10th revision; **LMP** = last menstrual period; **NHIS** = National Health Insurance Service; **OR** = odds ratio; **PS** = propensity score; **PS-aOR** = PS-adjusted odds ratio.

Classification of Evidence

This study provides Class III evidence that prenatal exposure to valproic acid increases the risk of overall congenital anomalies while other ASMs, including carbamazepine, levetiracetam, oxcarbazepine, and topiramate, do not increase the risk of overall congenital anomalies.

Introduction

Epilepsy is one of the most common neurologic disorders that requires continued treatment with antiseizure medications (ASMs) during pregnancy.[1-3] Furthermore, the clinical applications of ASMs extend beyond epilepsy, encompassing mood disorders, chronic pain, and migraine.[2,4] Even under these circumstances, some women may require the continued administration of ASMs throughout pregnancy.[5]

The teratogenicity associated with prenatal exposure to ASMs is a critical concern when treating women of childbearing potential with ASMs. The US Food and Drug Administration issued warnings in 2013, and the European Medicines Agency published tightened restrictions in 2014 on the use of valproate in female patients.[6,7] Prenatal exposure to carbamazepine, phenobarbital, and phenytoin has also been shown to increase the risk of congenital anomalies.[8] Lamotrigine, levetiracetam, and oxcarbazepine have been reported to be relatively safe.[8,9] However, the teratogenic potential of other ASMs has not been definitively established. Moreover, data on the effects of prenatal exposure to ASMs on specific congenital anomalies remain limited and inconsistent, except for the association between valproate and spina bifida.[8-10]

To date, the effects of prenatal exposure to ASMs have been studied primarily in Western populations, despite the inclusion of some Asian countries in international registries, such as the EURAP.[11] However, ethnic differences exist in the incidence of congenital anomalies and pharmacogenomic profiles.[12,13] In addition, key evidence regarding the safety profiles of ASM use during pregnancy has largely been derived from epilepsy registry studies.[8,14] Registry studies provide detailed information about participants' disease status (e.g., epilepsy syndrome, seizure classifications, and seizure control) and clinically confirmed congenital anomaly outcomes. However, this type of study also has several limitations, including reliance on only voluntary participants with specific disorders and the frequent absence of unexposed control groups, which precludes direct comparisons between ASM-exposed and unexposed pregnancies, restricting analyses to comparisons among different ASMs.

In this study, we aimed to assess the risk of overall and specific congenital anomalies in offspring associated with exposure to individual ASMs compared with a propensity score (PS)–matched control, using a large population-based mother-child linkage database in Korea. We further examined whether these associations varied according to exposure patterns (monotherapy vs polytherapy with or without valproate) and the presence of a dose-response relationship.

Methods

Data Source, Design, and Study Cohort

We conducted a nationwide population-based retrospective cohort study using the Korean National Health Insurance Service (NHIS) database between January 2013 and December 2021. The NHIS is a single universal health insurance system covering the entire population of over 50 million people in South Korea, more than 98% of the population since 2005.[15] The NHIS database provides comprehensive individual-level information, including demographics, socioeconomic status, health care utilization (e.g., including diagnoses and filled prescriptions from both inpatient and outpatient settings), health examination records, and vital statistics data.[16]

This study included all pregnancies that resulted in live singleton births among women aged 20 to 45 at the time of delivery during the study period. We excluded mothers with a diagnosed congenital anomaly themselves and children diagnosed with a chromosomal abnormality. We also excluded pregnant individuals who were exposed to known teratogenic drugs from 90 days before the last menstrual period (LMP) to the end of the first trimester. All live-born infants were linked to their mothers based on the unique insurance identification number shared by family members. Infant outcomes were ascertained from birth to 1 year or death, whichever came first (eFigure 1). We calculated the date of the LMP using an algorithm to estimate the gestational age in administrative databases.[17] Childbirths were identified using procedure codes of delivery. Congenital anomalies and chromosomal abnormalities were identified using the ICD-10 codes,

whereas exposure to teratogenic drugs was determined using anatomical therapeutic chemical codes. The detailed diagnosis, procedure, and medication codes are listed in eTable 1.

ASM Exposure

We defined the exposed group as women who received 1 or more dispensings of ASMs during the first trimester (starting from the LMP to 90 days after LMP) of pregnancy, which represents the critical period for embryogenesis. In Korea, prescriptions are often issued for several months at a time, and we considered individuals exposed even if they had only 1 prescription record. The unexposed group included women with no dispensing of ASMs starting from 90 days before the LMP to the end of the first trimester (eFigure 1). We included all 16 ASMs available by prescription in South Korea: carbamazepine, clobazam, ethosuximide, gabapentin, lacosamide, lamotrigine, levetiracetam, oxcarbazepine, perampanel, phenobarbital, phenytoin, pregabalin, topiramate, valproate, vigabatrin, and zonisamide. In the analyses of the associations between overall congenital anomalies and individual ASMs, 6 ASMs (ethosuximide, lacosamide, perampanel, phenobarbital, phenytoin, and vigabatrin) were excluded because they had fewer than 10 exposure cases. The risk of specific anomalies and the dose-response relationships were analyzed for 8 individual ASMs (carbamazepine, gabapentin, lamotrigine, levetiracetam, oxcarbazepine, pregabalin, and valproate) that each had at least 100 exposure cases during the study period. ASM exposure patterns were categorized into monotherapy and polytherapy that included or excluded valproate, which is associated with the highest risk of congenital anomalies.[8] Monotherapy or polytherapy (≥2 ASMs) was defined based on the number of ASMs dispensed during the first trimester. To assess the dose-response relationship, we included only monotherapy exposures and defined low and high doses for individual ASMs based on the median of the mean daily doses prescribed during the first trimester (eTable 2).

Outcome

We identified congenital anomalies using the ICD-10 code, as defined by the European Concerted Action on Congenital Anomalies and Twins (EUROCAT).[18,19] The primary outcome was the risk of overall congenital anomalies diagnosed within the first year of birth, and we also investigated congenital anomalies classified by organ systems (eTable 1).[2,3,18,20] Furthermore, we selected 14 specific congenital anomalies, each with an incidence exceeding 1 in 10,000 live births in Korea, particularly those relevant to prenatal exposure to ASMs.[8,10,21] We analyzed the relationship between specific congenital anomalies and individual ASMs when used as monotherapy, which had at least 100 exposure cases.

Covariates

In addition to ASMs, maternal health status and socioeconomic factors can contribute to the occurrence of congenital anomalies.[22] To address this, we identified a broad list of potential confounders or proxies of potential confounders: maternal demographic characteristics, including socioeconomic status; maternal disorders (e.g., epilepsy, migraine, bipolar disorder, depression, alcohol abuse, hypertension and diabetes); concomitant medications; obstetric conditions (e.g., obstetric comorbidity index)[23]; and health care utilization. A full list of covariates and their assessment periods is presented in eFigure 1 and eTable 3.

Statistical Analyses

Continuous variables (age and health care utilization) were summarized using means and SDs, and categorical variables were summarized as absolute frequencies and proportions. The baseline characteristics of women exposed and those not exposed to ASMs were compared using absolute standardized differences (aSDs; ≥0.1 indicates a significant imbalance between the 2 groups).

The absolute risks and risk differences (per 1,000 births) were calculated for congenital anomalies classified by organ systems. In addition, we calculated the population-attributable fraction to estimate the impact of ASM exposure on outcomes within the study population.[24] In this study, the population-attributable fraction refers to the proportion of congenital anomalies in pregnant women that can be attributed to ASMs.[20]

The PS fine stratification method was used to adjust for measured baseline confounders when estimating the overall and organ system-specific risks of congenital anomalies associated with ASM exposure.[25] We used multivariate logistic regression analysis when investigating the relationship between individual ASMs and specific congenital anomalies.

We performed a sensitivity analysis to account for potential outcome misclassification. In this analysis, we redefined the outcome as 2 or more hospital visits with an ICD-10 code for congenital anomalies that occurred at any time from birth until the end of the study. In addition, we conducted quantitative bias analysis that used bias-correction methods based on published estimates of live birth probabilities to evaluate the potential selection bias from excluding nonlive births.

All statistical analyses were performed using SAS Enterprise Guide 7.1 for Windows (SAS Institute Inc., Cary, NC), and statistical significance was defined as $p < 0.05$.

Standard Protocol Approvals, Registrations, and Participant Consents

This study was approved by the Institutional Review Board of the National Medical Center (Approval No. NMC-2025-02-019) and the NHIS Bioethics Policy (NHIS-2023-1-367), with a waiver of informed consent because of the use of anonymized secondary data.

Data Availability

Anonymized data from the NHIS used in this study are not publicly available because of legal and ethical restrictions.

Qualified researchers may request access through the NHIS data request system (nhiss.nhis.or.kr) after obtaining institutional review board approval and following the NHIS Bioethics Policy. Data are only accessible at the NHIS analysis center and cannot be transferred outside the center. The study protocol, statistical analysis plan, and analysis codes can be shared.

Results

Demographics and Baseline Characteristics

Demographics and baseline characteristics are presented in Table 1 and Figure 1. A total of 2,494,958 pregnancies were included in the study, of which 5,880 (0.24%) were exposed to ASMs during the first trimester. Among the 4,771 monotherapy cases, gabapentin exhibited the highest number of exposures (1,131, 23.7%), followed by lamotrigine (718, 15%), valproate (667, 14%), levetiracetam (542, 11.4%), topiramate (507, 10.6%), pregabalin (449, 9.4%), carbamazepine (427, 8.9%) and oxcarbazepine (164, 3.4%).

The mean maternal age at delivery was slightly greater in the exposed group (32.9 years, SD: 4.6 years) than in the unexposed group (32.4 years, SD: 4.3 years) (aSD = 0.10), indicating a greater proportion of pregnancies over 36 years in the exposed group. The ASM-exposed group was more likely to receive medical aid, which indicates an inability to pay for health insurance premiums (5.3% vs 0.5%, aSD = 0.29) and was disproportionately represented in the highest income quartile (25.7% vs 31.4%, aSD = 0.13).

Compared with the unexposed group, the ASM-exposed group had a greater prevalence of epilepsy (47.9% vs 0.06%), migraine (16.0% vs 5.0%), and bipolar or depressive disorders (15.5% vs 0.9%). In addition, the obstetric comorbidity index and health care utilization rates were significantly elevated in the ASM-exposed group. After PS adjustment, all characteristics of the cohorts were well balanced, exhibiting an aSD of less than 0.1.

Risks of Overall Congenital Anomalies

Among the 5,880 ASM-exposed pregnancies, 637 (10.8%) resulted in congenital anomalies, whereas 173,861 (7.0%) in the unexposed group resulted in congenital anomalies. ASM exposure was significantly associated with overall congenital anomalies (PS-adjusted odds ratio [PS-aOR] of 1.26, 95% CI 1.11–1.43, $p < 0.001$) (Figure 1 and Table 2). The population-attributable fraction of congenital anomalies due to prenatal ASM exposure was estimated to be 0.14% (Table 2). In a sensitivity analysis, which redefined the outcome as 2 or more hospital visits for congenital anomalies, the association with ASM exposure and overall congenital anomalies remained significant (PS-aOR of 1.19, 95% CI 1.03–1.38, $p = 0.0187$) (eTable 4).

When stratified by ASM exposure patterns, the incidence of congenital anomalies was 10.4% with a PS-aOR of 1.19 (95% CI 1.05–1.34, $p = 0.006$) in the monotherapy group, 11.6% (PS-aOR 1.26, 95% CI 0.92–1.71, $p = 0.145$) in the polytherapy group without valproate, and 17.7% (PS-aOR 2.06, 95% CI 1.32–3.20, $p = 0.001$) in the polytherapy group with valproate.

In monotherapy analyses of 10 individual ASMs with 10 or more exposure cases for overall congenital anomalies, the crude OR was elevated for most ASMs, except for carbamazepine, clobazam, and zonisamide. After PS adjustment, valproate was the only ASM that remained significantly associated with an increased risk of congenital anomalies (PS-aOR 1.46, 95% CI 1.11–1.91, $p = 0.007$) (Figure 1).

Risk of Congenital Anomalies Classified by Organ System

A comparative analysis of the risk of congenital anomalies classified by organ system between the ASM-exposed and unexposed groups is presented in Table 2. The most significant difference in incidence per 1,000 pregnancies between the 2 groups was noted for heart defects, with 28.4 per 1,000 pregnancies, followed by nervous system anomalies, with 3.2 per 1,000 pregnancies. The highest population-attributable fraction (0.49%) was observed in ear-face-neck anomalies. The crude ORs increased for nervous system anomalies, eye anomalies, ear-face-neck anomalies, heart defects, oral clefts, genital organ anomalies, limb anomalies, and other anomalies. After PS adjustment, the associations remained significant for ear-face-neck anomalies (PS-aOR 4.17, 95% CI 2.18–8.00) and heart defects (PS-aOR 1.32, 95% CI 1.13–1.54).

In a sensitivity analysis, where the outcome was redefined as 2 or more hospital visits for congenital anomalies, heart defects and genital anomalies were statistically significant (eTable 4). A quantitative bias analysis that accounted for the bias due to the inclusion of only live births revealed that the corrected odds ratio (OR) for congenital anomalies slightly increased in relation to the reduced survival probability in the exposed group (eAppendix 1).

Dose-Dependent Risk of Congenital Anomalies Related to Individual ASMs

In this study, the median daily doses were 400 mg for carbamazepine, 300 mg for gabapentin, 100 mg for lamotrigine, 1,000 mg for levetiracetam, 600 mg for oxcarbazepine, 150 mg for pregabalin, 50 mg for topiramate, and 500 mg for valproate (eTable 2). A dose-dependent increase in the risk of congenital anomalies was observed only with valproate (Table 3). A significant association was identified at doses of 500 mg/d or higher (PS-aOR 1.57, 95% CI 1.12–2.19), whereas the association was not significant at doses below 500 mg/d (PS-aOR 1.25, 95% CI 0.80–1.96). By contrast, the risk of congenital anomalies was elevated in the low-dose topiramate group (<50 mg/d) (PS-aOR 1.80, 95% CI 1.22–2.66), whereas no increased risk was observed at doses of 50 mg or higher (PS-aOR 1.01, 95% CI 0.65–1.57). For the remaining 6 ASMs, no significant associations were found in any of the dichotomized dose ranges.

Table 1 Demographics and Baseline Characteristics of Pregnancies With and Without Exposure to ASMs During the First Trimester of Pregnancy

	Unadjusted			Propensity score–adjusted		
Characteristics	Unexposed (n = 2,489,078)	Exposed to ASMs (n = 5,880)	aSD	Unexposed (n = 2,277,948)	Exposed to ASMs (n = 5,260)	aSD
Age at delivery, y, mean (SD)	32.4 (4.3)	32.9 (4.6)	0.10	32.7 (4.7)	32.9 (4.6)	0.05
Maternal age group, n (%)						
20–25	148,347 (6)	402 (6.8)	0.04	179,711 (7.9)	341 (6.5)	0.05
26–30	619,518 (24.9)	1,313 (22.3)	0.06	529,996 (23.3)	1,160 (22.1)	0.03
31–35	1,150,988 (46.2)	2,429 (41.3)	0.10	919,653 (40.4)	2,209 (42.0)	0.03
36–40	503,807 (20.2)	1,479 (25.2)	0.12	547,066 (24.0)	1,323 (25.2)	0.03
41–45	66,418 (2.7)	257 (4.4)	0.09	101,521 (4.5)	227 (4.3)	0.01
Year of delivery, n (%)						
2013	355,139 (14.3)	703 (12.0)	0.07	281,473 (12.4)	624 (11.9)	0.02
2014	352,995 (14.2)	720 (12.2)	0.06	279,153 (12.3)	643 (12.2)	0.00
2015	351,735 (14.1)	673 (11.4)	0.08	270,030 (11.9)	605 (11.5)	0.01
2016	322,770 (13.0)	650 (11.1)	0.06	263,667 (11.6)	587 (11.2)	0.01
2017	278,190 (11.2)	650 (11.1)	0.00	242,756 (10.7)	591 (11.2)	0.02
2018	247,981 (10)	645 (11.0)	0.03	247,521 (10.9)	579 (11.0)	0.00
2019	222,421 (8.9)	613 (10.4)	0.05	233,481 (10.2)	539 (10.2)	0.00
2020	190,374 (7.6)	617 (10.5)	0.10	223,895 (9.8)	524 (10.0)	0.00
2021	167,473 (6.7)	609 (10.4)	0.13	235,972 (10.4)	568 (10.8)	0.01
Socioeconomic status						
Insurance type, n (%)						
Health insurance	2,475,890 (99.5)	5,568 (94.7)	0.29	2,253,038 (98.9)	5,199 (98.8)	0.01
Medical aid	13,188 (0.5)	312 (5.3)	0.29	24,910 (1.1)	61 (1.2)	0.01
Income level, quartile, n (%)						
First (deprived)	420,483 (18.0)	1,088 (20.7)	0.07	453,948 (19.9)	1,087 (20.7)	0.02
Second	454,861 (19.5)	1,223 (23.2)	0.09	507,036 (22.3)	1,223 (23.3)	0.02
Third	723,609 (31.0)	1,598 (30.4)	0.01	702,067 (30.8)	1,598 (30.4)	0.01
Fourth (affluent)	732,213 (31.4)	1,352 (25.7)	0.13	614,897 (27)	1,352 (25.7)	0.03
Living area, n (%)						
Urban living	1,096,693 (44.1)	2,462 (41.9)	0.04	951,703 (41.8)	2,200 (41.8)	0.00
Rural living	1,392,385 (55.9)	3,418 (58.1)	0.04	1,326,245 (58.2)	3,060 (58.2)	0.00
Maternal condition, n (%)						
Epilepsy/seizure	1,474 (0.06)	2,818 (47.9)	1.35	1,085,573 (47.7)	2,543 (48.3)	0.01
Migraine/headache	124,762 (5.0)	940 (16.0)	0.36	385,177 (16.9)	833 (15.8)	0.03
Bipolar disorders/depressive disorders	22,347 (0.9)	910 (15.5)	0.55	327,874 (14.4)	750 (14.3)	0.00
Hypertension	22,078 (0.9)	58 (1.0)	0.01	24,791 (1.1)	47 (0.9)	0.02
Diabetes	17,003 (0.7)	123 (2.1)	0.12	52,050 (2.3)	107 (2.0)	0.02
Alcohol or drug dependence	1,486 (0.1)	40 (0.7)	0.10	15,047 (0.7)	33 (0.6)	0.00

Continued

Table 1 Demographics and Baseline Characteristics of Pregnancies With and Without Exposure to ASMs During the First Trimester of Pregnancy *(continued)*

Characteristics	Unadjusted			Propensity score–adjusted		
	Unexposed (n = 2,489,078)	Exposed to ASMs (n = 5,880)	aSD	Unexposed (n = 2,277,948)	Exposed to ASMs (n = 5,260)	aSD
Obstetric condition, n (%)						
Primiparous	1,275,319 (51.2)	2,955 (50.3)	0.02	1,170,422 (51.4)	2,678 (50.9)	0.01
Multiparous	1,213,759 (48.8)	2,925 (49.7)	0.02	1,107,526 (48.6)	2,582 (49.1)	0.01
Obstetric comorbidity index						
0	1,688,026 (67.8)	3,496 (59.5)	0.17	1,364,131 (59.9)	3,139 (59.7)	0.00
1	664,100 (26.7)	1,775 (30.2)	0.08	678,486 (29.8)	1,598 (30.4)	0.01
2+	136,952 (5.5)	609 (10.4)	0.18	235,331 (10.3)	523 (9.9)	0.01
Health care utilization, n (% or SD)						
No. of other distinct prescription medications, excluding ASMs, mean (SD)	1.8 (1.5)	3.3 (2.2)	0.85	3.4 (2.1)	3.2 (2.1)	0.07
No. of distinct maternal health-related diagnosis, mean (SD)	5.3 (3.0)	8.1 (4.2)	0.76	8.2 (4.1)	7.9 (4.0)	0.07
No. of distinct maternal health-related outpatient visit, mean (SD)	5.5 (5.7)	10.7 (9.5)	0.66	10.2 (8.7)	10.3 (8.7)	0.01
No. of patients with distinct maternal health-related ED visit (%)	162,242 (6.5)	842 (14.3)	0.26	403,763 (17.7)	710 (13.5)	0.12
No. of patients with distinct maternal health-related hospitalization (%)	135,581 (5.4)	789 (13.4)	0.28	326,540 (14.3)	665 (12.6)	0.05

Abbreviations: aSD = absolute standardized difference; ASM = antiseizure medication; ED = emergency department.

Risks of Specific Congenital Anomalies

The ASMs related to the 14 selected specific congenital anomalies are listed in Table 4 and eTable 5. Carbamazepine was associated with a significantly increased risk of congenital hydrocephalus (aOR 25.69, 95% CI 6.28–105.13), levetiracetam with hypospadias (aOR 19.51, 95% CI 1.11–341.91), oxcarbazepine with atrial septal defects (aOR 2.11, 95% CI 1.08–4.13), and valproate with cleft palate without cleft lip (aOR 5.55, 95% CI 1.93–15.92). Topiramate was significantly related to a greater risk of tetralogy of Fallot (aOR 7.36, 95% CI 1.70–31.81) and talipes equinovarus (aOR 2.62, 95% CI 1.28–5.37).

Classification of Evidence

This study provides Class III evidence that prenatal exposure to valproic acid increases the risk of overall congenital anomalies, while other ASMs, including carbamazepine, levetiracetam, oxcarbazepine, and topiramate, do not increase the risk of overall congenital anomalies.

Discussion

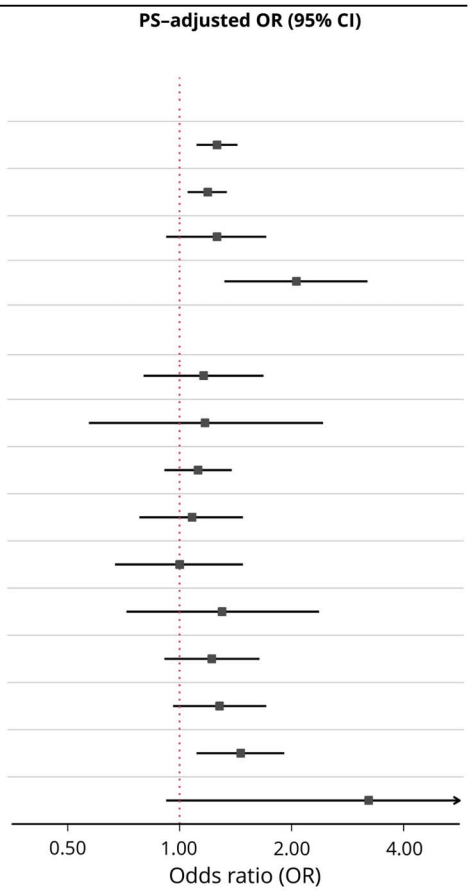
This nationwide population-based cohort study on perinatal exposure to ASMs found that only valproate was significantly associated with overall congenital anomalies, with a 1.5-fold increased risk. Polytherapy without valproate did not significantly increase the risk of overall congenital anomalies. Nonetheless, prenatal exposure to carbamazepine, levetiracetam, oxcarbazepine, or topiramate was associated with increased risks of specific types of congenital anomalies.

Over the past few decades, a consistent association between in utero exposure to ASMs and congenital anomalies in offspring has been documented in studies using prospective cohorts, registries, and health records.[14] A pooled analysis reported a rate of congenital anomalies of 6.1% in the offspring prenatally exposed to ASMs, compared with 2.8% in the offspring of untreated women with epilepsy and 2.2% in the offspring of mothers without epilepsy.[22] Valproate has been consistently reported to have the highest incidence of congenital anomalies, with absolute risk differences ranging from 5% to 9% compared with other ASM monotherapies and relative risks of 2.3–5.5 compared with unexposed groups.[8] In addition, associations between congenital anomalies and other older ASMs (e.g., carbamazepine, phenytoin, and phenobarbital) as well as topiramate have been observed.[2,8]

Our study did not reveal a relationship between ASMs other than valproate and overall congenital anomalies after PS adjustment. Even for valproate, the relative risk was observed to

Figure 1 Risks of Overall Congenital Anomalies in Children After ASM Exposure During the First Trimester of Pregnancy

Drug exposure (number)	Number of congenital malformations (%)	Crude OR (95% CI)	PS-adjusted OR (95% CI)	*p* Value
Unexposed (2,489,078)	173,861 (7)			
All ASMs exposure (5,880)	637 (10.8)	1.62 (1.49–1.76)	1.26 (1.11–1.43)	<0.001*
All monotherapy exposure (4,771)	494 (10.4)	1.54 (1.40–1.69)	1.19 (1.05–1.34)	0.006*
All polytherapy exposure excluding valproate (878)	102 (11.6)	1.75 (1.42–2.15)	1.26 (0.92–1.71)	0.145
All polytherapy exposure including valproate (231)	41 (17.7)	2.87 (2.05–4.03)	2.06 (1.32–3.20)	0.001*
Individual ASMs, monotherapy				
Carbamazepine (427)	40 (9.4)	1.38 (0.99–1.91)	1.16 (0.80–1.68)	0.420
Clobazam (86)	8 (9.3)	1.37 (0.66–2.83)	1.17 (0.57–2.43)	0.668
Gabapentin (1,131)	111 (9.8)	1.45 (1.19–1.76)	1.12 (0.91–1.38)	0.284
Lamotrigine (718)	72 (10.0)	1.48 (1.16–1.89)	1.08 (0.78–1.48)	0.645
Levetiracetam (542)	50 (9.2)	1.35 (1.01–1.81)	1.00 (0.67–1.48)	0.995
Oxcarbazepine (164)	18 (11.0)	1.64 (1.01–2.68)	1.30 (0.72–2.37)	0.387
Pregabalin (449)	54 (12)	1.82 (1.37–2.42)	1.22 (0.91–1.64)	0.183
Topiramate (507)	60 (11.8)	1.79 (1.37–2.34)	1.28 (0.96–1.71)	0.098
Valproate (667)	76 (11.4)	1.71 (1.35–2.17)	1.46 (1.11–1.91)	0.007*
Zonisamide (34)	4 (11.8)	1.78 (0.63–5.04)	3.22 (0.92–11.27)	0.067



ASMs = antiseizure medications; OR = odds ratio; PS = propensity score. *$p < 0.05$, statistically significant.

be relatively low. There are a few possible explanations for this. First, the exposure doses in our study population may have been lower than those in previous studies. Second, meticulous adjustment for potential confounders attenuated the association that could have been biased by differences in underlying conditions between the exposed and unexposed groups. Third, ethnic differences may have affected susceptibility to ASM-related congenital anomalies. Fourth, methodologic variation, particularly in outcome ascertainment, may have contributed to the discrepancy. Studies based on primary data collection, such as registry studies, generally reported higher relative risks than those relying on secondary health data.[8]

Among ASMs with previously limited evidence of teratogenicity, zonisamide exhibited a high PS-aOR despite a lack of statistical significance. Previous meta-analyses documented only 130 pregnancies exposed to zonisamide, all derived from registry studies, and reported a risk comparable to that of lamotrigine or levetiracetam with a wide CI (2.7%, 95% CI 0.1–47.3).[8] A newly published study from the North American Antiepileptic Drug Pregnancy Registry reported consistent findings, showing no increase in the major malformation rate for zonisamide compared with lamotrigine (relative risk, 0.62 95% CI 0.20–1.98).[26] Our study provides population-based health record data on zonisamide exposure, and these 34 additional cases contribute additional real-world data to the existing evidence base. Clobazam and gabapentin have not been associated with an increased risk of congenital anomalies, but previous evidence has been limited because of small numbers of exposed pregnancies.[8,9,26] Our study involving a larger exposed population provides additional support for these findings. For pregabalin, our finding is consistent with those of a recent large population-based registry study from the Nordic countries, which found no significant increase in the risk of major congenital malformations.[27]

We found that polytherapy regimens excluding valproate did not increase the risk of overall congenital anomalies. Polytherapy (6%) resulted in a higher rate of congenital anomalies than did monotherapy (3.7%) in the UK Epilepsy and Pregnancy Register.[28] In the Australian Pregnancy Register, the risk of fetal malformations was not significantly different for ASM polytherapy and monotherapy when valproate was not included.[29] The type of ASM used in a polytherapy regimen is

Table 2 Risk of Congenital Anomalies Classified by Organ System Associated With Prenatal ASM Exposure

	Unexposed (n = 2,489,078)		Exposed to ASMs (n = 5,880)							
	n	Risk/1,000 births	n	Risk/1,000 births	RD1000[a]	PAF	Crude OR (95% CI)	*p* Value	PS-adjusted OR (95% CI)	*p* Value
Overall congenital anomalies	173,861	69.9	637	108.3	38.5	0.14%	1.62 (1.49–1.76)	<0.0001	1.26 (1.11–1.43)	<0.001[b]
Nervous system anomalies	14,973	6.0	54	9.2	3.2	0.12%	1.53 (1.17–2.00)	0.002	1.47 (0.98–2.21)	0.061
Eye anomalies	3,455	1.4	16	2.7	1.3	0.23%	1.96 (1.20–3.21)	0.007	1.94 (0.87–4.31)	0.106
Ear, face, and neck anomalies	1,502	0.6	11	1.9	1.3	0.49%	3.10 (1.71–5.62)	0.000	4.17 (2.18–8.00)	<0.001[b]
Heart defects	103,713	41.7	412	70.1	28.4	0.17%	1.73 (1.57–1.92)	<0.0001	1.32 (1.13–1.54)	<0.001[b]
Respiratory anomalies	1,546	0.6	3	0.5	−0.1	−0.04%	0.82 (0.26–2.55)	0.734	0.49 (0.09–2.54)	0.393
Oral clefts	3,534	1.4	15	2.6	1.1	0.19%	1.80 (1.08–2.99)	0.023	1.35 (0.61–2.97)	0.459
Digestive system anomalies	9,297	3.7	26	4.4	0.7	0.04%	1.18 (0.81–1.74)	0.389	0.75 (0.42–1.35)	0.338
Abdominal wall defects	1,253	0.5	4	0.7	0.2	0.08%	1.35 (0.51–3.61)	0.548	0.50 (0.14–1.79)	0.288
Urinary system anomalies	20,181	8.1	53	9.0	0.9	0.03%	1.11 (0.85–1.46)	0.439	0.91 (0.61–1.35)	0.633
Genital anomalies	7,886	3.2	30	5.1	1.9	0.14%	1.61 (1.13–2.31)	0.009	1.58 (0.89–2.81)	0.119
Limb anomalies	7,934	3.2	32	5.4	2.3	0.17%	1.71 (1.21–2.42)	0.003	1.76 (0.97–3.20)	0.064
Other anomalies	11,508	4.6	38	6.5	1.8	0.09%	1.40 (1.02–1.93)	0.039	0.96 (0.59–1.58)	0.883

Abbreviations: ASM = antiseizure medication; OR = odds ratio; PAF = population attributable fraction; PS = propensity score.
[a] RD1000, risk difference per 1,000 births.
[b] $p < 0.05$, statistically significant.

more important than whether monotherapy or polytherapy is administered.[14,30]

In the subgroup analysis by organ system, only heart defects and ear-face-neck anomalies were significantly related to in utero exposure to ASMs after PS adjustment. Cardiac anomalies are the most consistently reported congenital anomalies associated with ASMs, along with neural tube defects and facial clefts.[8,31] A meta-analysis of cohort studies indicated a significantly increased risk of craniofacial anomalies, including orofacial clefts, in children exposed to carbamazepine or valproate compared with unexposed children.[8] Recent studies have reported the occurrence of these anomalies in the offspring of mothers exposed to lamotrigine and oxcarbazepine, although these findings did not reach statistical significance.[2,32]

The relationship between individual ASMs and specific congenital anomalies has exhibited considerable variability across studies. Cardiac anomalies were most frequently associated with carbamazepine, lamotrigine, barbiturates, and phenytoin, whereas neural tube defects were commonly linked to valproate.[22] In this study, valproate was significantly associated only with cleft palate, and topiramate with tetralogy of Fallot and clubfoot. We found a significant association of carbamazepine with congenital hydrocephalus, levetiracetam with hypospadias, and oxcarbazepine with atrial septal defects. The association between valproate and cleft palate has also been shown in previous studies.[10,33] However, to our knowledge, no previous studies have reported an association between individual ASMs other than valproate and specific congenital anomalies similar to those observed in this study. These findings should be interpreted with caution because of the small number of cases, and further investigations in other populations are needed for confirmation.

In our study, in utero exposure to valproate increased the risk of congenital anomalies in a dose-dependent manner, consistent with previous studies.[2,3,34] Although the risk was not statistically significant at doses below 500 mg/d, it does not ensure safety, because previous studies reported a higher risk of congenital anomalies at doses ≤650–700 mg.[33,34] Unexpectedly, our study found that low doses of topiramate (<50 mg/d) were significantly linked to congenital anomalies. The 2018 EURAP registry reported no dose dependency for congenital anomalies associated with topiramate.[33] On the contrary, recent studies revealed that the risk ratio for congenital anomalies was significantly higher at topiramate doses >125 mg in the Nordic registries and >100 mg in the US Medicaid data.[2,35]

Table 3 Dose-Dependent Risk of Overall Congenital Anomalies Associated With Prenatal Exposure to Individual ASMs[a]

	No. of pregnancies exposed	No. of congenital malformation	PS-adjusted OR (95% CI)	*p* Value
Carbamazepine (<400 mg/d)	184	20	1.36 (0.84–2.20)	0.212
Carbamazepine (≧400 mg/d)	242	19	0.87 (0.50–1.51)	0.619
Gabapentin (<300 mg/d)	447	45	0.94 (0.66–1.34)	0.741
Gabapentin (≧300 mg/d)	684	66	1.22 (0.94–1.58)	0.14
Lamotrigine (<100 mg/d)	239	23	1.00 (0.61–1.62)	0.991
Lamotrigine (≧100 mg/d)	479	49	1.03 (0.70–1.52)	0.871
Levetiracetam (<1,000 mg/d)	225	22	1.08 (0.65–1.81)	0.762
Levetiracetam (≧1,000 mg/d)	317	28	0.85 (0.53–1.38)	0.517
Oxcarbazepine (<600 mg/d)	63	9	1.24 (0.50–3.09)	0.640
Oxcarbazepine (≧600 mg/d)	101	9	1.01 (0.45–2.25)	0.979
Pregabalin (<150 mg/d)	169	22	1.33 (0.84–2.11)	0.224
Pregabalin (≧150 mg/d)	280	32	1.17 (0.80–1.71)	0.429
Topiramate (<50 mg/d)	221	32	1.80 (1.22–2.66)	0.003[b]
Topiramate (≧50 mg/d)	285	28	1.01 (0.65–1.57)	0.964
Valproate (<500 mg/d)	270	30	1.25 (0.80–1.96)	0.318
Valproate (≧500 mg/d)	397	46	1.57 (1.12–2.19)	0.009[b]

Abbreviations: ASM = antiseizure medication; OR = odds ratio; PS = propensity score.
[a] ASMs with more than 100 exposure cases are included.
[b] $p < 0.05$, statistically significant.

In this study, the assessment of dose dependency may have been limited by the generally low daily dose of prenatal topiramate exposure (median 50 [interquartile range 25–100] mg/d). Individuals receiving topiramate monotherapy at doses below 50 mg were likely treated for migraine and may represent a relatively healthy population, in whom the effects of the drug could be evaluated with minimal confounding from underlying conditions. However, this finding should be interpreted with caution, as the number of individuals in each exposure group decreased substantially when stratified by individual ASM and dose levels.

In this study, the unadjusted incidence rate of congenital anomalies was higher in both ASM-exposed and unexposed groups compared with previous studies, which may be attributed to several factors. First, in particular, our study revealed a marked increase in the incidence of heart defects in both groups. We could not apply a lesion-size threshold (e.g., excluding septal defects <5 mm or patent foramen ovale) or consider clinical significance, which is a limitation inherent to studies using administrative health databases. Likewise, the incidence of nervous system anomalies in our study (6.0 per 1,000 births in the ASM-unexposed group) was several times higher than the EUROCAT estimates (1.3 per 1,000 births),[36] probably due to the inclusion of transient findings or diagnoses without a precise clinical definition that were coded as congenital anomalies in claims data. Health insurance claims data may record provisional or unconfirmed diagnoses, resulting in higher observed rates.[37] Consequently, we used the broader term "congenital anomalies" instead of "major congenital malformations," which might encompass minor or clinically insignificant anomalies. This distinction partially accounts for the higher incidence rates noted in comparison with registry-based studies, which generally include expert-adjudicated major congenital malformations. Second, Korea has one of the highest frequencies of prenatal ultrasounds among developed countries, with an average of 10.7 scans per pregnancy, which is significantly higher than the standard 3 scans conducted in many Western countries.[38] This increased screening likely enhances prenatal detection of congenital anomalies and leads to more comprehensive postnatal evaluations. Furthermore, our study found a relatively high average maternal age of 32.9 years, with nearly 30% of mothers aged 35 years or older, and highlights the high prevalence of older mothers. Korea has the second-highest average age for having a first child globally, and the average maternal age continues to rise rapidly each year.[39,40] A recent meta-analysis has revealed that advanced maternal age over 35 years strongly elevates the occurrence of nonchromosomal congenital anomalies.[41]

This study has several limitations inherent in the use of claim data from the NHIS. First, false-negative outcomes may occur if anomalies do not require intervention and thus are

Table 4 Risks of Specific Congenital Anomalies Associated With Individual ASMs[a] During the First-Trimester Exposure

	Unexposed (n = 2,489,078)	Carbamazepine (n = 427)		Gabapentin (n = 1,131)		Lamotrigine (n = 718)		Levetiracetam (n = 542)		Oxcarbazepine (n = 164)		Pregabalin (n = 449)		Topiramate (n = 507)		Valproate (n = 667)	
Congenital anomalies	**n (%)**	**n (%)**	**aOR (95% CI)**	**n (%)**	**aOR (95% CI)**	**n (%)**	**aOR (95% CI)**	**n (%)**	**aOR (95% CI)**	**n (%)**	**aOR (95% CI)**	**n (%)**	**aOR (95% CI)**	**n (%)**	**aOR (95% CI)**	**n (%)**	**aOR (95% CI)**
Spina bifida	5,503 (0.22)	N/A		5 (0.44)	1.45 (0.54–3.87)	1 (0.14)	0.57 (0.07–4.85)	N/A		N/A		2 (0.45)	1.61 (0.40–6.47)	2 (0.39)	1.54 (0.37–6.34)	3 (0.45)	2.25 (0.70–7.20)
Microcephaly	2,473 (0.10)	N/A		N/A		3 (0.42)	2.79 (0.59–13.15)	1 (0.18)	1.35 (0.13–14.60)	1 (0.61)	9.32 (0.67–130.48)	1 (0.22)	1.77 (0.25–12.67)	2 (0.39)	3.40 (0.79–14.59)	1 (0.15)	N/A
Congenital hydrocephalus	1,066 (0.04)	2 (0.47)	25.69 (6.28–105.13)[b]	1 (0.09)	2.13 (0.30–15.15)	N/A		1 (0.18)	18.30 (0.35–964.10)	N/A		1 (0.22)	4.53 (0.63–32.48)	N/A		N/A	
Ventricular septal defect	20,989 (0.84)	1 (0.23)	0.25 (0.03–1.83)	9 (0.80)	0.74 (0.35–1.55)	3 (0.42)	0.39 (0.12–1.31)	8 (1.48)	1.20 (0.49–2.91)	2 (1.22)	0.61 (0.08–4.63)	5 (1.11)	1.20 (0.50–2.90)	7 (1.38)	1.10 (0.45–2.70)	8 (1.20)	1.00 (0.41–2.44)
Atrial septal defect	81,249 (3.26)	22 (5.15)	1.29 (0.80–2.09)	56 (4.95)	1.15 (0.87–1.54)	35 (4.87)	1.28 (0.86–1.92)	30 (5.54)	1.33 (0.84–2.11)	13 (7.93)	2.11 (1.08–4.13)[b]	29 (6.46)	1.17 (0.78–1.74)	31 (6.11)	1.27 (0.85–1.89)	38 (5.70)	1.40 (0.97–2.02)
Tetralogy of Fallot	1,197 (0.05)	N/A		N/A		1 (0.14)	1.82 (0.16–20.93)	N/A		N/A		1 (0.22)	3.11 (0.43–22.35)	2 (0.39)	7.36 (1.70–31.81)[b]	N/A	
Pulmonary valve stenosis	4,047 (0.16)	1 (0.23)	1.44 (0.20–10.26)	2 (0.18)	0.96 (0.24–3.83)	1 (0.14)	0.44 (0.05–3.66)	N/A		N/A		1 (0.22)	1.07 (0.15–7.60)	N/A		4 (0.60)	2.96 (0.91–9.65)
Discordant ventriculoarterial connection	534 (0.02)	N/A		N/A		N/A		N/A		1 (0.61)	10.12 (0.65–157.69)	N/A		N/A		N/A	
Coarctation of aorta	1,009 (0.04)	N/A		1 (0.09)	2.24 (0.31–15.97)	N/A		N/A		N/A		1 (0.22)	4.75 (0.66–34.05)	N/A		N/A	
Cleft palate without cleft lip	3,086 (0.12)	N/A		2 (0.18)	1.15 (0.38–6.06)	1 (0.14)	0.72 (0.08–6.51)	1 (0.18)	0.92 (0.10–8.75)	1 (0.61)	3.06 (0.32–29.05)	1 (0.22)	1.82 (0.25–12.97)	2 (0.39)	2.70 (0.63–11.51)	4 (0.60)	5.55 (1.93–15.92)[b]
Cleft lip with or without cleft palate	1,910 (0.08)	1 (0.23)	2.64 (0.29–23.67)	2 (0.18)	1.23 (0.17–8.76)	1 (0.14)	1.05 (0.10–10.60)	1 (0.18)	1.35 (0.12–14.70)	N/A		N/A		1 (0.20)	2.08 (0.27–16.01)	N/A	
Hypospadias	2,427 (0.10)	1 (0.23)	5.15 (0.72–36.99)	3 (0.27)	1.80 (0.45–7.21)	1 (0.14)	3.30 (0.30–36.26)	2 (0.37)	19.51 (1.11–341.91)[b]	N/A		N/A		N/A		2 (0.30)	1.97 (0.27–14.39)
Diaphragmatic hernia	3,399 (0.14)	N/A		1 (0.09)	0.61 (0.09–4.35)	1 (0.14)	0.68 (0.08–5.94)	2 (0.37)	1.43 (0.26–7.72)	N/A		1 (0.22)	1.44 (0.20–10.29)	N/A		2 (0.30)	1.90 (0.46–7.91)
Talipes equinovarus	18,372 (0.74)	6 (1.41)	1.98 (0.83–4.74)	4 (0.35)	0.51 (0.19–1.37)	7 (0.97)	1.62 (0.65–4.02)	5 (0.92)	1.64 (0.49–5.53)	N/A		5 (1.11)	1.74 (0.72–4.21)	9 (1.78)	2.62 (1.28–5.37)[b]	5 (0.75)	1.40 (0.57–3.41)

Abbreviations: aOR = adjusted odds ratio; ASM = antiseizure medication; N/A = not applicable.
[a] Exposure to ASM monotherapy.
[b] Indicating statistical significance.

unrecorded. Conversely, as mentioned above, false-positive outcomes may arise from difficulties in distinguishing between suspected and confirmed diagnoses, and from the potential for reimbursement-driven coding inaccuracies, in contrast to the standardized data collection in prospective cohort studies.[37] Although the validity of congenital anomaly codes has not been specifically evaluated, the overall diagnostic codes in the NHIS database have shown a positive predictive value of 82% when compared with medical records.[42] The validity of epilepsy diagnoses in the NHIS database has also been evaluated in previous research, showing higher accuracy in younger individuals.[43] However, clinicians were not blinded to exposure status, and thus, there remains a potential for detection bias. Second, we were unable to directly confirm whether the pregnant women actually took the prescribed medications in this study. Third, although a broad range of covariates was considered, we cannot rule out the possibility of residual confounding factors, such as paternal factors and folic acid supplements. In Korea, folic acid is often taken as an over-the-counter medication and is, therefore, not recorded in the NHIS database.[37] In addition, our cohort included cases in which ASMs were prescribed for indications other than epilepsy, such as migraine or psychiatric disorders. Although we excluded individuals exposed to known teratogens and adjusted for the number of medications, confounding from indication-specific concomitant medications may still exist. Finally, as previously noted, because this study included only live births, the association between ASM exposure and the risk of severe malformations—particularly those with a high likelihood of resulting in elective termination or stillbirth—may have been underestimated. However, sensitivity analysis revealed that substantial overall termination rates and unrealistically significant differences between the ASM-exposed and unexposed groups would be required to distort the observed associations, indicating that the findings are likely robust against this potential bias.

Our study used a nationwide database covering the entire population of Korea, enabling the consecutive identification of drug exposures and congenital anomalies while minimizing the risk of selection or recall bias and ensuring a comparable control group. To our knowledge, this is the first population-based study conducted in East Asia to explore the association between prenatal exposure to ASMs and congenital anomalies. In addition, we investigated the relationships between individual ASMs and specific congenital anomalies while controlling for various potential confounding factors.

In conclusion, this nationwide population-based study conducted in Korea confirmed that prenatal exposure to valproate increased the risk of congenital anomalies in a dose-dependent manner. ASMs other than valproate did not increase overall risk, even in polytherapy. However, these findings should be interpreted with caution because of the generally low doses of ASMs. In addition, given the limited number of cases, the observed associations between certain ASMs and specific congenital anomalies require further investigation.

Author Contributions

H.K. Kim: drafting/revision of the manuscript for content, including medical writing for content; major role in the acquisition of data; study concept or design; analysis or interpretation of data. H. Lee: major role in the acquisition of data; study concept or design; analysis or interpretation of data. S.A. Choi: analysis or interpretation of data. H.J. Lee: analysis or interpretation of data. D. Lee: analysis or interpretation of data. H.-J. Moon: analysis or interpretation of data. S.-H. Han: study concept or design; analysis or interpretation of data. S.-Y. Lee: drafting/revision of the manuscript for content, including medical writing for content; study concept or design; analysis or interpretation of data. E.-h. Kim: analysis or interpretation of data. M. Yoon: analysis or interpretation of data.

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Disclosure

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