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Comparative risk of major congenital malformations with antiseizure medication combinations versus valproate monotherapy in pregnancy

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Abstract

Background and Objectives: Valproate should be avoided in pregnancy, but it is the most effective drug for generalized epilepsies. Alternative treatment may require combinations of other drugs. Our objectives were to describe first trimester use of antiseizure medication (ASM) combinations that are relevant alternatives to valproate and determine whether specific combinations were associated with a lower risk of major congenital malformations (MCM) compared with valproate monotherapy.

Methods: We conducted a population-based cohort study using linked national registers from Denmark, Finland, Iceland, Norway, and Sweden and administrative healthcare data from the US and New South Wales, Australia. We described first trimester use of ASM combinations among pregnant people with epilepsy from 2000-2020. We compared the risk of MCM after first trimester exposure to ASM combinations versus valproate monotherapy, and low-dose valproate plus lamotrigine or levetiracetam versus high-dose valproate (≥1000 mg/day). We used log-binomial regression with propensity score weights to calculate adjusted risk ratios (aRRs) and 95% confidence intervals (CIs) for each dataset. Results were pooled using fixed effects meta-analysis.

Results: Among 50,905 pregnancies in people with epilepsy identified from 7.8 million total pregnancies, 788 used lamotrigine and levetiracetam, 291 lamotrigine and topiramate, 208 levetiracetam and topiramate, 80 lamotrigine and zonisamide, and 91 levetiracetam and zonisamide. After excluding pregnancies with use of other ASMs, known teratogens, or a child diagnosed with MCM of infectious or genetic cause, we compared 587 exposed to lamotrigine-levetiracetam duotherapy and 186 exposed to lamotrigine-topiramate duotherapy with 1959 exposed to valproate monotherapy. Pooled aRRs were 0.41 (95% CI 0.24-0.69) and 1.26 (0.71-2.23), respectively. Duotherapy combinations containing low-dose valproate were infrequent and comparisons with high-dose valproate monotherapy were inconclusive but suggested a lower risk for combination therapy. Other combinations were too rare for comparative safety analyses.

Discussion: Lamotrigine-levetiracetam duotherapy in first trimester was associated with a 60% lower risk of MCM than valproate monotherapy, while lamotrigine-topiramate was not associated with a reduced risk. Duotherapy with lamotrigine and levetiracetam may be favored to treat epilepsy in people with childbearing potential compared to valproate with respect to MCM, but whether this combination is as effective as valproate remains to be determined.

Classification of Evidence: This study provides Class II evidence that in people with epilepsy treated in the first trimester of pregnancy, the risk of major congenital malformations is lower with lamotrigine-levetiracetam duotherapy than with valproate alone, but similar with lamotrigine-topiramate.

Introduction

In recent years, there have been increasing calls to avoid valproate use in pregnancy due to the increased risk of major congenital malformations (MCM) and adverse effects on fetal neurodevelopment. Safety advisories were issued by Health Canada in 2011,[1] the US Food & Drug Administration in 2011 and 2013,[2, 3] and the European Medicines Agency's (EMA's) Pharmacovigilance Risk Assessment Committee in 2014.[4] Measures endorsed by EMA in March 2018 include, "…a ban on the use of such medicines for migraine or bipolar disorder during pregnancy, and a ban on treating epilepsy during pregnancy unless there is no other effective treatment available."[5] The measures also restrict the use of valproate in people who may become pregnant.

Valproate is an effective treatment for almost all types of epileptic seizures and is considered the most effective drug for generalized epilepsy.[6] Therefore, to find alternative effective treatments, a combination of drugs such as lamotrigine, levetiracetam, or topiramate may be warranted.[7, 8] Alternatively, it may be possible to reduce the teratogenic risk by lowering the dose of valproate and adding another antiseizure medication (ASM).[9] Finding an effective treatment that can be used safely during pregnancy is important to maintain seizure control and avoid seizure-related injury and sudden unexpected death in epilepsy (SUDEP).[10]

Lamotrigine and levetiracetam are considered to be the safest ASMs in terms of teratogenic effects.[11-14] Therefore, a polytherapy combination including lamotrigine and levetiracetam could be safer than valproate monotherapy but this has not yet been studied. However, interactions between two drugs could make their combination more fetotoxic than taking each drug individually, so evidence for the safety of the combination of two drugs is needed.

Some of the best evidence for ASM pregnancy safety derives from exposure registries;[14-17] however, the relatively infrequent use of polytherapy and the various possible ASM combinations have made it difficult to study the safety of specific combinations. Very large cohort studies are needed to study both rare

exposures and rare outcomes. The linked Nordic health registers provide comprehensive information on the use of prescribed drugs in pregnancy in the entire population and precise diagnoses in the offspring. Similar cohorts can be identified in the US and Australia based on administrative data. Altogether these data sources allowed us to study a total population of nearly eight million pregnancies.

The study had two main objectives. First, to describe the first trimester use of ASM combinations that are potential alternatives to valproate. Second, to determine whether specific ASM combination therapies were associated with a lower risk of MCM compared with valproate monotherapy, including comparison of combinations with low-dose valproate to high-dose valproate monotherapy. Our primary research questions addressed, among pregnant people with epilepsy, is first trimester use of lamotrigine-levetiracetam duotherapy or lamotrigine-topiramate duotherapy associated with a lower risk of major congenital malformations compared with use of valproate alone.

Methods

Standard Protocol Approvals, Registrations, and Patient Consents

This study was approved by the ethical review boards in each country or institution, and each waived the requirement for obtaining informed consent for the secondary use of existing data (eTable 1). In Denmark, ethical approval is not required for register-based studies. The Danish part of the study was registered with the Danish Data Protection Agency at Aarhus University.

Study design and data sources

This study was carried out by the International Pregnancy Safety Study (InPreSS) Consortium, a collaboration among research groups from the five Nordic countries, US, and Australia.[18] We carried out a population-based cohort study based on national registers from Denmark, Finland, Iceland, Norway, and Sweden and administrative healthcare data from the US and New South Wales (NSW), Australia. Data were obtained from the medical birth registers of Denmark (1997-2017), Finland (1996-2016), Iceland (2003-2017), Norway (2004-2020), and Sweden (2005-2019) and linked with registers for filled

prescriptions, specialist healthcare (inpatient and outpatient specialist care), causes of death, and congenital malformations.[19] Data from the US were from administrative healthcare claims databases, both the Medicaid Analystic eXtract (MAX, 2000-2014), state-based public insurance, and IBM MarketScan© Commercial Claims and Encounters Data (2003-2015), private employer-sponsored health insurance plans.[20, 21] From Australia, the population was identified from the NSW state-wide Perinatal Data Collection (2006-2012) and individually linked to other healthcare data including filled prescriptions, hospital admissions, deaths, and congenital conditions (Maternal Use of Medications and Safety, MUMS database).[22]

Study population

The cohorts consisted of pregnancies with complete information on filled prescriptions from three months before pregnancy to birth, diagnoses before and during pregnancy, and outcomes in linked infants (eMethods). When earlier data were available (Denmark, Finland), we restricted to years after 1999 when there was the possibility to use at least one of the ASM combinations of interest. Our study population was restricted to pregnant people with epilepsy, which was identified according to country-optimized algorithms (eTable 2). In Norway and Finland, we identified epilepsy from the indication for reimbursement of antiseizure medication. In Denmark, Iceland, and Sweden, we identified epilepsy from diagnoses made in inpatient or outpatient specialist care from one year before pregnancy to birth. In the US, epilepsy was identified based on diagnoses from inpatient or outpatient care from 90 days before pregnancy to delivery. In Australia, epilepsy was identified from diagnoses of epilepsy from all available hospitalization history, including the delivery hospitalization. Although the focus of the study was on medications that are treatment alternatives for valproate, it should be noted that we included all epilepsy types in the cohort since codes may not be specific enough to identify epilepsy subtypes.

For the descriptive analysis, no further restrictions were made. For the analysis on the comparative safety of specific ASM duotherapies versus valproate monotherapy, we further excluded pregnancies in which the mother had used a known teratogenic drug in first trimester (eTable 3), and pregnancies in which one

or more of the infants had been diagnosed with a chromosomal anomaly or genetic syndrome, or a teratogenic infection (eTable 4).

Exposure definition

ASMs were identified by the Anatomic Therapeutic Chemical (ATC) code in the group N03A "antiepileptics" or by the generic drugs names in the US databases. The main drug combinations of interest included drugs used in treatment of generalized epilepsy: lamotrigine, levetiracetam, topiramate, and zonisamide.[7, 8, 23] We excluded drugs that are considered effective mainly for focal epilepsies, clobazam since it may be used sporadically for anxiety, and ASMs that are rarely used in pregnant people.[24] We defined first trimester use of ASM as having filled at least one prescription from the first day of the last menstrual period (LMP) until end of first trimester. Valproate monotherapy was defined as having first trimester use of valproate and having no filled prescriptions for any other ASM from 90 days before LMP to end of first trimester to ensure that no other ASMs were available for use during first trimester. We pre-defined ≥1000 mg per day as the high-dose cut-off for valproate, corresponding to approximately 30% of the estimated valproate monotherapy doses in the Nordic database. We used information from prescriptions up to 90 days before pregnancy to capture dose at the start of pregnancy (eMethods). Polytherapy was defined as use of two or more different ASMs in the first trimester. Duotherapy was defined as use of two different ASMs in first trimester and having no filled prescriptions for other ASMs from 90 days before LMP to end of first trimester.

In this paper, we use the terms polytherapy and duotherapy, but our definitions are based on filled prescriptions and cannot distinguish combination therapy from switching between ASMs. However, even if the intention is to switch from one monotherapy to another, a period of transitional duotherapy in which both drugs are used is recommended.[25] We were particularly concerned about the group using lamotrigine-topiramate duotherapy due to earlier safety data on topiramate suggesting increased risk of MCM, first published in 2012.[15, 26] We therefore carried out preliminary analyses in which we assessed evidence of

true combination therapy, defined as having prescription fills for both drugs on the same day, or an alternating fill pattern (drug A, drug B, drug A).

Outcome definition

The outcome was any MCM identified with ICD-9 or ICD-10 codes in one or more infants in the pregnancy (eTable 4). MCM was defined according to the similar and widely used classification systems used for surveillance in Europe (EUROCAT; used for the Nordic and Australian databases)[27] and the US (Metropolitan Atlanta Congenital Defects Program, CDC; used for the US databases) with adaptation to fit the national coding systems.[28] MCMs were diagnosed within one year of birth in the Nordic countries and recorded in medical birth, patient, and malformation registers, or as cause of infant death.[29] MCM were diagnosed within 3 months of birth in US databases using inpatient and outpatient claims, and within 18 months in Australia using hospital discharge diagnoses based on previously established and validated approaches.[30, 31]

Confounders

We controlled for confounding by indication mainly by restricting analyses to pregnancies among people with epilepsy. At minimum, we adjusted for birth year, maternal age, and country. Additional confounders included parity, multifetal gestation, maternal education, civil status (married or cohabiting), body mass index in early pregnancy, smoking in early pregnancy, prescribed folic acid use, pre-existing diabetes, psychiatric or neurodevelopmental disorders, use of drugs with suspected teratogenic potential, and markers of recent healthcare utilization in the 90 days before LMP including any hospitalization, emergency department visit, and outpatient visits to a neurologist (eTable 5). We adjusted for as many confounders as possible in each data source for cohort-optimized adjusted estimates.

Statistical analysis

Data from Finland (excluding causes of death), Iceland, Norway, and Sweden were individually pooled at the Norwegian Institute of Public Health and analyzed as one cohort. Data from Denmark, the two US

databases, and Australia were each analyzed separately. We described the number of pregnancies with first trimester ASM polytherapy combinations of interest, and the prevalence per 1000 pregnant people with epilepsy in each cohort.

For the comparative safety assessment, our main analyses compared lamotrigine-levetiracetam duotherapy or lamotrigine-topiramate duotherapy with valproate monotherapy. Other combinations of interest including those with zonisimide were considered too rare to include in comparative safety analyses. Our secondary analyses compared low-dose valproate plus lamotrigine or levetiracetam with high-dose valproate monotherapy. We used log-binomial regression to estimate adjusted risk ratios (RRs) and 95% confidence intervals (CIs). Minimally-adjusted estimates included variables for birth year, maternal age, and country in the regression models. Due to the low prevalence of the outcome, we used propensity scores (PS) with fine stratification weights to control for confounding when we included additional confounders. We estimated the PS using logistic regression and included confounders available for the specific dataset in addition to birth year, maternal age, and country (eMethods). In the US MAX database, we carried out a sensitivity analysis restricting the lamotrigine-topiramate duotherapy group to pregnancies meeting a stricter definition of true combination therapy.

The adjusted RRs from each of the five cohorts were combined using fixed-effects meta-analysis to arrive at the final pooled adjusted RR estimate for MCM. In cases in which there were no exposed MCM events in one of the cohorts, the RR could not be estimated and therefore, was not included in the meta-analysis. Due to personal data integrity reasons, cell counts <5 could not be shared or reported for the Nordic countries or Australia, and similarly cells <11 from the US MAX data. For the main analyses, we estimated the approximate absolute risk reduction and confidence intervals by multiplying the pooled adjusted RR and confidence interval limits by the risk of MCM among all of the valproate monotherapy exposed pregnancies in the study.

Data Availability

This was a multi-database study where analyses were carried out in a distributed manner. JMC and RMS had full access to data from Finland, Iceland, Norway and Sweden; SPU and MN had full access to the data from Denmark; KFH and EAS had full access to the data from the US; AS and AH had full access to the data from Australia. These authors jointly take responsibility for the data, analyses, interpretation, and conduct of the research and have the right to publish any and all data with no guidance from the study funders. The Principal Author had access to the results from all cohorts which were statistically pooled and presented in the paper.

Results

We identified 7,796,930 pregnancies that met the inclusion criteria across the five separate cohorts, and of these 50,905 (0.65%) in people with epilepsy (Table 1). The prevalence of epilepsy was highest in the MAX and MUMS cohorts, which generally include more people with disabilities. Among the selected ASM polytherapies, the most prevalent combinations included lamotrigine and levetiracetam, with a total of 788 pregnancies with first trimester use (15 per 1000 pregnancies with epilepsy, ranging from 9 to 24 per 1000 depending on the cohort). The next most prevalent combinations included lamotrigine and topiramate (n=291 total, 6 per 1000 pregnancies with epilepsy), and levetiracetam and topiramate (n=208 total, 4 per 1000 pregnancies with epilepsy). Few used zonisamide in combination with lamotrigine (n=80) or levetiracetam (n=91).

After excluding pregnancies with exposure to teratogenic drugs, or in which one or more infants was diagnosed with a chromosomal/genetic anomaly or teratogenic infection (eTable 6), we compared specific duotherapies with valproate monotherapy (Table 2). In general, use of specific duotherapies increased over time while use of valproate decreased in recent years (eTables 7-11). Few of the pregnancies included in the lamotrigine-topiramate group did not meet the stricter definition of duotherapy tested in preliminary analyses in some of the cohorts: n=<5/65 (<7%) in the Nordic pooled cohort, n=13/56 (23%) in the MAX database, n=2/19 (11%) in MarketScan.

When we compared lamotrigine-levetiracetam duotherapy with valproate monotherapy, the minimally adjusted estimates ranged from RR 0.26 (95% CI 0.12-0.56) to RR 0.61 (0.18-2.13), with an overall pooled estimate of 0.38 (0.23-0.63) (sFigure). When we adjusted for additional confounders, the estimates remained similar, with an overall pooled estimate of 0.41 (0.24-0.69), and an I^2=0.0%, suggesting no heterogeneity in the estimates beyond what is expected due to random error (Figure 1a). The overall risk of MCM among the valproate monotherapy exposed pregnancies in the study was 7.96%, and thus our RR corresponded to an absolute risk reduction of 4.70% (95% CI 2.47-6.05). When we compared lamotrigine-topiramate duotherapy with valproate monotherapy, the minimally adjusted estimates ranged from RR 0.97 (95% CI 0.29-3.27) to RR 1.87 (0.26-13.25), with an overall pooled estimate of 1.12 (0.65-1.94) (sFigure). With adjustment for additional confounders, the estimates remained similar and imprecise, with an overall pooled estimate of 1.26 (0.71-2.23), and an I^2=0.0% (Figure 1b). In the sensitivity analysis in which we compared lamotrigine-topiramate duotherapy group restricted to true combination therapy (n=43) to valproate monotherapy in the MAX database, the adjusted RR increased to 1.29 (0.28-5.88).

Our secondary comparisons were of duotherapies containing low-dose valproate with high-dose valproate monotherapy (Table 3). These were very infrequently used, and we were unable to estimate RRs for two or more cohorts in each analysis. We observed a lower risk of MCM for low-dose valproate and lamotrigine duotherapy versus high-dose valproate monotherapy in the pooled Nordic cohort with a wide confidence interval after minimal adjustment: RR 0.30 (0.09-0.98). However, the other estimates from Denmark (RR 0.72, 0.13-3.97) and MAX (RR 0.98, 0.25-3.87), and overall pooled (RR 0.54, 0.24-1.19) were imprecise. The fully adjusted pooled estimate was most compatible with a 36% reduction in the risk of MCM, but with wide confidence intervals (RR 0.64, 0.28-1.49) (Figure 2a). Similarly for low-dose valproate plus levetiracetam, the estimates were inconclusive (Figure 2b).

Classification of Evidence: This study provides Class II evidence that in people with epilepsy treated in the first trimester of pregnancy, the risk of major congenital malformations is lower with lamotrigine-levetiracetam duotherapy than with valproate alone, but similar with lamotrigine-topiramate.

Discussion

Main findings

In this study by the InPreSS consortium, we analyzed data from almost 7.8 million pregnancies in the five Nordic countries, US, and Australia to assess whether combinations of antiseizure medications may be associated with a lower risk of MCM than valproate alone. Our main finding was that lamotrigine-levetiracetam duotherapy was associated with a lower risk of MCM than valproate monotherapy. This result was consistent across the separate analyses and the final pooled result had a relatively narrow confidence interval which ranged from 31% to 75% lower risk of MCM. Our results did not favor lamotrigine-topiramate duotherapy over valproate monotherapy. Findings were inconclusive for the comparison of combinations of low-dose valproate plus lamotrigine or levetiracetam with high-dose valproate monotherapy but suggested a reduced risk.

Results in the context of prior studies

Our results are in line with prior research that supports the safety of lamotrigine and levetiracetam during pregnancy with regard to risk of MCM.[13, 29, 32, 33] However, there have been very little data published about the safety of the combination of the two drugs; a network meta-analysis published in 2017 found just six exposed pregnancies in the literature.[33] A study from the Australian Pregnancy Register published in 2018 found no major malformations among 50 pregnancies with use of lamotrigine and levetiracetam, of which 36 used only those two ASMs.[17] Given the link between MCM risk and adverse neurodevelopmental outcomes for ASMs, a recent Nordic-wide study provides additional support for the safety of lamotrigine and levetiracetam monotherapy and combined in duotherapy (n=414) with regards to risk of autism spectrum disorder and intellectual disability.[34] Our study did not compare lamotrigine-levetiracetam duotherapy with an unexposed reference group as we did not think this was a clinically relevant comparison, and risked confounding by indication. We therefore can conclude that the combination is

associated with a lower risk of MCM than valproate monotherapy, but we cannot rule out a possible increase in the risk of MCM compared with no ASM treatment (unlikely to be a treatment option for women with epilepsy that requires duotherapy) or monotherapy of either treatment.

Our finding that lamotrigine-topiramate duotherapy was not associated with a lower risk of MCM than valproate monotherapy was not surprising, given accumulating evidence that topiramate is teratogenic.[15, 26] Further, it is consistent with earlier findings that polytherapy combinations containing either valproate or topiramate were associated with a higher risk of MCM than polytherapy without either drug.[17, 35] Two recently published Nordic studies reported increased risks of similar magnitude for topiramate and valproate for the outcomes MCM and neurodevelopmental disorders.[29, 34] However, the number of pregnancies exposed to topiramate was much lower than that for valproate in both of these studies, which resulted in less precise effect estimates. Lamotrigine-topiramate duotherapy was infrequently used and this limited our ability to make firm conclusions regarding comparative safety.

Strengths and limitations

One of the key strengths of the study was the combination of data/databases from multiple countries to assemble a large cohort in which the pregnancies among people with epilepsy were identified. This enhanced both the study size and the generalizability of our findings. Our descriptive results highlight the difficulty of studying the safety of specific ASM polytherapies as each combination is infrequently used. We used a common protocol with country-optimized definitions of important study variables and confounder adjustment to generate high-quality, valid estimates from each cohort that could be combined for an overall estimate with higher precision. Despite this, the infrequent use of specific combinations of drugs limited the possibility of sharing some results due to restrictions for data privacy, of making firm conclusions for some of the comparisons, and to estimate narrow confidence intervals. For Finland, Iceland, Norway, and Sweden, we had the possibility to individually pool the data and therefore, it could be informative if there were exposed pregnancies with no outcomes in one country.

A limitation of the study is that we had to assume that filled prescriptions in first trimester equated to actual use of the medication. People with epilepsy are less likely to discontinue ASMs in pregnancy than those who use ASMs for other indications.[24] We restricted the study to pregnancies in people with epilepsy to control for confounding by indication and reduce exposure misclassification. In the case of duotherapy, we further had to assume that fills for two different drugs implied use of both drugs concurrently rather than switching. However, our preliminary analyses were reassuring that most we defined as using lamotrigine-topiramate duotherapy in first trimester used both drugs at the same time. We also only defined use based on prescriptions filled during the first trimester, instead of also including additional prescriptions from before LMP that may have overlapped the first trimester to reduce the risk of bias toward a null association.[36] We could not assess all medications that can be effective for generalized epilepsies since some were too rarely used. As in most observational studies, residual confounding cannot be entirely ruled out. For example, we adjusted for dispensed folic acid, but this does not capture the majority of folic acid supplementation in pregnancy since it is available over the counter. Results require replication in other cohorts, though our study shows this is only feasible for very large cohorts.

Other treatment considerations

We could not compare the efficacy or tolerability of the treatments in this study. Randomized controlled trials and dedicated pregnancy exposure registries (e.g. North America AED Pregnancy Registry, EURAP, Australian Pregnancy Registry) record more detailed clinical information about type of epilepsy, seizure frequency, and side effects. These data sources are therefore better suited to study effectiveness and tolerability than large healthcare databases. The SANAD study concluded that valproate was the most effective treatment for generalized epilepsy after comparing valproate, topiramate, and lamotrigine monotherapies.[37] A single arm study of levetiracetam suggested it may be an effective first-line treatment in female patients in whom valproate should be avoided.[38] However, the SANAD II study concluded that levetiracetam monotherapy is not as effective for seizure control or as cost effective as valproate for newly diagnosed generalized epilepsy.[39] While lamotrigine or levetiracetam monotherapy may be effective at

seizure control in a substantial proportion of patients with generalized epilepsy, patients with insufficient control on monotherapy who need to avoid valproate may consider a combination of these drugs. A case-control study identified lower odds of SUDEP in those treated with polytherapy instead of monotherapy, particularly drug combinations containing lamotrigine, levetiracetam, and valproate.[40] Recently, a panel of Italian epileptology experts recommended using levetiracetam and lamotrigine as first-line treatments in generalized epilepsy to avoid using valproate in people who may become pregnant.[41] Pregnancies with use of lamotrigine and levetiracetam in polytherapy had the highest proportion seizure-free before and during pregnancy among the polytherapy combinations assessed in the Australian Pregnancy Registry.[17] Therefore, while neither drug may have similar efficacy to valproate individually in treatment of generalized epilepsy, polytherapy may offer improved efficacy.

Conclusions

Relevant polytherapy alternatives to valproate are rarely used in the first trimester. Using lamotrigine-levetiracetam duotherapy in first trimester was associated with a 60% lower risk of MCM than valproate monotherapy. Lamotrigine-topiramate duotherapy was not associated with a lower risk. Results were inconclusive for duotherapies containing low-dose valproate compared to high-dose valproate monotherapy but suggested a reduced risk. Given our results and the previous literature, therapies containing topiramate in monotherapy or polytherapy would not be a safer alternative to valproate with respect to the risk of fetal harm. Duotherapy with lamotrigine and levetiracetam for the treatment of epilepsy in people of childbearing potential may be favored over valproate with respect to the risk of MCM, but whether this combination is as effective as valproate for seizure control remains to be determined.

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Disclosures

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Tables

Table 1. Descriptive results. Total number of pregnancies in the study population before and after restricting to epilepsy, and the number of users of specific combinations of antiseizure medications in first trimester of pregnancy

	All Cohorts	**Finland 2001-2016, Iceland 2004-2017, Norway 2005-2020, Sweden 2006-2019**	**Denmark, 2000-2017**	**Medicaid Analytic Extract, United States 2000-2014**	**IBM MarketScan, United States 2003-2015**	**MUMS, New South Wales, Australia 2006-2012**
Total pregnancies, N	7,796,930	3,376,948	1,069,676	1,889,352	1,313,258	147,696
Restricted to epilepsy, n (%)	50,905 (0.65%)	14,514 (0.43%)	4696 (0.44%)	23,319 (1.23%)	6933 (0.53%)	1443 (0.98%)
First trimester use, N (per 1000 with epilepsy)[a]						
Lamotrigine and levetiracetam	788 (15)	354 (24)	108 (23)	213 (9)	97 (14)	16 (11)
Lamotrigine and topiramate	291 (6)	88 (6)	53 (11)	99 (4)	34 (5)	17 (12)
Levetiracetam and topiramate	208 (4)	52 (4)	11 (2)	107 (5)	33 (5)	5 (3)
Lamotrigine and zonisamide	80 (2)	23 (2)	5 (1)	38 (2)	14 (2)	0 (0)
Levetiracetam and zonisamide	91 (2)	21 (1)	6 (1)	52 (2)	12 (2)	0 (0)

[a]Treatment may have also included additional ASMs

Table 2: Number and percent of pregnancies with a major congenital malformation for valproate monotherapy, lamotrigine-levetiracetam duotherapy, and lamotrigine-topiramate duotherapy

Database	Valproate monotherapy		Lamotrigine-levetiracetam duotherapy		Lamotrigine-topiramate duotherapy	
	Total, N	MCM, n (%, 95% CI)	Total, N	MCM, n (%)[a]	Total, N	MCM, n (%)[a]
Denmark	216	16 (7.4, 4.3-11.8)	86	<5 (-%)	39	<5 (-%)
Nordic[b]	1064	77 (8.2, 5.8-9.0)	281	8 (2.8)	61	7 (11.5)
MAX	488	38 (7.8, 5.6-10.5)	132	<11 (-%)	56	<11 (-%)
MKSN	73	8 (11.0, 4.9-20.4)	76	3 (3.9)	19	0
MUMS	118	7 (5.9, 2.4-11.8)	12	0	11	<5 (-%)
All cohorts	1959	156 (8.0, 6.8-9.3)	587	-	186	-

Footnote: CI=Confidence Interval, MAX=Medicaid Analytic eXtract database, MKSN=Marketscan database, MCM=major congenital malformation, MUMS= Maternal Use of Medications and Safety database from New South Wales, Australia

[a]Small cell counts cannot be published and thus limited calculation of the exact percent and sum of the total for all cohorts. [b]Nordic refers to the pooled database containing pregnancies from Finland, Iceland, Norway, and Sweden

Table 3: Number and percent of pregnancies with a major congenital malformation for high-dose valproate monotherapy (≥1000 mg per day), low-dose valproate (<1000 mg per day) plus lamotrigine, and low-dose valproate (<1000 mg per day) plus levetiracetam

Database	High-dose valproate monotherapy		Low-dose valproate + lamotrigine duotherapy		Low-dose valproate + levetiracetam duotherapy	
	Total, N	MCM, n (%)[a]	Total, N	MCM, n (%)[a]	Total, N	MCM, n (%)[a]
Denmark	58	<5 (-%)	33	<5 (-%)	7	0
Nordic[b]	387	46 (11.9)	75	<5 (-%)	37	<5 (-%)
MAX	260	25 (9.6)	22	<11	12	<11
MKSN	35	6 (17.1)	5	0	4	0
MUMS	42	<5 (-%)	<5	0	<5	0
All cohorts	782	-	≥136	-	≥61	-

Footnote: MAX=Medicaid Analytic eXtract database, MKSN=Marketscan database, MCM=major congenital malformation, MUMS= Maternal Use of Medications and Safety database from New South Wales, Australia

[a]Small cell counts cannot be published and thus limited calculation of the exact percent and sum of the total for all cohorts. [b]Nordic refers to the pooled database containing pregnancies from Finland, Iceland, Norway, and Sweden.

Figure Titles and Legends

Figure 1. Forest plots showing adjusted risk ratios and the overall pooled risk ratios from the meta-analysis of a) lamotrigine-levetiracetam duotherapy, b) lamotrigine-topiramate duotherapy versus valproate monotherapy and the risk of major congenital malformations

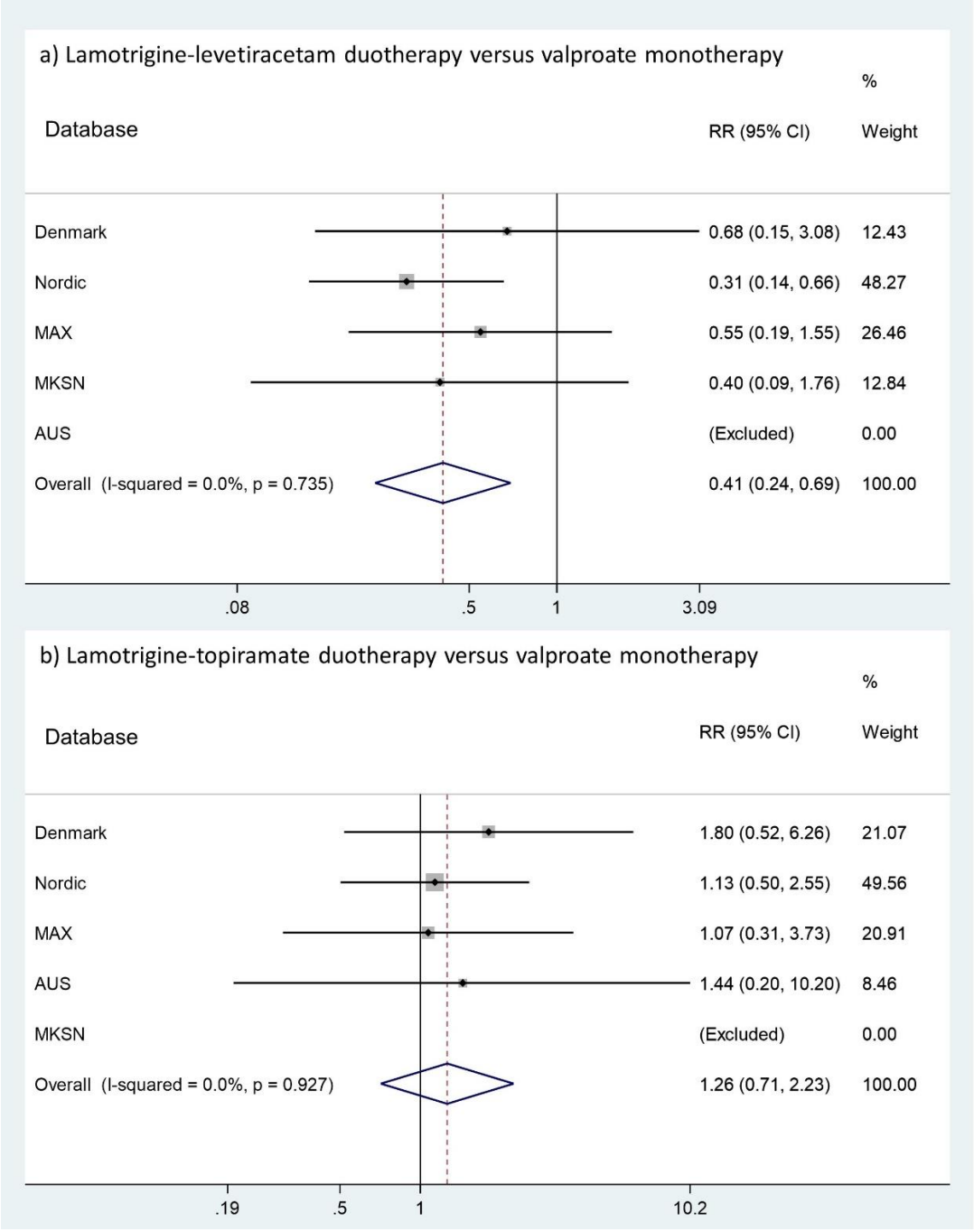
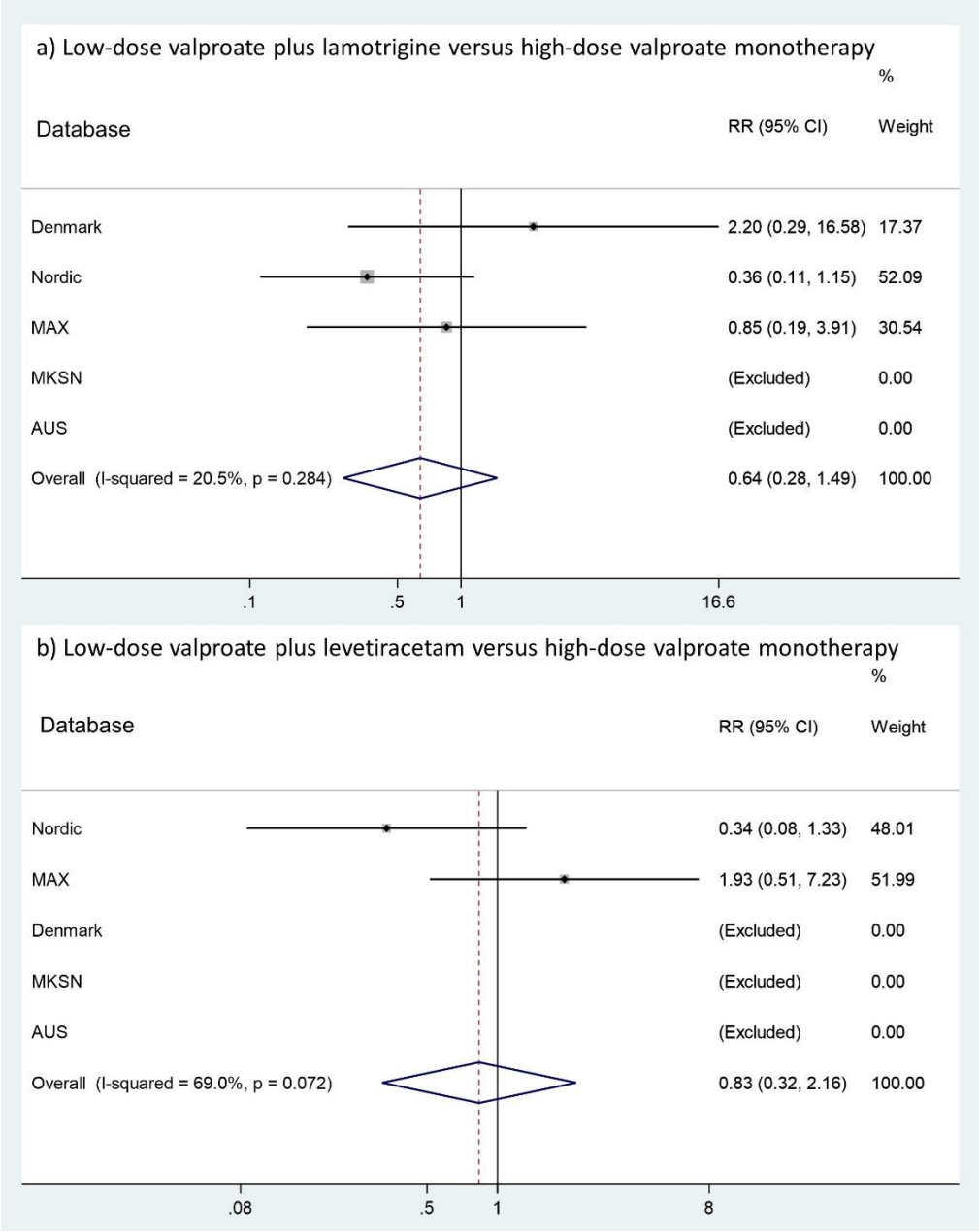


Figure 2. Forest plots showing adjusted risk ratios and the overall pooled risk ratios from the meta-analysis of a) low-dose valproate plus lamotrigine, b) low-dose valproate plus levetiracetam versus high-dose valproate (≥1000 mg) monotherapy and the risk of major congenital malformations. For low-dose valproate plus levetiracetam versus high-dose valproate, only the minimally adjusted estimates are shown. The fully adjusted estimate was only available for the pooled Nordic cohort, RR 0.40 (95% CI 0.09-1.74).



Supplementary material

eTable 1: Ethical boards providing approval for data use & approval numbers

Country	Ethical Board	Approval Number
Denmark	No Ethical Board approval needed. The study is reported to the Danish Data Protection Agency through registration at Aarhus University	KEA-2016051-000001/ 1833
Finland	No Ethical Board approval needed	THL/1551/6.02.00/2018, THL/1673/5.05.00/2019, KELA 117/522/2019
Iceland	National Bioethics Committee	VSNb2018060017/03.01
Norway	Regional Committee for Medical Research Ethics South/East Norway The Norwegian Data Inspectorate in Norway	2017/2546/REC South-East 17/02068/Norwegian Data Inspectorate
Sweden	Swedish Ethical Review Authority (Etikprövningsmyndigheten)	DNR 2015/1826-31/2, 2017/2238-32, 2018/1790-32, 2018/2211-32
USA	Brigham and Women's Hospital Institutional Review Board	2017P002780
Australia	New South Wales Population and Health Services Research Ethics Committee Australian Institute of Health and Welfare Ethics Committee	2012/06/397 EC 2012/2/22

eTable 2: Description of the data sources and codes used to define epilepsy in the different countries

Country	Time window	Data source	Codes
Norway	LMP-90 to birth	Norwegian Prescription Database	Drug dispensing of ATC code N03A with reimbursement codes N88 (ICPC-2), G40 (ICD-10), 7 (reimbursement code defined by the Norwegian Medicines Agency)
Finland	LMP to birth	Special Refund Entitlement Register	Indication codes 111, 181, 182, 183, 199 (SVA3)
Denmark, Iceland, Sweden	LMP-365 to birth	National Patient Register	ICD-10 codes G40, G41
US	LMP-90 to birth	Inpatient or outpatient visit claims	ICD-9 codes 345.xx, 780.3x (excluding 780.31, 780.32), 649.4x
Australia	All available history to birth	Hospital discharge summary	ICD-10-AM G40, G41

eTable 3: Teratogenic drugs for exclusion criteria

Drug name*	**ATC code**
Warfarin	B01AA03
Antineoplastic agents	L01
Isotretinoin	D10BA01 (oral), D10AD04 (topical), D10AD54 (combinations, topical)
Systemic retinoids for psoriasis, dermatitis	D05BB, D11AH04
Misoprostol	A02BB01, G02AD06, M01AE56, M01AB55 (misoprostol+diclofenac)
Thalidomide	L04AX02
Methotrexate (low dose)	L04AX03

*In US claims data, these drugs were identified by their generic names (warfarin, actinomycin, busulfan, chlorambucil, cyclophosphamide, doxorubicin, mercaptopurine, methotrexate, vinblastine, vincristine, isotretinoin, misoprostol, thalidomide)

eTable 4: Definition of major congenital malformations

	Denmark, Iceland, Norway, Sweden	Finland	US	Australia
Basis for definition	EUROCAT	EUROCAT	CDC	EUROCAT
Data source(s)	National health registers - birth, patient*, cause of death	Register of Congenital Malformations	Inpatient and outpatient** claims	Hospitalization admission records
Time window	1 year	1 year	3 months	18 months
Type of codes	ICD-10	ICD-9A	ICD-9-CM	ICD-10-AM, ACHI procedure codes
Teratogenic infection	P350, P351, P371,	7710, 7711, 77121,	771.0, 771.1	P35.0, P35.1, P35.2
Congenital malformation syndromes	D821, Q751, Q754, Q87,	27911, 75581, 75604, 7598 except 75989	279.11, 756.0, 759.8x	D82.1, Q87.04, Q87.06, Q87.09, Q87.12, Q87.13, Q87.14, Q87.17, Q87.19, Q87.21, Q87.22, Q87.27, Q87.31, Q87.32, Q87.4, Q87.5, Q87.82, Q87.84, Q87.86, Q87.87, Q87.89 Q87.00, Q87.02, Q87.03, Q87.07, Q87.08, Q87.11, Q87.15, Q87.16, Q87.18, Q87.23, Q87.24, Q87.25, Q87.26, Q87.81, Q87.83, Q87.85, Q87.88
Chromosomal anomalies	Q90-Q99 except Q95	758 except 7584	758.0-758.3, 758.5-758.9	Q90.9, Q91.0, Q91.3, Q91.5, Q91.7, Q92.8, Q92.9, Q93.3, Q93.4, Q93.5, Q93.8, Q96.3, Q96.4, Q96.8, Q96.9, Q97.0, Q97.3, Q98.0, Q98.1, Q98.4, Q99.1, Q99.8, Q99.9, Q90.0, Q90.1, Q90.2, Q91.1, Q91.2, Q91.4, Q91.6, Q92.1, Q92.3, Q92.5, Q92.6, Q92.7, Q92.71, Q93.1, Q93.2, Q93.7, Q93.9, Q96.0, Q96.1, Q97.1, Q97.2, Q97.8, Q98.5, Q98.6, Q98.7, Q98.8, Q98.9, Q99, Q99.0, Q99.2
Nervous system	Q00-Q07	740-742 except 74280	740.xx-742.xx	Q00.09, Q01.0, Q01.2, Q01.81, Q01.89, Q01.9, Q02, Q03.0, Q03.1, Q03.8, Q03.9, Q04.01, Q04.09, Q04.2, Q04.33, Q04.34, Q04.35, Q04.39, Q04.4, Q04.5, Q04.60, Q04.8, Q04.9, Q05.11, Q05.20, Q05.22, Q05.40, Q05.60, Q05.70, Q05.71, Q05.72, Q05.80, Q05.81, Q05.82, Q05.90, Q05.92, Q06.1, Q06.2, Q06.8, Q06.9, Q07.0, Q07.89, Q07.9, Q01.1, Q01.82, Q01.83, Q03.01, Q03.81, Q04.00, Q04.1, Q04.31, Q04.36, Q05.00, Q05.10, Q05.12, Q05.21, Q05.30, Q05.31, Q05.32, Q05.41, Q05.42, Q05.50, Q05.52, Q05.61, Q05.62, Q06.4, Q07.81
Eye	Q10-Q15 except Q101-	743 except 74345, 74361-74363, 74365	743.xx (exclude if only	Q07.82, Q10.4, Q11.1, Q11.2, Q11.3, Q12.0, Q13.0, Q13.2, Q13.4, Q13.5, Q13.8, Q13.9, Q14.0, Q14.1, Q14.2,

	Q103, Q105, Q135		743.6x and 743.8x)	Q14.3, Q14.8, Q15.0, Q15.8, Q15.9, Q11.0, Q12.2, Q12.3, Q12.8, Q13.1, Q13.3, Q13.41, Q13.49
Ear			744.xx (exclude if only 744.1x, 744.21, 744.29, and 744.4x-744.9x)	
Ear, face, and neck	Q16-Q18 Except Q170-Q175, Q179, Q180-Q182, Q184-Q187, Q189	744 Except 7441, 74420-74424, 74430, 7444, 74480-74483, 7449		Q16.1, Q16.4, Q16.5, Q16.9, Q17.8, Q17.9, Q16.0, Q16.2, Q16.3
Cardiac	Q20-Q26 Except Q246, Q250 and preterm, Q256 and preterm, Q261	745, 746, 7470-7474 Except 74550, 74687, 7470 and preterm 74723, 747325 and preterm, 74741, 74749	745.0x, 745.1x, 745.2x, 745.3x, 745.4x, 745.5x AND no preterm, 745.6x, 746.00, 746.01, 746.09, 746.1x, 746.2x, 746.83, 747.3x AND no preterm, 746.02 AND no preterm, 747.1x, 747.2x, 746.3x, 746.5x, 746.7x, 746.81, 746.82, 746.84, 747.0x AND no preterm, (416.0x or 747.83) AND no preterm, 747.4x, 745.7x, 745.8x, 746.8, 746.85-746.87, 746.89, 745, 745.9, 746, 746.9x (exclude if only 746.99), 747	
Cardiovascular				Q20.0, Q20.1, Q20.3, Q20.4, Q20.5, Q20.8, Q20.81, Q20.89, Q21.00, Q21.01, Q21.02, Q21.09, Q21.10, Q21.11, Q21.12, Q21.19, Q21.2, Q21.20, Q21.3, Q21.4, Q21.8, Q21.9, Q22.0, Q22.1, Q22.3, Q22.42, Q22.5, Q22.6, Q22.8, Q22.9, Q23.01, Q23.02, Q23.21, Q23.22, Q23.4, Q23.8, Q23.9, Q24.0, Q24.1, Q24.2, Q24.3, Q24.4, Q24.5, Q24.9, Q25.1, Q25.10, Q25.2, Q25.3, Q25.4, Q25.43, Q25.5, Q25.6, Q25.7, Q25.8,

				Q26.2, Q26.3, Q26.9, Q27.1, Q27.3, Q27.8, Q27.9, Q28.2, Q28.3, Q28.9, Q20.2, Q20.30, Q20.31, Q20.40, Q20.41, Q20.42, Q20.49, Q20.50, Q20.59, Q20.82, Q21.0, Q21.03, Q21.1, Q21.13, Q21.21, Q21.22, Q21.24, Q21.29, Q21.83, Q22.30, Q22.31, Q22.39, Q22.4, Q22.41, Q22.81, Q22.82, Q23.0, Q23.2, Q23.81, Q23.82, Q23.83, Q24.83, Q24.86, Q24.87, Q25.11, Q25.12, Q25.13, Q25.19, Q25.30, Q25.31, Q25.39, Q25.40, Q25.44, Q25.47, Q25.49, Q25.70, Q25.79, Q26.01, Q26.02, Q26.4, Q26.5, Q26.8, Q26.81, Q28.0, Q28.1, Q28.30, Q28.31, Q28.39
Other vascular			747.6x-747.9x (exclude if only 747.83)	
Respiratory	Q30, Q32-Q34 Except Q301-Q309, Q320, Q322, Q331, Q336	748 Except 7481, 7482-7483 (other), 74840, 74851, 74859, 74862	748.xx (exclude if only 748.1x)	Q30.0, Q30.02, Q30.2, Q30.8, Q30.9, Q31.0, Q31.1, Q31.8, Q32.1, Q32.4, Q33.01, Q33.2, Q33.8, Q33.9, Q34.8, Q34.9, Q30.01, Q30.1, Q31.2, Q32.3, Q33.3, Q34.0
Oro-facial clefts	Q35-Q37 Except Q357, or if occurring with Q00, Q042	749 Except 74908, or if occurring with 740, 74226	749.0x 749.1x 749.2x	
Digestive system	Q38-Q45, Q790 Except Q381, Q382, Q400, Q401, Q430, Q444	750, 751, 7566 Except 75000, 75011-75013, 75024, 75050, 75051, 7506, 75101, 7513, 75166	750.xx-751.xx (exclude if only 750.0x, 750.1x, 750.50, 751.0x)	
Gastrointestinal				Q35.1, Q35.11, Q35.12, Q35.3, Q35.30, Q35.31, Q35.32, Q35.5, Q35.9, Q36.0, Q36.1, Q36.9, Q37.0, Q37.1, Q37.2, Q37.3, Q37.4, Q37.5, Q37.8, Q37.9, Q38.3, Q38.4, Q38.5, Q38.6, Q38.8, Q39.0, Q39.11, Q39.12, Q39.19, Q39.21, Q39.3, Q40.2, Q40.3, Q41.0, Q41.01, Q41.1, Q41.2, Q41.9, Q42.1, Q42.20, Q42.21, Q42.22, Q42.29, Q42.3, Q42.8, Q42.9, Q43.10, Q43.11, Q43.12, Q43.19, Q43.31, Q43.32, Q43.39, Q43.5, Q43.6, Q44.1, Q44.2, Q44.3, Q44.5, Q44.71, Q44.79, Q45.1, Q45.39, Q35.10, Q35.13, Q35.33, Q38.02, Q38.32, Q38.52, Q38.59, Q39.10, Q39.13, Q39.14, Q39.15, Q39.22, Q39.4, Q40.23,

				Q40.25, Q40.29, Q40.8, Q41.02, Q41.11, Q41.12, Q41.13, Q41.21, Q41.22, Q41.8, Q41.81, Q42.01, Q42.02, Q42.03, Q42.04, Q42.09, Q43.13, Q43.4, Q43.7, Q44.0, Q44.7, Q45.0, Q45.31, Q45.83
Abdominal wall	Q792, Q793, Q795	75670, 75671, 75679		
Genital	Q50-Q56 Except Q501, Q502, Q505, Q523, Q525, Q527, Q53, Q544	752 Except 75208, 75211, 75243, 75244, 7525, 75261 (urinary), 752621, 75282, 75286	752.xx (exclude if only 752.42, 752.52) (in addition, exclude 752.5x if preterm)	
Urinary	Q60-Q64, Q794 Except Q610, Q627, Q633	75261, 753, 75672 Except 75310, 75334, 753485	753.xx (exclude if only 753.7x)	
Genitourinary				Q50.00, Q51.3, Q52.2, Q52.6, Q52.7, Q52.8, Q52.9, Q53.0, Q54.0, Q54.1, Q54.2, Q54.3, Q54.4, Q54.8, Q54.9, Q55.00, Q55.01, Q55.02, Q55.1, Q55.22, Q55.29, Q55.4, Q55.5, Q56.4, Q60.0, Q60.2, Q60.3, Q60.4, Q60.5, Q60.6, Q61.1, Q61.3, Q61.40, Q61.41, Q61.42, Q61.8, Q62.0, Q62.11, Q62.14, Q62.18, Q62.2, Q62.31, Q62.32, Q62.34, Q62.39, Q62.51, Q62.59, Q62.62, Q62.8, Q63.01, Q63.11, Q63.9, Q64.0, Q64.19, Q64.21, Q64.31, Q64.32, Q64.75, Q64.79 Q51.0, Q51.1, Q51.2, Q51.5, Q51.7, Q51.8, Q52.0, Q52.1, Q52.41, Q53.00, Q53.02, Q53.03, Q53.09, Q55.40, Q55.41, Q55.42, Q55.43, Q56.0, Q56.1, Q56.41, Q60.1, Q61.2, Q61.43, Q61.44, Q61.45, Q62.12, Q62.13, Q62.17, Q62.19, Q62.30, Q62.35, Q62.60, Q62.61, Q62.63, Q62.69, Q63.09, Q63.12, Q63.19, Q64.11, Q64.20, Q64.22, Q64.33, Q64.34, Q64.39, Q64.5, Q64.51, Q64.73, Q64.74, Q64.76 Undescended testes: presence of an ICD10AM code: Q53.19, Q53.29, Q53.99, Q53.1, Q53.10, Q53.11, Q53.12, Q53.13, Q53.2, Q53.20, Q53.21, Q53.22, Q53.23, Q53.9, Q53.90, Q53.91, Q53.92, Q53.93

				and an ACHI procedure: 37803-00, 37803-01 (repair of undescended testes)
Limb	Q66-Q74 Except Q661-Q669, Q670-Q678, Q680, Q683, Q684, Q685	754-755 Except 7540-7542 (other), 7543, 75440-75443, 75451-75453, 75459, 7546, 7547, 75480-75482, 755525, 755606, 755616, 755645, 755646, 75566, 75581 (genetic)	755.xx (exclude if only 755.65)	
Musculoskeletal			754.xx and 756.xx (exclude if only 754.3x, 754.81, 754.82, 756.2x)	Q65.0, Q65.1, Q65.2, Q65.3, Q65.4, Q65.60, Q65.61, Q65.62, Q67.49, Q67.59, Q67.6, Q67.7, Q67.8, Q68.1, Q69.0, Q69.1, Q69.21, Q69.29, Q69.9, Q70.0, Q70.2, Q70.4, Q70.9, Q71.1, Q71.31, Q71.32, Q71.33, Q71.4, Q71.5, Q71.8, Q71.9, Q72.31, Q72.4, Q72.6, Q72.7, Q72.8, Q72.9, Q73.89, Q74.07, Q74.09, Q74.3, Q75.01, Q75.02, Q75.03, Q75.04, Q75.09, Q75.1, Q75.81, Q75.89, Q75.9, Q76.39, Q76.42, Q76.43, Q76.45, Q76.61, Q76.62, Q76.69, Q76.71, Q76.79, Q77.1, Q77.2, Q77.4, Q77.7, Q78.0, Q78.8, Q78.89, Q79.0, Q79.1, Q79.2, Q79.3, Q79.4, Q79.5, Q79.6, Q79.8, Q79.9, Q71.12, Q71.2, Q71.41, Q72.0, Q72.2, Q72.32, Q72.33, Q74.04, Q74.4, Q74.85, Q75.05, Q75.06, Q75.4, Q76.1, Q76.21, Q76.31, Q76.33, Q76.34, Q76.41, Q76.46, Q77.02, Q77.03, Q77.3, Q77.6, Q77.82, Q78.1, Q78.2, Q78.5, Q78.82, Q79.11, Q79.12, Q79.84 Talipes: presence of an ICD10AM code: Q66.0, Q66.00, Q66.01, Q66.02, Q66.1, Q66.4 and an ACHI procedure: 49718-01, 49724-00, 49724-01, 49727-00, 50321-00, 50324-00, 50324-01, 50327-00 (for repair of talipes)
Integumentary				D18.1, Q80.9, Q81.8, Q81.9, Q82.1, Q82.3, Q83.1, Q83.8, Q83.9, Q84.0, Q84.3, Q84.81, Q85.1, Q85.81, Q85.8, Q80.0, Q80.1, Q80.2, Q80.3, Q80.4, Q80.8, Q81.0, Q81.1, Q81.2, Q82.0, Q82.81, Q82.82, Q83.2, Q85.84

Situs inversus				Q89.30, Q89.31, Q89.39, Q89.32, Q89.33, Q89.34, Q89.35
Congenital due to specified exogenous causes***				Q86.0, Q86.1, Q86.81, Q86.82, Q86.85, Q86.89
Other	Q27, Q28, Q31, Q75-Q85, Q89 Except Q270, Q314, Q751 (genetic), Q752, Q753, Q754 (genetic), Q760, Q790 (digestive), Q792 (abdominal wall), Q793 (abdominal wall), Q794 (urinary), Q795 (abdominal wall), Q825, Q828, Q833, Q845, Q846, Q899	7475-7479, 7482-7483, 7540-7542, 756, 757, 759 Except 7475, 74836, 7540, 7541, 75421, 75604 (genetic), 756085, 75610, 7562, 75630, 75632, 75633, 7566 (digestive), 75670 (abdominal wall), 75671 (abdominal wall), 75672 (urinary), 75679 (abdominal wall), 75686, 7572, 7573, 75751, 75758, 75765, 75902, 75904, 75911, 7598 (genetic), 7599	757.xx; 759.xx (exclude if only 757.2-757.6, 759.81-759.83)	E03.0, E03.1, E70.0, E70.1, E84.0, E84.1, E84.8, E84.9, P83.2, Q20.6, Q89.01, Q89.09, Q89.12, Q89.19, Q89.21, Q89.26, Q89.29, Q89.79, Q89.89, Q89.9, D21.5, Q89.00, Q89.02, Q89.05, Q89.10, Q89.11, Q89.14, Q89.22, Q89.25, Q89.81, Q89.82

Blank cells indicate that the category was not used in that particular the data source. *When an MCM was only diagnosed in the outpatient setting, we required at least two MCM diagnoses within the same organ system to be recorded during separate visits. **Required at least two MCM diagnoses within the same organ system to be recorded during separate visits unless the infant died or had a corrective procedure code. *******Neither included nor excluded in the Nordic countries' analyses to avoid excluding congenital malformations attributed to the drugs in question.

eTable 5: Covariate definitions

Covariate	Look-back window	Definition	Categories	Notes
Calendar year of delivery	n/a	As recorded in MBR (Nordic), perinatal data collection (NSW), or claims database (US)	Not predefined	Analyzed as categorical due to incomplete overlap in study years in pooled data
Maternal age at delivery	n/a	As recorded in MBR, perinatal data collection, or claims database	<20 20-24 25-29 30-34 (ref) 35-39 ≥40	Analyzed as categorical to account for the increased risk of major congenital malformations in the youngest and oldest
Parity	n/a	As recorded in MBR or perinatal data collection	0 (ref) 1 2+	US MAX: multipara or not US MarketScan: not available
Multiple gestation	n/a	As recorded in MBR, perinatal data collection, or claims database	Yes No	US MAX and MarketScan used ICD-9-CM codes from delivery: V27.2-V27.6, V31-V37, 651, 652.6x, 660.5x, 662.3x, 761.5x, 651.3x
Maternal education	pregnancy	Highest achieved education	Compulsory education Secondary education University education Post-graduate Missing	Finland: not available in pooled dataset US, Australia: not available
Relationship status/ cohabitation with partner	pregnancy	As recorded in MBR or perinatal data collection	Yes No Missing	Denmark: only possible to include married and registered partnerships US: not available
Body Mass Index (BMI) in early pregnancy	n/a	As recorded in MBR, or calculated from maternal weight and height at first antenatal visit (kg/m^2)	Underweight <18.5 Normal 18.5 to <25 (ref) Overweight 25 to <30 Obese ≥30 Missing	Denmark: nearly complete from 2004 Finland: available since 2004 Iceland: available since 2012 Norway: available since 2006 with a lot of missing (expected to be missing completely at random, based on when hospitals updated their IT systems) US: obese/overweight or not (based on ICD-9-CM codes 278.0x, 649.1x, V85.3, V85.4) Australia: not available

Smoking, early pregnancy	n/a US: LMP-90 to LMP+90	As recorded in MBR or perinatal data collection	Yes No Missing	Iceland: not available US: smoking or not based on ICD-9-CM and CPT codes (ICD-9-CM: 305.1x, 649.0x, 989.84, V15.82; CPT: 99406, 99407, C9801, C9802, G0375, G0376, G0436, G0437, G8453, G9458, G9906, S9075, S9453)
High-dose folic acid	LMP-90 to LMP+97 US: LMP-90 to LMP+90	PDR (Nordic), PBS (NSW), or prescription claims (US): ATC code B03BB01	Yes No	Finland: not available US: generic drug names used instead of ATC codes
Pre-existing diabetes	LMP-90 to birth US: LMP-90 to LMP+90	Recorded in MBR or NPR, hospital admission record (NSW), or claims database (US): E10-E14, O24.0, O24.1, O24.2, O24.3, (US: 250.x, 648.0x, V58.67)	Yes No	Norway: MBR includes check-box
Psychiatric and neurodevelopmental disorder	LMP-90 to birth US: LMP-90 to LMP+90	Recorded in MBR or NPR: F10-F99 (US 295.xx - 319.xx)	Yes No	
Use of drugs with suspected teratogenic potential during first trimester	LMP-90 to LMP+97 US: LMP-90 to LMP+90	PDR, PBS, or prescription claims: ATC codes A) Drugs acting on the renin-angiotensin system including ACE inhibitors, ARBs, RAS-acting (C09) B) Anti-thyroid drugs (H03B) C) Immunosuppresive drugs (L04AA06 mycophenolic acid, L04AA13 leflunomide, L04AA31 teriflunomide) E) Thalidomide-related drugs (L04AX04 lenalidomide, L04AX06 pomalidomide)	Yes No	US: generic drug names used instead of ATC codes

		F) Ergot alkaloids (N02C)		
Recent healthcare utilization before pregnancy variables				
Any hospitalization	LMP-90 to LMP-1			
Any ER visit	LMP-90 to LMP-1			Nordic: only available for Sweden as unplanned hospitalization Australia: not available
Outpatient visit to neurologist	LMP-90 to LMP-1	NPR outpatient visit with G40 diagnosis code		Australia: not available US: outpatient visits with Dx of epilepsy

Abbreviations: Anatomical Therapeutic Chemical, ATC; last menstrual period, LMP; medical birth register, MBR; national patient register, NPR; New South Wales, NSW; Pharmaceutical Benefits Scheme (PBS), prescribed drug register, PDR;

eTable 6: Total number of pregnancies in the source cohorts, and number meeting the inclusion and exclusion criteria

	Finland 2001-2016, Iceland 2004-2017, Norway 2005-2020, Sweden 2006-2019	Denmark, 2000-2017	Medicaid Analytic Extract, United States 2000-2014	IBM MarketScan, United States 2003-2015	MUMS, New South Wales, Australia 2006-2012
Total pregnancies	3,376,948	1,069,676	1,889,352	1,313,258	147,696
Restricted to epilepsy	14,514 (0.43%)	4696 (0.44%)	23,319 (1.23%)	6933 (0.53%)	1443 (0.98%)
Excluded - known teratogenic drug exposure	53	14	75	15	0
Excluded - chromosomal anomaly or teratogenic infection	55	25	245	80	<5
Reference 1: Valproate motherapy	1064	216	488	73	118
Lamotrigine + levetiracetam duotherapy	281	86	132	76	12
Lamotrigine + topiramate duotherapy	61	39	56	19	11
Reference 2: Valproate monotherapy (≥ 1000 mg/day)	387	58	260	35	42
Valproate <1000 mg/day + lamotrigine duotherapy	75	33	22	5	<5
Valproate <1000 mg/day + levetiracetam duotherapy	37	7	17	<5	<5

eTable 7: Characteristics of pregnancies in Denmark in which valproate monotherapy, lamotrigine-levetiracetam duotherapy, or lamotrigine-topiramate duotherapy were used. Table shows the characteristics that were available in the database and possible to adjust for in the analysis.

	VPA monotherapy N=216	LTG-LEV duotherapy N=86	LTG-TPM duotherapy N=39
Year of delivery			
2000-2012	199 (92.1)	35 (40.7)	26 (66.7)
2013-2018	17 (7.9)	51 (59.3)	13 (33.3)
Maternal age			
<25	33 (15.3)	13 (15.1)	6 (15.4)
25-29	66 (30.6)	35 (40.7)	9 (23.1)
30-34	77 (35.6)	23 (26.7)	14 (35.9)
≥35	40 (18.5)	15 (17.4)	10 (25.6)
Parity			
Nulliparous	90 (41.7)	47 (54.7)	24 (61.5)
Primiparous	93 (43.1)	30 (34.9)	15 (38.5)
Multiparous	33 (15.3)	9 (10.5)	0
Married/cohabiting			
No	97 (44.9)	44 (51.2)	18 (46.2)
Yes	119 (55.1)	42 (48.8)	21 (53.8)
Maternal education			
Compulsory	58 (26.9)	24 (27.9)	12 (30.8)
Secondary	97 (44.9)	34 (39.5)	20 (51.3)
University	61 (28.2)	28 (32.6)	7 (17.9)
Smoking in early pregnancy	55 (25.5)	15 (17.4)	8 (20.5)
Multiple gestation	<5	<5	<5
Psychiatric or neurodevelopmental disorder	10 (4.6)	<5	0
Suspected teratogenic drug	<5	<5	<5
Any hospitalization, baseline 3m	15 (6.9)	7 (8.1)	<5
Any ER visit, baseline 3m	25 (11.6)	11 (12.8)	<5
Outpatient visit for epilepsy, baseline 3m	35 (16.2)	33 (38.4)	17 (43.6)

eTable 8: Characteristics of pregnancies in the Nordic pooled data in which valproate monotherapy, lamotrigine-levetiracetam duotherapy, or lamotrigine-topiramate duotherapy were used. Table shows the characteristics that were available in the database and possible to adjust for in the analysis.

	VPA monotherapy N=1065	LTG-LEV duotherapy N=281	LTG-TPM duotherapy N=61
Country			
Finland	664 (62.4)	41 (14.6)	19 (31.1)
Iceland	9 (0.8)	6 (2.1)	0
Norway	137 (12.9)	97 (34.5)	20 (32.8)
Sweden	254 (23.9)	137 (48.8)	22 (36.1)
Year of delivery			
2001-2007	593 (55.7)	34 (12.1)	21 (34.4)
2008-2020	471 (44.3)	247 (87.9)	40 (65.6)
Maternal age			
<25	210 (19.7)	42 (14.9)	5 (8.2)
25-29	297 (27.9)	88 (31.3)	19 (31.1)
30-34	367 (34.5)	109 (38.8)	22 (36.1)
≥35*	190 (17.9)	42 (14.9)	15 (24.6)
Parity			
Nulliparous	461 (43.3)	132 (47.0)	29 (47.5)
Primiparous	380 (35.7)	103 (36.7)	23 (37.7)
Multiparous	223 (21.0)	46 (16.4)	9 (14.8)
Married/cohabiting			
No	122 (11.5)	25 (8.9)	8 (13.1)
Yes	942 (88.5)	256 (91.1)	53 (86.9)
Multiple gestation	18 (1.7)	<5	<5
Preexisting diabetes	27 (2.5)	<5	0
Psychiatric or neurodevelopmental disorder	94 (8.8)	33 (11.7)	<5
Suspected teratogenic drug	14 (1.3)	8 (2.8)	<5
Any hospitalization, baseline 3m	56 (5.3)	21 (7.5)	<5
Outpatient visit for epilepsy, baseline 3m	190 (17.9)	80 (28.5)	18 (29.5)

VPA=valproate, LTG=lamotrigine, LEV=levetiracetam, TPM=topiramate. *****Analysis had separate categories for 25-39 and ≥40, but not shown due n's<5

eTable 9: Characteristics of pregnancies in the US Medicaid Analytic Extract (MAX) database in which valproate monotherapy, lamotrigine-levetiracetam duotherapy, or lamotrigine-topiramate duotherapy were used. Table shows the characteristics that were available in the database and possible to adjust for in the analysis.

	VPA monotherapy N=488	LTG-LEV duotherapy N=132	LTG-TPM duotherapy N=56
Year of delivery			
2001-2005	231 (47.3)	18 (13.6)	<11
2006-2010	182 (37.3)	55 (41.7)	32 (57.1)
2011-2014	75 (15.4)	59 (44.7)	*
Maternal age**			
<25	285 (58.4)	77 (58.3)	32 (57.1)
25-29	125 (25.6)	39 (29.6)	13 (23.2)
≥30	78 (16)	16 (12.1)	11 (19.6)
Multiparous	286 (58.6)	76 (57.6)	30 (53.6)
Multiple gestation	<11	<11	<11
Obesity/overweight	<11	<11	<11
Smoking	28 (5.7)	11 (8.3)	<11
Pre-existing diabetes	<11	<11	<11
Psychiatric or neurodevelopmental disorder	188 (38.5)	40 (30.3)	27 (48.2)
Suspected teratogens	21 (4.3)	<11	<11
High dose folic acid	159 (32.6)	70 (53.0)	0 (0)
Recent hospitalization	40 (8.2)	<11	<11
Recent ER visit	195 (40)	47 (35.6)	29 (51.8)
Recent neurologist visit	180 (36.9)	79 (59.9)	31 (55.4)

*Number suppressed to prevent calculation of small cells. **More categories used in the analysis, collapsed to mask small cells

eTable 10: Characteristics of pregnancies in the US MarketScan© Commerical Claims and Encounters database in which valproate monotherapy, lamotrigine-levetiracetam duotherapy, or lamotrigine-topiramate duotherapy were used. Table shows the characteristics that were available in the database and possible to adjust for in the analysis.

	VPA monotherapy N=73	LTG-LEV duotherapy N=76	LTG-TPM duotherapy N=19
Year of delivery			
2003-2010	60 (82.2)	31 (40.8)	9 (47.4)
2011-2015	13 (17.8)	45 (59.2)	10 (52.6)
Maternal age			
<25	2 (2.7)	7 (9.2)	6 (31.6)
25-29	19 (26.0)	18 (23.7)	10 (52.6)
30-34	33 (45.2)	27 (35.5)	2 (10.5)
35-39	12 (16.4)	18 (23.7)	0 (0)
≥40	7 (9.6)	6 (7.9)	1 (5.3)
Multiple gestation	6 (8.2)	3 (4.0)	0
Obesity/overweight	0	2 (2.6)	0
Smoking	0	0	0
Pre-existing diabetes	3 (4.1)	5 (6.6)	0 (0)
Psychiatric or neurodevelopmental disorder	11 (15.1)	12 (15.8)	2 (10.5)
Suspected teratogens	2 (2.7)	2 (2.6)	3 (15.8)
High dose folic acid	32 (43.8)	34 (44.7)	0 (0)
Recent hospitalization	2 (2.7)	2 (2.6)	1 (5.3)
Recent ER visit	6 (8.2)	7 (9.2)	4 (21.1)
Recent neurologist visit	50 (68.5)	64 (84.2)	14 (73.7)

eTable 11: Characteristics of pregnancies in the MUMS database from New South Wales, Australia in which valproate monotherapy, lamotrigine-levetiracetam duotherapy, or lamotrigine-topiramate duotherapy were used. Table shows the characteristics that were available in the database and possible to adjust for in the analysis.

	VPA monotherapy N=118	LTG-LEV duotherapy N=12	LTG-TPM duotherapy N=11
Year of delivery			
2004-2005	35 (29.7)	0 (0)	5 (45.5)
2006-2010	65 (55.1)	5 (41.7)	6 (54.5)
2011-2012	18 (15.3)	7 (58.3)	
Maternal age			
<25	46 (39)	5 (41.7)	5 (45.5)
25-29	33 (28)		6 (54.5)
30-34	25 (21.2)	7 (58.3)	
35-39	14 (11.9)		0
40+		0	0
Parity			
Nullliparous	35 (29.7)	7 (58.3)	<5
Primiparous	31 (26.3)	5 (41.7)	7 (63.6)
Multiparous	52 (44.1)		<5
Married/cohabitating	63 (53.4)	7 (58.3)	*
Pre-existing diabetes	<5	0 (0)	0 (0)
Psychiatric or neurodevelopmental disorder	54 (45.8)	<5	<5
Recent hospitalization	23 (19.5)	0 (0)	0 (0)

*Number suppressed to prevent calculation of small cells

eMethods

Pregnancy cohort construction

Within each Nordic country, the different health and socioeconomic registers were deterministically linked by study-specific personal identifiers based on the personal identity number assigned to each resident at birth or immigration.[19] We excluded births from the medical birth registers with a missing maternal identifier, and those with a missing or invalid gestational age. We considered recorded gestational ages <154 days (<22 weeks), >314 days (>44 weeks), and <35 weeks with a recorded birthweight >4 SD from the mean for gestational age and sex at to be invalid.[42] In the Nordic countries, linkage between parents and children was based on the birth record. In the US MAX database, linkage between parents and children was based on the family enrollment ID, state and zip-code.[20] In the US MarketScan database, linkage was based on the family enrollment ID.[21] In the Australian data, linkage between mothers and children was based on the birth record[43] while other records were linked probabilistically, based on the name, date of birth, and address.[22]

Pregnancy cohort eligibility criteria

In the Nordic data, we excluded births occurring less than a year after availability of the data from prescribed drug registers that were established after 2000 (January 2003 in Iceland, January 2004 in Norway, July 2005 in Sweden) since they did not have complete prescription data. In the US databases, we required continuous health plan enrollment from at least three months before pregnancy to one month after delivery, and linkage to a liveborn infant who was enrolled in the plan for at least three months, unless they died sooner. In Australian data, we required that the mother was enrolled as a concessional beneficiary (eligible for reduced copayment for all prescription drugs due to low income, chronic illness, or disability) from three months before pregnancy to birth and linked to a liveborn infant to ensure complete drug dispensing data.

Exposure definitions

The end of first trimester was defined as 90 days after LMP in the US databases and 97 days after LMP in the Nordic and Australian data. We used information about the prescribed daily dose according to the first prescription filled in the 90 days before LMP to end of first trimester in the US databases. In the other data sources that contain structured information on the strength and amount of drug dispensed, we estimated the first trimester dose by dividing the amount of drug dispensed in the first prescription in the 90 days before LMP by the number of days until the subsequent refill. If there was no refill, we used information on the median number of days to refill among those with at least two valproate prescriptions from 90 days before LMP to end of first trimester. Those with only one prescription fill for valproate in the window may have discontinued treatment or alternatively had a prior fill more than 90 days before pregnancy with a subsequent fill later in pregnancy.

Statistical analysis

We trimmed the pregnancies in non-overlapping regions of the propensity score distributions of the duotherapy and valproate monotherapy groups, then stratified according to the distribution of the propensity score among the exposed with a requirement for at least three pregnancies from each comparison group in each stratum. Then we calculated stratum specific weights which we included in the regression models. We compared the characteristics of the pregnancies before and after weighting to assess covariate balance. In the US MAX database, we additionally carried out a sensitivity analysis for the covariates that remained imbalanced after weighting in the regression model. This did not meaningfully change the estimates.

Database	Variables adjusted for in the analysis
Denmark	Year of birth, maternal age, parity, married/registered partnership, education, smoking, pre-existing diabetes, multiple gestation, psychiatric or neurodevelopmental disorder, suspected teratogenic drugs, any hospitalization, any ER visit, outpatient visit for epilepsy
Nordic pooled	Year of birth, maternal age, country, parity, married/cohabiting, pre-existing diabetes, multiple gestation, psychiatric or neurodevelopmental disorder, suspected teratogenic drugs, any hospitalization, outpatient visit for epilepsy
MAX	Year of birth, maternal age, parity, multiple gestation, obesity/overweight, smoking, pre-existing diabetes, psychiatric disorders, suspected teratogens, high dose folic acid, any hospitalization, any ER visit, outpatient visit to neurologist

MKSN	Year of birth, maternal age, multiple gestation, pre-existing diabetes, psychiatric disorders, suspected teratogens, high dose folic acid, any hospitalization, any ER visit, outpatient visit to neurologist
MUMS	Year of birth, maternal age, parity, marital status, psychiatric diagnosis

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sFigure: Forest plots showing minimally adjusted risk ratios and the overall pooled risk ratios from the meta-analysis of a) lamotrigine-levetiracetam duotherapy, b) lamotrigine-topiramate duotherapy versus valproate monotherapy and the risk of major congenital malformations