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NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

PASS information

Title	A Population-based Study of the Safety of Gabapentin Use During Pregnancy
Protocol number	A9451182
Version identifier of the final study report	1.0
Date	08 September 2022
EU Post Authorization Study (PAS) register number	EUPAS38620
Active substance	Gabapentin (ATC N03AX12)
Medicinal product	Neurontin®
Product reference	DE/H/0,899 MRP (Neurontin®) DE/H/2852 DCP (Gabapentin Pfizer) 20000710/11 Bulgaria National (Neurontin®) HR-H-198579675/HR-H-227912224 Croatia National (Neurontin®)
Marketing Authorization Holder (MAH)	Pfizer OFG Germany GmbH, Linkstr. 10, 10785 Berlin Germany
Joint PASS	No

Research question and objectives	The study objectives are to: 1. Describe the use of gabapentin in pregnancy. 2. Estimate the risk of major congenital malformations, other birth outcomes, and selected postnatal neurodevelopmental outcomes in pregnancies with exposure to gabapentin as compared with pregnancies with no exposure to antiepileptic drugs (AEDs); exposure to pregabalin; exposure to lamotrigine; exposure to pregabalin or lamotrigine.
Countries of study	Denmark, Finland, Norway, Sweden
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1. ABSTRACT (STAND-ALONE DOCUMENT)

Please refer to the stand-alone document.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Attention deficit hyperactivity disorder
AE	Adverse event
AED	Antiepileptic drug
ASD	Autism spectrum disorders
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
CPE	Centre for Pharmacoepidemiology, Sweden
DCP	Decentralised Procedure
DDD	Defined daily dose
DPP	Drugs and Pregnancy Project database
DUS	Drug utilisation study
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EURAP	The European Registry of Antiepileptic Drugs and Pregnancy
EUROCAT	European Network of Congenital Anomaly Registers
GAD	General anxiety disorder
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practice
HCP	Health Care Professional
ICD-10	International Classification of Diseases, Tenth Revision
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
KI	Karolinska Institutet, Sweden
LMP	Last Menstrual Period
MAH	Marketing Authorisation Holder
MH	Mantel-Haenszel
MRP	Mutual Recognised Procedure
NA AED	North American Antiepileptic Drug registry
NI	Non-interventional
NICU	Neonatal intensive care unit
NOMESCO	Nordic Medico-Statistical Committee
NSAID	Non-steroidal anti-inflammatory drug

Abbreviation	Definition
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PS	Propensity score
RCT	Randomised controlled trial
SD	Standard deviation
SGA	Small for gestational age
SmPC	Summary of product characteristics
SMD	Standardized mean difference
TIS	Teratology information services
TOPFA	Termination of pregnancy for anomaly
UK	United Kingdom
USA	United States of America
VSD	Ventricular Septal Defect

3. INVESTIGATORS

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4. OTHER RESPONSIBLE PARTIES

Not applicable.

5. MILESTONES

Milestone	Planned date	Actual date*	Comments
Registration in the EU PAS register	30 November 2020	30 November 2020	
Start of data collection†	30 December 2020	30 December 2020	
End of data collection‡	30 April 2021	19 January 2022	
Final report of study results	30 September 2022	08 September 2022	

EU: European Union; PAS: post-authorization study.

*Subject to change due to protocol approval timelines and data queues at the government data custodians at each of the participating countries.

† For studies with secondary data collection, the start of data collection is defined as the planned date for starting data extraction for the purposes of the primary analysis.

‡ For studies with secondary data collection, the end of data collection is defined as the planned date on which the analytical dataset will be first completely available; the analytic dataset is the minimum set of data required to perform the statistical analysis for the primary objective(s).

6. RATIONALE AND BACKGROUND

Gabapentin (Neurontin®) received first regulatory approval on 05 February 1993 in the United Kingdom (UK). Gabapentin has received marketing authorisation in 111 countries and is currently marketed in 93 countries. In the European Union (EU), gabapentin is indicated as adjunctive therapy in the treatment of partial seizures with and without secondary generalization in adults and children aged 6 years and above, and as monotherapy in the treatment of partial seizures with and without secondary generalization in adults and adolescents aged 12 years. In addition, gabapentin is used for the treatment of peripheral neuropathic pain such as painful diabetic neuropathy and post-herpetic neuralgia in adults.[1] Per current EU Mutual Recognition Procedure (MRP) Reference Member States (RMS) summary of product characteristics (SmPC), gabapentin should not be used during pregnancy unless the potential benefit to the mother clearly outweighs the potential risk to the foetus.[1]

To date, gabapentin use in pregnancy has been relatively low. As per the most recent PSUR (Periodic Safety Update Report, PSUSA/00001499/202202) covering the period from 02 February 2019 to 01 February 2022), there have been 11,778,784 cumulative patient-years of exposure worldwide. Owing to the low use in pregnancy, evidence about gabapentin in pregnancy remains limited.[2-5] A 2016 Cochrane review did not report an increased risk of congenital malformations associated with prenatal gabapentin monotherapy; however, it highlighted the low use during pregnancy.[2] A 2017 systematic review and network meta-analysis of comparative safety of antiepileptic drugs (AEDs) in pregnancy based on data from 96 studies rated gabapentin as “moderately safe”, citing a potential association with cardiac malformations and hypospadias and also noting lack of sufficient data on teratogenicity.[3] The North American Antiepileptic Drug Registry (NA AED) is the largest existing AED registry worldwide. The 2021 annual report (available upon request from Pfizer Inc) of the NA AED provided data from 251 gabapentin monotherapy-exposed pregnancies among 11,648 women. After excluding genetic disorders, 3 (1.2%) malformed infants were identified among the exposed group between birth and 12 weeks of age, and the report concluded that there is no increased risk of major congenital malformations associated with gabapentin monotherapy compared with the expected prevalence in the population. Owing to low use, estimates of association are judged uninformative and therefore not computed for gabapentin. Two comparative cohort studies with the largest number to date of pregnancies exposed to gabapentin monotherapy did not report an increased risk of major congenital malformations, with malformation prevalence of 0.7% (0.02%-3.8%) in the US[6] and 1.7% in Sweden.[7] The background prevalences of major malformations are 2-4% in the US[8] and range from 3.7%-5.4% in the Nordic registry data.[9-11] A 2017 study in France reported no evidence for an increased risk of 26 major congenital malformations associated with gabapentin monotherapy as compared with other AEDs.[12] A population-based study in Northern Italy assessing the comparative risk of spontaneous abortions, terminations of pregnancy (TOPs), major congenital malformations, preterm births and small for gestational age (SGA) newborns following in-utero gabapentin exposure concluded that the study was underpowered to provide information on the risks associated with single antiepileptic agents.[13] A US study of gabapentin exposure during pregnancy and a range of maternal and pregnancy outcomes among Medicaid beneficiaries reported no evidence for an association

with major malformations overall, although gabapentin exposure was associated with higher prevalences of cardiac malformations, preterm birth, SGA, and neonatal intensive care unit (NICU) admission.[14] Furthermore, a large population-based cohort study in the Nordic countries reported no increased risk of autism and intellectual disability following prenatal exposure to gabapentin.[15]

The aim of this non-interventional study was to evaluate the use and safety of gabapentin in pregnancy using data on pregnancies identified from population-based registries in Denmark, Finland, Norway, and Sweden. To reduce confounding by indication or disease severity,[16] in addition to the use of the AED-unexposed pregnancies as a comparator, this study also included, as active comparators,[17] agents with indications similar to those of gabapentin: pregabalin (indications: epilepsy, neuropathic pain), and lamotrigine (indication: epilepsy).

This study has been designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the European Medicines Agency (EMA).

7. RESEARCH QUESTION AND OBJECTIVES

The study objectives are to:

1. Describe the use of gabapentin in pregnancy.

2. Estimate the risk of major congenital malformations, other birth outcomes, and selected postnatal neurodevelopmental outcomes of pregnancies with exposure to gabapentin as compared with pregnancies with: no exposure to AEDs; exposure to pregabalin; exposure to lamotrigine; exposure to pregabalin or lamotrigine.

7.1. Primary objectives

The primary objectives of the study were to:

- Describe use of gabapentin, pregabalin, and lamotrigine during pregnancy overall (for any therapeutic use), and by:
  - trimester of pregnancy;
  - indication;
  - cumulative dose;
  - calendar year of delivery;

Description of exposure was performed for all pregnancies, including pregnancies with monotherapy exposure (defined as no concomitant administration with other AEDs) and pregnancies with polytherapy exposure (defined as concomitant administration with other AEDs), as well as the subset of only pregnancies with monotherapy exposure.

- Calculate the prevalence of major congenital malformations in pregnancies with first- trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.

- Perform a sensitivity analysis to calculate the prevalence of major congenital malformations that includes stillbirth and pregnancies ending in therapeutic 2nd trimester induced abortion in the definition of prevalence in pregnancies with first-trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.

- Estimate the associations between first-trimester exposure to gabapentin and prevalence of major congenital malformations, as compared with:
  - no exposure to AEDs during the first trimester;
  - exposure to pregabalin during the first trimester;
  - exposure to lamotrigine during the first trimester;
  - exposure to pregabalin or lamotrigine during the first trimester.

- Calculate the prevalence of pre-specified birth outcomes including stillbirth, low birth weight, small for gestational age (SGA), preterm birth, low Apgar score, microcephaly, among pregnancies with any trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.

- Estimate the associations between exposure to gabapentin any time during gestation and other pre-specified birth outcomes, including stillbirth, low birth weight, small for gestational age (SGA), preterm birth, low Apgar score, microcephaly, as compared with:
  - no exposure to AEDs any time during gestation;
  - exposure to pregabalin any time during gestation;
  - exposure to lamotrigine any time during gestation;
  - exposure to pregabalin or lamotrigine any time during gestation.

7.2. Secondary objectives

The secondary objectives of the study were to:

- Calculate the incidence rates of pre-specified postnatal neurodevelopmental outcomes (attention-deficit hyperactivity disorders, pervasive developmental disorders, learning disorders and intellectual disabilities) with any trimester exposure to:
  - gabapentin;
  - pregabalin;
  - lamotrigine;
  - pregabalin or lamotrigine.

- Estimate the associations between exposure to gabapentin any time during gestation and the pre-specified postnatal neurodevelopmental outcomes, as compared with:
  - no exposure to AEDs any time during gestation;
  - exposure to pregabalin any time during gestation;
  - exposure to lamotrigine any time during gestation;
  - exposure to pregabalin or lamotrigine any time during gestation.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

This study was conducted using the Study Protocol dated 02 October 2020 (Appendix 2. Study Protocol), and registered in the EU Postauthorisation study (PAS) Register (EUPAS38620 http://www.encepp.eu/encepp/viewResource.htm?id=38621).

9.1. Study design

This PASS is a population-based study and is based on routinely collected data from national administrative and medical registers in four Nordic countries: Denmark, Finland, Norway, and Sweden.[18]

The study population consisted of live and stillbirths of single and multifetal pregnancies from 1 January 2005 to 31 December 2017 in Denmark, from 1 January 2005 to 31 December 2015 in Norway and Finland, and between 1 July 2006 and 31 December 2018 in Sweden. Follow-up for the postnatal neurodevelopmental outcomes, when available, was a minimum of 1 year postnatally and for the maximum period available in the dataset for each newborn at the time of the end of the data collection, censored at emigration or death.

9.2. Setting

Each participating country is a welfare state with tax-supported universal health care,[18] routinely and prospectively collected data on outpatient dispensings, live and still births, hospital diagnoses, migrations and deaths, and individual-level data linkage including exact mother-child linkage (mother's personal identifier is a data field in the child's birth record).

Population-based healthcare registries in the Nordic countries are a well-established setting for examining safety of medicines in pregnancy. Their most important strengths are capture of all births and clinically relevant birth and postnatal outcomes; last menstrual period (LMP), depending on country, is either directly recorded in the birth registry or estimated from gestational age; routine capture of dispensings of prescription medications to pregnant women; extensive information about maternal and offspring demographic and clinical characteristic ; and exact mother-child and personal linkage.

9.3. Subjects

9.3.1. Inclusion criteria

All births or identifiable pregnancies from 1 January 2005 through 31 December 2015 (both dates inclusive) in Denmark, Finland, and Norway and all births identified from 1 July 2006 through 31 December 2016 (both dates inclusive) in Sweden.

9.3.2. Exclusion criteria

The following were excluded from the study:

1. Births with exposure to known teratogenic medications during the first trimester;

2. Births with a chromosomal abnormality diagnosis.

9.4. Variables

9.4.1. Exposure

For the purposes of identifying timing of exposure, trimesters of pregnancy were defined as follows based on the first day of the last menstrual period (LMP):

- First trimester: LMP-90 days to LMP+97 days (both dates inclusive);
- Second trimester: from LMP+98 days to LMP+202 days (both dates inclusive);
- Third trimester: from LMP+203 days (inclusive) until pregnancy end date (not included).

LMP was determined using the following hierarchy/data availability: ultrasound determined LMP; self-reported LMP (if ultrasound-reported is unavailable); date of delivery minus gestational age in days (if LMP unavailable by ultrasound or self-report). If gestational age was missing, LMP was imputed by subtracting 280 days from date of delivery in Sweden and excluded in Denmark, Finland and Norway.

Exposure during the first trimester:

Gabapentin exposure during the first trimester was defined as at least one maternal dispensing of gabapentin during the first trimester. Gabapentin monotherapy exposure during the first trimester was defined as at least one maternal dispensing of gabapentin during the first trimester and not any other AED.

Comparators/reference groups:

No exposure to AEDs-This comparator included births with no maternal dispensing of any AED during the first trimester.

Pregabalin exposure in the first trimester was defined by at least one maternal dispensing of pregabalin during the first trimester. Pregabalin monotherapy in the first trimester was defined as first-trimester exposure to pregabalin and no first-trimester dispensing for any other AED.

Lamotrigine exposure in the first trimester was defined by at least one maternal dispensing of lamotrigine during the first trimester. Lamotrigine monotherapy in the first trimester was defined as first-trimester exposure to lamotrigine and no first-trimester dispensing for any other AED.

Pregabalin or lamotrigine exposure in the first trimester was defined by at least one maternal dispensing of pregabalin and/or lamotrigine during the first trimester. Pregabalin or lamotrigine monotherapy in the first trimester was defined as first-trimester dispensing of pregabalin and/or lamotrigine and no first-trimester dispensing for any other AED.

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded.

9.4.1.1. Exposure any time during gestation

Gabapentin exposure any time during gestation was defined by at least one maternal dispensing of gabapentin during any trimester. Gabapentin monotherapy any time during gestation was defined as any-pregnancy exposure to gabapentin and no dispensing for any other AED during any trimester.

Comparators:

No exposure to AEDs-This reference group consisted of births with no maternal dispensing of any AED during any trimester.

Pregabalin exposure any time during gestation was defined by at least one maternal dispensing of pregabalin during any trimester. Pregabalin monotherapy any time

during gestation was defined as any-pregnancy exposure to pregabalin and no dispensing for any other AED during any trimester.

Lamotrigine exposure any time during gestation was defined by at least one maternal dispensing of lamotrigine during any trimester. Lamotrigine monotherapy any time during gestation was defined as any-pregnancy exposure to lamotrigine and no dispensing for any other AED during any trimester.

Pregabalin or lamotrigine exposure any time during gestation was defined by at least one maternal dispensing of pregabalin and/or lamotrigine during any trimester. Pregabalin or lamotrigine monotherapy any time during gestation was defined as any pregnancy exposure to pregabalin and/or lamotrigine and no dispensing for any other AED during any trimester.

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded.

9.4.2. Outcomes

9.4.2.1. Primary outcomes (birth outcomes)

- Major congenital malformations, any and specific malformation type, according to the EUROCAT classification[19]
- Stillbirth, as recorded in each country's birth registry
- Low birth weight (birth weight < 2500 g)
- SGA, defined, for singleton pregnancies, as a dichotomous variable (yes/no) of birth weight below 2 standard deviations (SDs) of sex- and gestational week specific distributions, using country-specific reference standard.[20 21] SGA non-singleton gestations were defined if appropriate reference standard can be defined/identified; otherwise set to missing.
- Preterm birth, defined as gestational age <37 weeks
- Low Apgar score at 5 minutes, defined as a dichotomous variable (score 0-6 vs. score 7-10)
- Microcephaly, defined as a dichotomous variable (yes/no) of head circumference at birth (cm) smaller than 2 SD of sex- and gestational week specific distribution, using country-specific reference standard

9.4.2.2. Secondary Outcomes (Postnatal neurodevelopmental outcomes)

Postnatal neurodevelopmental outcomes (ICD-10 (International Classification of Diseases, Tenth Revision) codes):

- Attention-deficit hyperactivity disorders (F90);
- Pervasive developmental disorders (autism spectrum disorders) (F84);

- Learning disorders (Specific developmental disorders of speech and language (F80), and Specific developmental disorders of scholastic skills (F81)) and Intellectual disabilities (mental retardation) (F70-F79).

Follow-up for the postnatal neurodevelopmental outcomes, when available, was a minimum of 1 year postnatally and for the maximum period available in the dataset for each birth. However, for a variety of reasons (e.g. emigration, death), follow-up could be infeasible in individual cases. Not all livebirths have available follow-up information into the school age, and as postnatal neurodevelopmental disorders are diagnosed primarily at school age, the number of events in gabapentin exposed (and other comparator groups) pregnancies in the study period may not be sufficient to yield stable estimates of association.[22]

9.4.3. Covariables

Measured covariables were calendar year of delivery, maternal age at conception, parity (number of live and still births prior to the on- study pregnancy), indication for AED use, marital/cohabiting status, maternal pre-gravid body mass index (BMI) as recorded at the first antenatal visit or via a hospital diagnosis of obesity, smoking during pregnancy as recorded at the first antenatal visit, single or multiple gestation, Caesarean delivery, and child's sex. Caesarean delivery and child's sex were reported but were not used for adjustment since these variables were not deemed confounders in this study. Indication for gabapentin (and other AEDs) use in 12 months pre-LMP was reported descriptively.

The covariables considered for inclusion in the propensity-score model are listed below but may differ in the final model of the country-specific analysis:

- calendar year of delivery;
- maternal age in years at conception;
- marital/cohabiting status;
- smoking during pregnancy;
- obesity (BMI $\geq$ 30 kg/m^2) or a hospital ICD diagnosis of obesity;
- single or multiple gestation;
- hospital-recorded co-morbidity based on inpatient and outpatient specialist care or proxy medication use in 12 months pre-LMP: migraine or other headache syndromes, other neurologic disorders, depression, bipolar disorder, alcohol abuse or dependence, drug abuse or dependence, hypertension, haematological diseases, diabetes, asthma, liver diseases, renal impairment, rheumatic diseases, disorders of female pelvic organs/genital tract, thyroid disorders, infections (infections were assessed in 90 days pre-LMP). In Finland, in addition to the hospital diagnoses, diagnoses from primary care were also available and used;
- indicators of maternal health care utilisation in the 12 months pre-LMP (number of inpatient and specialised outpatient encounters);
- for the outcome congenital malformations: maternal medication use each as a dichotomous variable, defined by at least one dispensing during the first

trimester (AEDs, antidepressants, hypnotics, antipsychotics, analgesics, antihypertensives, non-steroidal anti-inflammatory drugs, drugs for peptic ulcer/gastroesophageal reflux, folic acid, drugs for in-vitro fertilization, thyroid hormones, systemic corticosteroids, and anti-infectives for systemic use);

- for the outcomes other than congenital malformations: maternal medication use each as a dichotomous variable, defined by at least one dispensing during any trimester (AEDs, antidepressants, hypnotics, antipsychotics, analgesics, antihypertensives, non-steroidal anti-inflammatory drugs, drugs for peptic ulcer/gastroesophageal reflux, folic acid, drugs for in-vitro fertilization, thyroid hormones, systemic corticosteroids, and anti-infectives for systemic use).

Full list of the study variables and their operational definitions are provided in Study Protocol (Appendix 2. Study Protocol).

9.5. Data sources and measurement

The list of data sources used to construct the analysis dataset for this study are presented in Table 1. The population of Denmark (5.8 million), Finland (5.5 million), Norway (5.4 million), and Sweden (10.4 million) combined is approximately 27 million people. These Nordic countries are welfare states.[18] The data sources used in Denmark were the Danish Central Person Registry, the Danish Medical Birth Registry, the Danish National Patient Registry, and the Danish Health Services Dispensing Database. These data sources have been described in the literature, and many algorithms were validated (Table 1).The data sources used in Finland were the Finnish Medical Birth Register, the Finnish Register on Induced Abortions, the Finnish Prescription Register, the Finnish Special Reimbursement Register, the Finnish Register of Congenital Malformations, the Finnish Care Register for Health Care, the Finnish Causes of Death Register, the Finnish Digital and the Population Data Services Agency (Table 1). The data sources used in Norway were the Medical Birth Registry of Norway, the Norwegian Register of Pregnancy Terminations, the Norwegian Prescription Database, the Norwegian Patient Registry, and the National Registry of Norway (Table 1). The data sources used in Sweden were the Swedish Total Population Register, the Swedish Medical Birth Register, the Swedish Prescribed Drug Register and the National Patient Register (Table 1). Individual-level records from these data sources are linkable in each country via a unique personal identifier. For births recorded in the birth registries, a maternal unique identifier is a variable in the record of the offspring, enabling exact linkage between a given offspring and maternal history of medication dispensing or diagnoses before or during pregnancy. Registration in the data sources in each country is mandatory, and they are maintained by government agencies.

Diagnoses in all countries are registered based on the International Classification of Diseases, 9th revision (ICD-9) or the International Classification of Diseases, 10th revision (ICD-10) coding system and accessed through registers as specified in Table 1. Similarly, medications are classified according to the Anatomical Therapeutic Chemical (ATC) coding system and accessed through prescription registers. The medical birth registers in the included countries

contain similar information on other relevant covariables (calendar year of delivery, maternal age at conception, parity, marital/cohabiting status, pre-gravid BMI, smoking during pregnancy, single or multiple pregnancy, and child's sex).

Table 1. National registries in Denmark, Finland, Norway, and Sweden and type of data used from each registry

Study variable/role	Type of data	Data source(s)
Person identification (mothers and children)	Unique personal identifier for data linkage	Danish Civil Registration System[23] Finnish Medical Birth Register* National Registry of Norway (delivered by Medical Birth Registry of Norway) Swedish Total Population Register[24]
Study population	Pregnancies ending in singleton/multiple live birth or stillbirth	Danish Medical Birth Registry Finnish Medical Birth Register* Medical Birth Registry of Norway Swedish Medical Birth Register
	Pregnancies ending in therapeutic 2nd trimester induced abortion	Danish National Patient Registry[25 26] Finnish Register on Induced Abortions* Norwegian Register of Pregnancy Terminations (part of the Medical Birth Registry of Norway) Not available in Sweden
Exposure	Maternal dispensings of gabapentin and active comparators	Danish National Health Services Prescription Database[27 28] Finnish Prescription Register[27] Finnish Special Reimbursement Register Norwegian Prescription Database[27] Swedish Prescribed Drug Register[27]
Outcome	Major congenital malformations	Danish Medical Birth Registry (stillbirths)/ Danish National Patient Registry (livebirths/induced abortions) Finnish Register of Congenital Malformations* Finnish Register on Induced Abortions* Finnish Care Register for Health Care Medical Birth Registry of Norway Swedish Medical Birth Register Swedish National Patient Register[29]
	Birth weight, gestational age, Apgar score at 5 minutes, head circumference, stillbirth	Danish Medical Birth Registry Finnish Medical Birth Register* Medical Birth Registry of Norway Swedish Medical Birth Register

Table 1. National registries in Denmark, Finland, Norway, and Sweden and type of data used from each registry

Study variable/role	Type of data	Data source(s)
	Neurodevelopmental outcomes	Danish National Patient Registry[25] Danish Psychiatric Central Research Register[30] Danish National Health Services Prescription Database[27 28] Finnish Care Register for Health Care Finnish Register of Primary Health Care visits Finnish Prescription Register[27] Norwegian Patient Registry[31] Norwegian Prescription Database[27] Swedish National Patient Register[29]
Covariables (for full list see Appendix 2. Study Protocol)	Mother: parity, marital status, mode of delivery, smoking during pregnancy, body mass index Offspring: sex, multiplicity of gestation	Danish Medical Birth Registry Finnish Medical Birth Register* Medical Birth Registry of Norway Swedish Medical Birth Register[32] Swedish National Patient Register
	Maternal morbidity (including indication for gabapentin) Markers of health care utilization	Danish National Patient Registry[25] Danish National Health Services Prescription Database[27 28] Finnish Care Register for Health Care Finnish Register of Primary Health Care visits Finnish Special Reimbursement Register. Finnish Prescription Register[27] Norwegian Prescription Database[29] Norwegian Patient Registry[31] Swedish National Patient Register[29] Swedish Prescribed Drug Register[27]
	Maternal medications	Danish National Health Services Prescription Database [27 28] Finnish Prescription Register[27] Norwegian Prescription Database[27] Swedish Prescribed Drug Register[27]
Loss to follow-up	Death, emigration†	Danish Civil Danish Civil Registration System[23] Finnish Causes of Death Register Finnish Digital and Population Data Services Agency National Registry of Norway (delivered by

Table 1. National registries in Denmark, Finland, Norway, and Sweden and type of data used from each registry

Study variable/role	Type of data	Data source(s)
		Medical Birth Registry of Norway) Swedish Cause of Death Register[33] Swedish Total Population Register

* Data for the Medical Birth Register, the Register on Induced Abortions, and the Malformation Register were obtained from the Finnish Drugs and Pregnancy Project database
†Emigration data not available in the Norwegian dataset

9.6. Bias

All epidemiologic studies are subject to biases, typically classified into confounding, information bias and selection bias. As with most pharmacoepidemiologic studies, confounding by indication is likely, since epilepsy itself is known to be associated with adverse pregnancy outcomes.[34] Other sources of confounding include residual confounding from unmeasured confounders and from misclassification of measured confounders. Contrasts using active comparators may still be confounded by severity. To reduce confounding, PS stratification was used, which is a preferred method when exposure is rare and many covariables need to be controlled for.[35]

Information bias manifests as misclassification of exposure, outcome, or confounders. Dispensing records may not always accurately represent the actual amount and timing of medication intake (exposure misclassification), and estimation of dose response patterns is limited by the small number of exposed pregnancies. We included a 90-day period before LMP as part of first-trimester exposure to capture use in early pregnancy that may be missed if we included only dispensings after LMP since drugs are typically dispensed for a 3-month period in the Nordic countries. However, this may also misclassify some unexposed after LMP as exposed in the first trimester. Inpatient and outpatient clinic specialist care diagnoses, used in identifying most study variables, are all subject to measurement error.

Selection bias in perinatal epidemiology may stem from the reality that malformations in pregnancies ending in spontaneous and first trimester induced abortions may not be observed. In addition to reducing precision by depleting the number of cases, if such selective dropout (i.e., selection bias) was associated with gabapentin exposure, measures of association based on prevalent outcomes would be biased.[36] Given its design of a fixed study period, this study may provide insufficient follow-up for live births to observe all postnatal neurodevelopmental outcomes. For example, not all live-born children have follow-up into the school age at the time of the follow-up end, and the number of gabapentin-exposed pregnancies in the earlier study period may not be sufficient to yield stable estimates of association. Children of mothers diagnosed and treated for epilepsy during pregnancy may undergo more medical surveillance compared to children of the general population, potentially leading to spurious association

observed owing to this detection bias. Selection bias for postnatal outcomes stemming from omitting of some eligible pregnancies due to spontaneous abortions and first trimester induced terminations is of less concern in this study, as postnatal outcomes are of interest among liveborns.

9.7. Study size

Table 2 shows estimated number of total pregnancies ending in live or stillbirth and pregnancies with AED exposure (any use, i.e., pregnancies exposed to monotherapy and pregnancies exposed to polytherapy). In observational studies based on routinely collected data, where researchers do not control study size, it serves (as in Appendix 2. Study Protocol) to evaluate the precision of resulting effect estimates.[37]

Table 2. Estimated numbers of pregnancies ending in live or still birth (any use, i.e., pregnancies exposed to monotherapy or polytherapy)*

	Denmark (2005-2016)	Finland (2005-2016)	Norway (2005-2016)	Sweden (2006-2016)	TOTAL
Live/still births	728,052	701,550	717,219 (657,451)	1,152,002	3,298,823
Pregnancies with dispensing of					
Gabapentin, first trimester	374	374	344	500	1,592
Gabapentin, any time during gestation	388	388	467	500	1,743
Pregabalin, first trimester	372	935	227	1,230	2,870
Pregabalin, any time during gestation	377	965	307	1,275	2,930
Lamotrigine, first trimester	2,266	961	1,688	2,838	7,993
Lamotrigine, any time during gestation	2,379	1,012	1,934	2,991	8,584

*Number of exposed in Denmark and Sweden are the actual numbers for 2005-2016; estimated for Finland and Norway based on 2005-2015 prevalence before applying any exclusion criteria in this table.

Table 3 shows the upper limits of 95% confidence interval (CI) for prevalence ratios of selected outcomes, which can be ruled out with 80% probability, for different scenarios with respect to the size of the exposed and comparator groups based on counts provided in Table 2.

Table 3. Upper limits of 95% confidence interval for risk or prevalence ratios depending on the prevalence of selected outcomes representative of prevalence of various study outcomes

Outcome	Estimated prevalence of outcome	Upper limit of 95% confidence interval for risk ratio can be ruled out with at least 80% probability (based on actual or estimated frequencies; approximate the analysis with **gabapentin-unexposed** as a comparator*)
Malformations of the nervous system, mental retardation	0.2%	4.801 (use first-trimester counts)
Stillbirth, postnatal outcomes, ASD	0.6%	2.373 (use any time during pregnancy counts)
Cardiac congenital malformations postnatal outcomes, ADHD	1%	1.950 (use any time during pregnancy counts)
Any major congenital malformation	3%	1.465 (use any time during pregnancy counts)
Preterm birth/SGA	10%	1.223 (use any time during pregnancy counts)
		Upper limit of 95% confidence interval for risk ratio can be ruled out with at least 80% probability (based on actual or estimated frequencies; approximate the analysis with **gabapentin-pregabalin** as a comparator*)
Malformations of the nervous system, mental retardation	0.2%	7.069 (use first-trimester counts)
Stillbirth, postnatal outcomes, ASD	0.6%	2.977 (use any time during pregnancy counts)
Cardiac congenital malformations, postnatal outcomes, ADHD	1%	2.324 (use any time during pregnancy counts)
Any major congenital malformation	3%	1.619 (use any time during pregnancy counts)
Preterm birth/SGA	10%	1.289 (use any time during pregnancy counts)
		Upper limit of 95% confidence interval for risk ratio can be ruled out with at least 80% probability (based on actual or estimated frequencies; approximate the analysis with **gabapentin-lamotrigine** as a comparator*)
Malformations of the nervous system, mental retardation	0.2%	5.571 (use first-trimester counts)
Stillbirth, postnatal outcomes, ASD	0.6%	2.579 (use any time during pregnancy counts)
Cardiac congenital malformations, postnatal outcomes, ADHD	1%	2.080 (use any time during pregnancy counts)
Any major congenital malformation	3%	1.520 (use any time during pregnancy counts)
Preterm birth/SGA	10%	1.247 (use any time during pregnancy counts)

Table 3. Upper limits of 95% confidence interval for risk or prevalence ratios depending on the prevalence of selected outcomes representative of prevalence of various study outcomes

		Upper limit of 95% confidence interval for risk ratio can be ruled out with at least 80% probability (based on actual or estimated frequencies; approximate the analysis with **gabapentin-pregabalin or lamotrigine** as a comparator*)
Malformations of the nervous system, mental retardation	0.2%	5.447 (use first-trimester counts)
Stillbirth, postnatal outcomes, ASD	0.6%	2.547 (use any time counts)
Cardiac congenital malformations, postnatal outcomes, ADHD	1%	2.060 (use any time counts)
Any major congenital malformation	3%	1.511 (use any time counts)
Preterm birth/SGA	10%	1.243 (use any time counts)

*Can include exposed to other AEDs i.e., monotherapy or polytherapy; calculations made without applying any exclusion criteria. The computations were done using SAS software based on the 'Study size' worksheet of the Episheet[38]

9.8. Data transformation

Data retrieval and management was conducted separately in each country. Investigators in each country obtained all necessary permissions and prepared a data applications to country-specific data custodians. A data manager in each country ensured correctness of the delivered raw data before data management started. Records from different registries were merged by a unique personal identifier or its pseudonym and de-identified or pseudonymised before the analysis. Data were cleaned and coded, and analytic datasets were prepared according to the specifications provided in the Study Protocol (Appendix 2. Study Protocol). All four countries use similar coding systems for medications, diagnoses, and procedures. Any slight variations among the countries in the specific diagnostic or procedure codes were addressed in consultation with clinicians on a country-specific basis. Patient-level data were kept on secure servers within each respective country. Patient-level data from Finland, Norway, or Sweden were not made available to researchers at the 'PI organizing institution' (Aarhus University, Denmark). In addition, the marketing authorization holder (Pfizer) had no access to patient-level data. Aggregated data as specified in the Appendix 2. Study Protocol were provided to the Department of Clinical Epidemiology, Aarhus University, for meta-analysis and reporting.

SAS version 9.4 or R version 3.5.0 or later were used for data management and analysis.

9.9. Statistical methods

Details of data analysis are provided in Section 9.7 of the Study Protocol (Appendix 2. Study Protocol). For all data analyses, the birth was the unit of analysis. Given that a woman could have more than one birth during the study period, data analyses accounted for correlated observations using clustered robust variance estimates. All steps of the country-specific data analyses were conducted separately in each participating country according to the common Study Protocol. The country-specific output, including crude and adjusted estimates of association were transferred to Aarhus University Hospital, Denmark, for meta-analyses.

This report includes meta-analyses based on country-specific results from Denmark, Finland, Norway, and Sweden.

9.9.1. Main summary measures

Gabapentin use in pregnancy was described using overall and trimester-specific number and proportion of pregnancies exposed in the first trimester, and in any trimester (any therapy and monotherapy). Use of the active comparators was similarly described.

Distributions of the covariables in the study population were tabulated according to the gabapentin exposure categories: first trimester (exposed/unexposed); any trimester (exposed/unexposed) and separately for the monotherapy exposure category. Categorical variables were summarized using frequencies and proportions; continuous variables using either mean and SD, or median and interquartile range (IQR) as appropriate.

Crude prevalences of the major congenital malformations were reported according to first-trimester exposure to gabapentin (overall and in the subcategory of monotherapy) and each comparator. Crude prevalences of the other birth outcomes were reported according to any trimester exposure to gabapentin and each comparator, in the same fashion.

9.9.2. Main statistical methods

9.9.2.1. Measures of occurrence and measures of association

Prevalence of each birth outcome was computed as number of newborns from single or multiple pregnancies with a given outcome divided by the total number of newborns at risk. For the outcomes of congenital malformations and stillbirth in the analysis not including pregnancies ending in 2nd trimester abortion, the number of newborns at risk was the total number of live or stillborn children. For the outcomes of congenital malformations and stillbirth in the analysis including pregnancies ending in a 2nd trimester abortion, the number of newborns at risk was the number of live or stillborn children and the number of pregnancies ending in a 2nd trimester abortion. For all other birth outcomes, the number of newborns at risk was the number of live-born children.

Incidence rate of each postnatal outcome was computed as the number of first-recorded events during the follow-up divided by the total person-time at risk contributed by each

liveborn. The follow-up for each newborn began on the date of birth and ended on the date of a given postnatal outcome, emigration, death, or the end of the observation period and included a minimum of 1 year of follow-up.

Crude and adjusted prevalence ratios (PRs) and 95% Wald CIs for each birth outcome and a given population/contrast were estimated using log-binomial regression. In Norway, logistic regression was used (due to better convergence), i.e., the resulting odds ratios served to approximate the underlying PRs. For the most prevalent outcomes, this slightly overestimated the prevalence ratios and the belonging confidence intervals. Crude and adjusted hazard ratios (HRs) with 95% Wald CIs were estimated using Cox's proportional-hazards regression for each postnatal outcome. Robust (clustered) standard error estimates were used to account for dependent observations from pregnancies with more than one child in Denmark, Finland, and Norway. In Sweden, generalized estimating equation approach was used to compute standard errors for the measures of associations. The proportional hazards assumption was not routinely checked.

9.9.2.2. Propensity scores

For each pregnancy and each contrast, a propensity score (PS) was computed, using logistic regression, as the probability of being exposed to gabapentin vs. given comparator conditional on the measured covariables. PS was estimated a generic-outcome model, meaning that all candidate covariables were included in the PS-estimating model, regardless of the outcome. Wyss et al showed, in a simulation study, that such model performs well when multiple outcomes are being examined,[39] when, as in the current study, it is reasonable to assume that all confounders distort the association in the same direction for all outcomes. The final set of covariables included in propensity score and their categories could vary from country to country and depended on the convergence of each PS model (Appendix 4, Appendix 5). No interaction terms were entered into the PS models.

The adjusted analysis was conducted using PS fine stratification, following the approach by Patorno et al.[14 40] and developed by Desai et al.[35] Following PS estimation, distribution of PS for each contract was plotted and births with PS in non-overlapping areas were trimmed. Based on the trimmed distributions, strata of PS were defined using boundaries of the gabapentin-exposed pregnancies. The number of strata was determined by the number of exposed pregnancies and, therefore, was not prespecified and varied across countries. All exposed and unexposed observations included in a given PS estimation were classified into these strata based on their PS. A weight was assigned to each unexposed pregnancy based on its stratum; each exposed pregnancy was assigned the weight of 1. A weighted regression analysis was performed, in which adjusted prevalence ratios (aPRs) or adjusted hazards ratios (aHRs) were estimated using a weighted regression model.

Balance of the covariables following trimming and stratifications-strata specific weights was assessed in each country's dataset using standardized mean differences (SMDs). Covariables with SMD <0.2 were considered balanced.[41]

For the only instance of covariables with SMD≥0.2 (alcohold and drug abuse, sleep disorders and hypnotics) in the main analyses, double-adjustment[42] was applied in analyses of the outcome of major congenital malformations for pregnancies with exposure to gabapentin vs lamotrigine in Sweden. Double-adjustment for covariables with 0.1<SMD<0.2 could not be applied in the analyses from Denmark, Finland, Norway or Sweden due to models' non-convergence. The overview of PS balancing and covariable-specific SMD before and after PS adjustment for each contrast in each country are presented in Appendix 4, Supplementary propensity score tables. The PS distributions for each contrast in each country are presented in Appendix 5, Supplementary descriptive figures.

9.9.2.3. Meta-analysis

Crude and adjusted estimates of association from Sweden, Norway, and Finland were transferred to Aarhus University, Aarhus, Denmark for meta-analyses or other combined analyses. Because of the similarities between the healthcare systems in the Nordic countries and the use of a common study protocol with well-defined selection of exposures, outcomes and covariables, a fixed-effects meta-analysis is justifiably applied.[43] Because meta-analysis drops strata with zero exposed cases, Mantel-Haenszel pooling method was used.[35] Details of the analysis are described in the Appendix 2. Study Protocol. These methods were successfully applied in a recent similar PASS (EUPAS27339).[44]

9.9.3. Missing values

Missing data were reported as a separate category in descriptive tables and treated as missing in the statistical models without imputation attempts.

9.9.4. Sensitivity analyses

To evaluate the potential bias in the analysis of major congenital malformations from excluding information from termination of pregnancy due to foetal anomaly(TOPFA), a sensitivity analysis including TOPFA was conducted in the countries where this information was available (Denmark, Norway, and Finland). Information on induced abortions is not available in Sweden.

In the primary analyses, patients with at least one dispensing within the relevant timeframe were classified as exposed. However, some patients may have obtained a single dispensing (prescription) of an antiepileptic drug. Possible reasons for this may be that the drug was prescribed for an indication other than epilepsy, treatment was stopped due to an adverse reaction, etc. Two (2) gabapentin dispensing categories of '1 dispensing', and '>1 dispensing', were used to stratify select descriptive analyses of major congenital malformations. The number of major congenital malformation events, the total number of newborns at risk and the prevalence of major congenital malformation events for each of the 2 gabapentin dispensing categories were provided. As noted above, given the very small sample size of gabapentin first trimester-exposed pregnancies ending in a live or still birth, and the low prevalence of major congenital

malformations, it is not feasible to conduct any further stratified analyses (i.e., analyses simultaneously stratified by the number of dispensing and other variables).

9.9.5. Amendments to the statistical analysis plan

In the Swedish data, double-adjustment of covariables with $0.1 < SMD < 0.2$ was applied to the analysis of major congenital malformations for the gabapentin vs. lamotrigine contrast.

9.10. Quality control

Data storage, management and analyses were conducted according to each institution's standard procedures. Each institution follows its internal quality control procedures to ensure the necessary compliance with local data protection, storage and archiving, and patient privacy laws and regulations, and obtained all permission necessary to conduct this study. At a minimum, all study documents (protocol, report, publications) were reviewed by the entire research team, including a senior epidemiologist in each institution. Clinical expertise is available for appropriate interpretation of results. At the start of the project, a kick-off meeting established a regular communication plan (via e-mail and regular teleconferences); and internal timelines were established to allow review and quality control before submitting each deliverable.

9.11. Protection of human subjects

Subject information and consent

Processing data in the Nordic registries ensues under the legal basis of public health interest, and patient consent is either not required or waived. All parties ensured protection of patient-level personal data and did not include patient names, did not provide personal data to any sponsor forms, reports, publications, or in any other disclosures. No individual-level data were transferred to Pfizer or among the countries as a part of this study.

Independent Ethics Committee (IEC)/Institutional Review Board (IRB)

The study was approved by each country's relevant authority (Data Protection Agency and/or Ethics Committees).[45 46] The coordinating investigator in each of the four countries was responsible for obtaining all required approvals and compliance with all relevant local laws. Investigators did not have access to the personal identification numbers since those were transferred to study-specific dummy-IDs by the data holders.

In Denmark, no IRB/IEC approval is required for studies based on data from registries. An approval from the Danish Data Protection Agency, required for all studies, was obtained (2016-051-000001, serial number 544) and recorded by Aarhus University.

In Finland, no ethical review by the regional ethics committee is required for research based solely on data from the registries.

In Norway, the protocol was approved by the Regional Committee for Medical and Health Research Ethics (2017/1507/REK vest and 22440 REK vest) and the Norwegian Data Protection Authority (17/01659-2/CDG).

In Sweden, an IEC approval was obtained from the Regional Ethical Review Board in Stockholm (reference numbers 2015/1826-31/22017/2238-32 and 2018/1790-32).

Ethical conduct of the study

The study was conducted in accordance with legal and regulatory requirements, as well as with scientific purpose, value, and rigor and follow generally accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), and the EMA European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology. The study protocol was posted in the EU PAS register maintained by the EMA (EUPAS38620), which will also contain the summary of the results.

Protection of personal data

To avoid re-identification of subjects, for the purposes of this report, personal data were defined as explicit or implicit cell counts between 1 and 4 whenever applicable according to country-specific regulations and study-specific approvals.[47] Such counts were masked in the output whenever relevant.

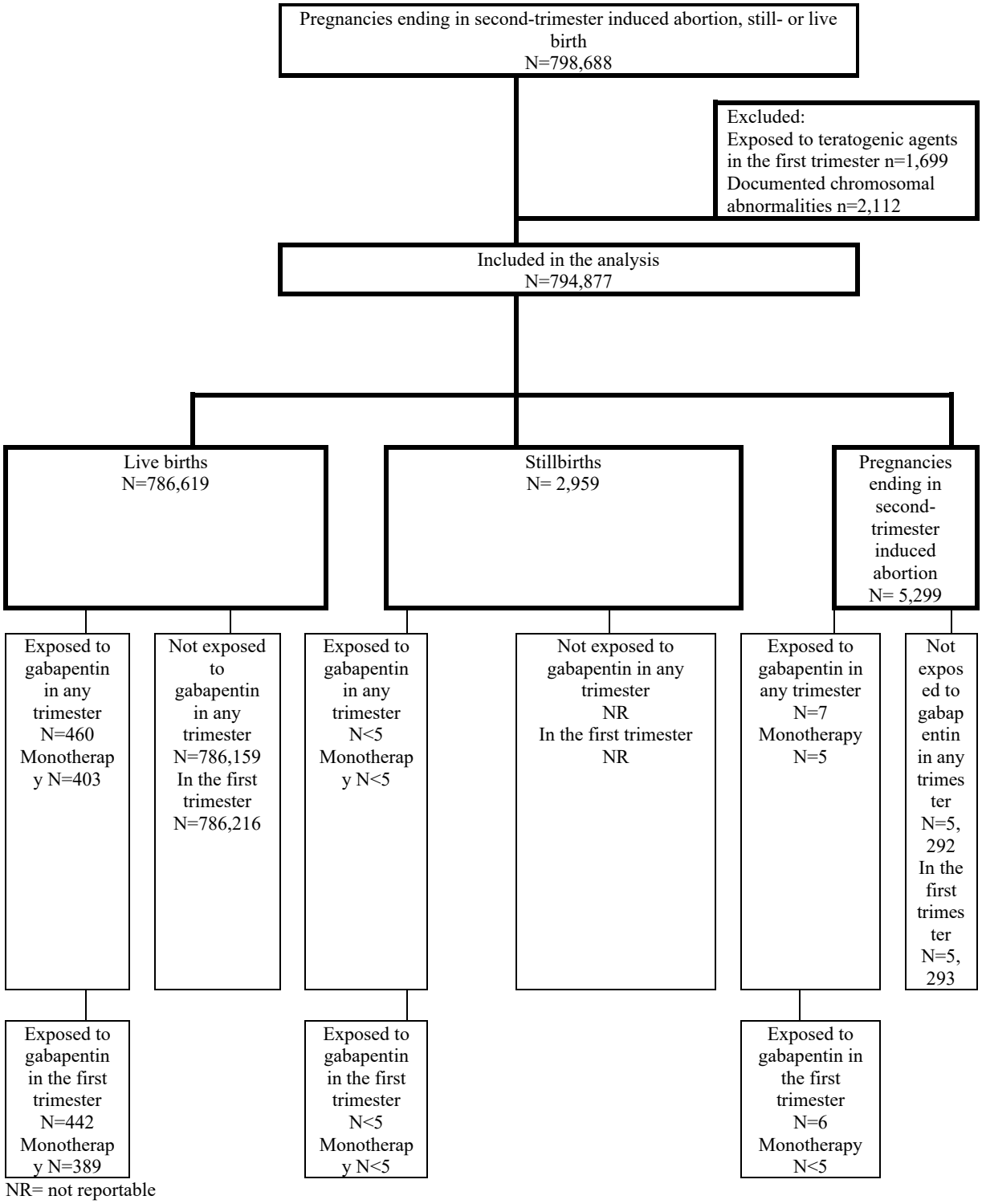
10. RESULTS

This report provides summary of country-specific results as well as meta-analyses of results from all participating countries.

10.1. Participants

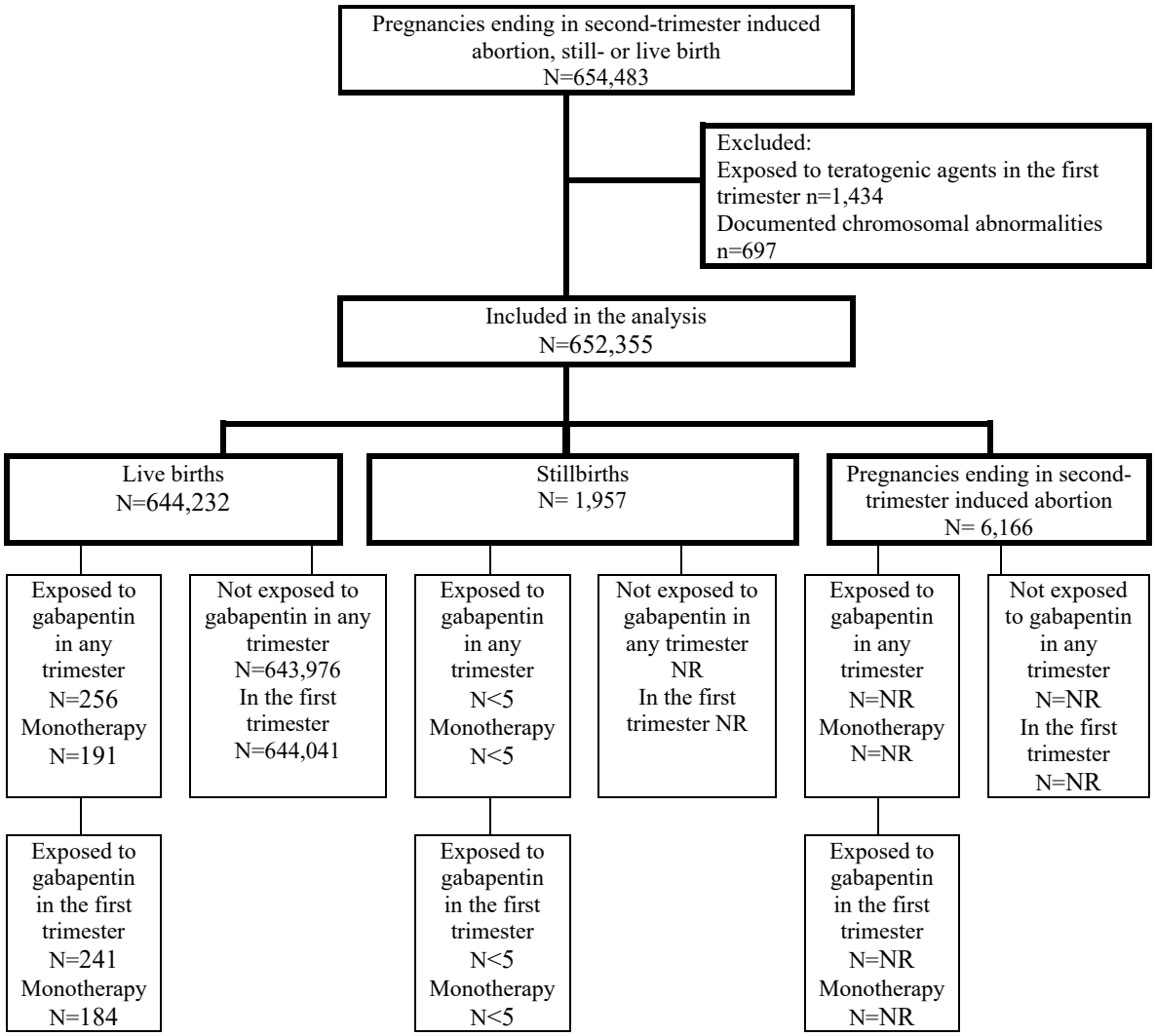
The numbers of pregnancies ending in a live or stillbirth or in a second-trimester induced abortions (TOPFA) (except for Sweden, where data on second-trimester induced abortions were unavailable) during the study period were 798,688 in Denmark (Figure 1), 654,483 in Finland (Figure 2), 666,449 in Norway (Figure 3), and 1,315,979 in Sweden (Figure 4). Figure 1-Figure 4 show the number of births by birth outcome (live birth, stillbirth, second-trimester induced abortion) in Denmark, Finland, Norway, and Sweden.

Figure 1. Identification of the study population, Denmark, Jan 2005-Dec 2017



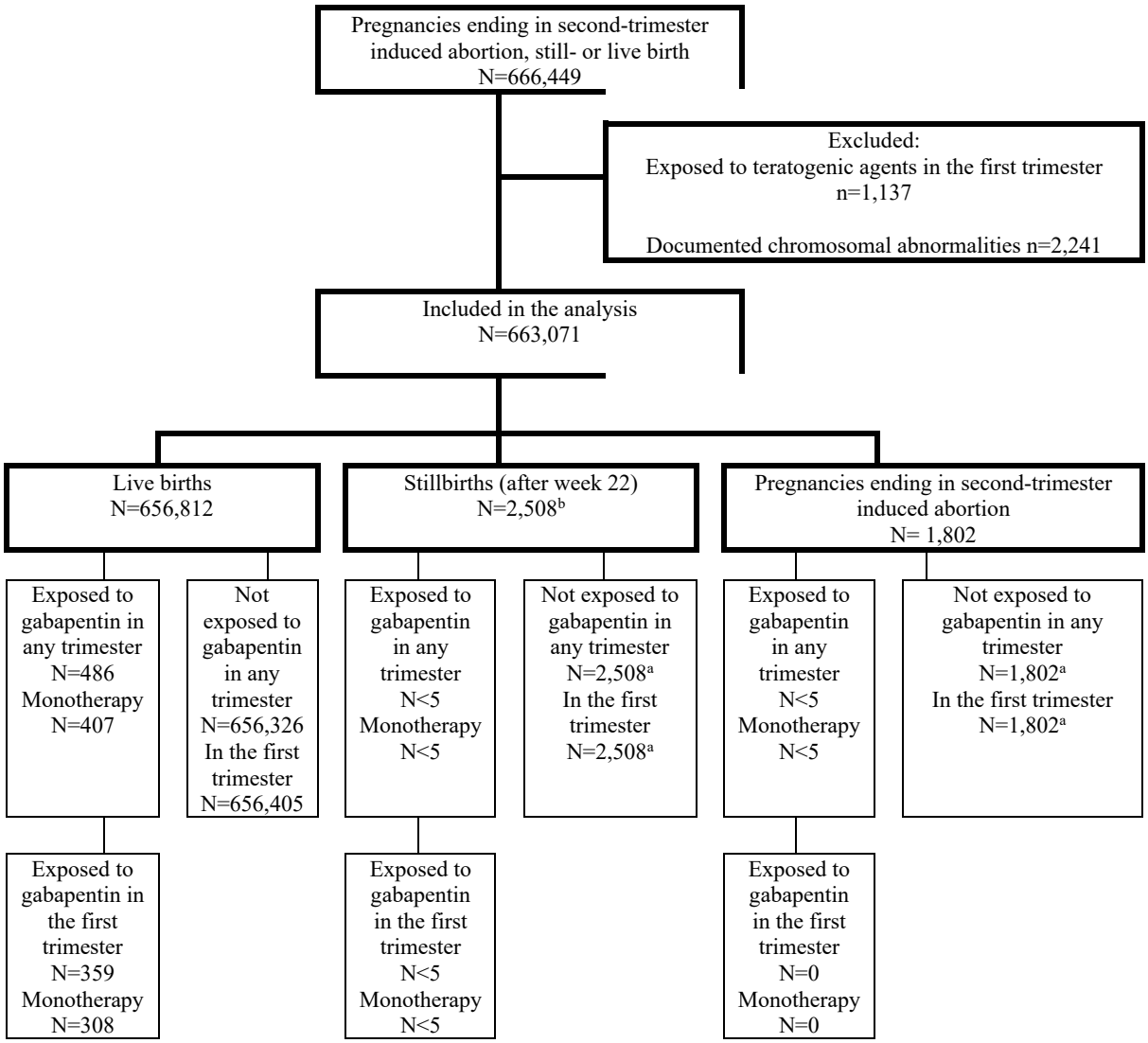
NR= not reportable

Figure 2. Identification of the study population, Finland, Jan 2005- Dec 2015



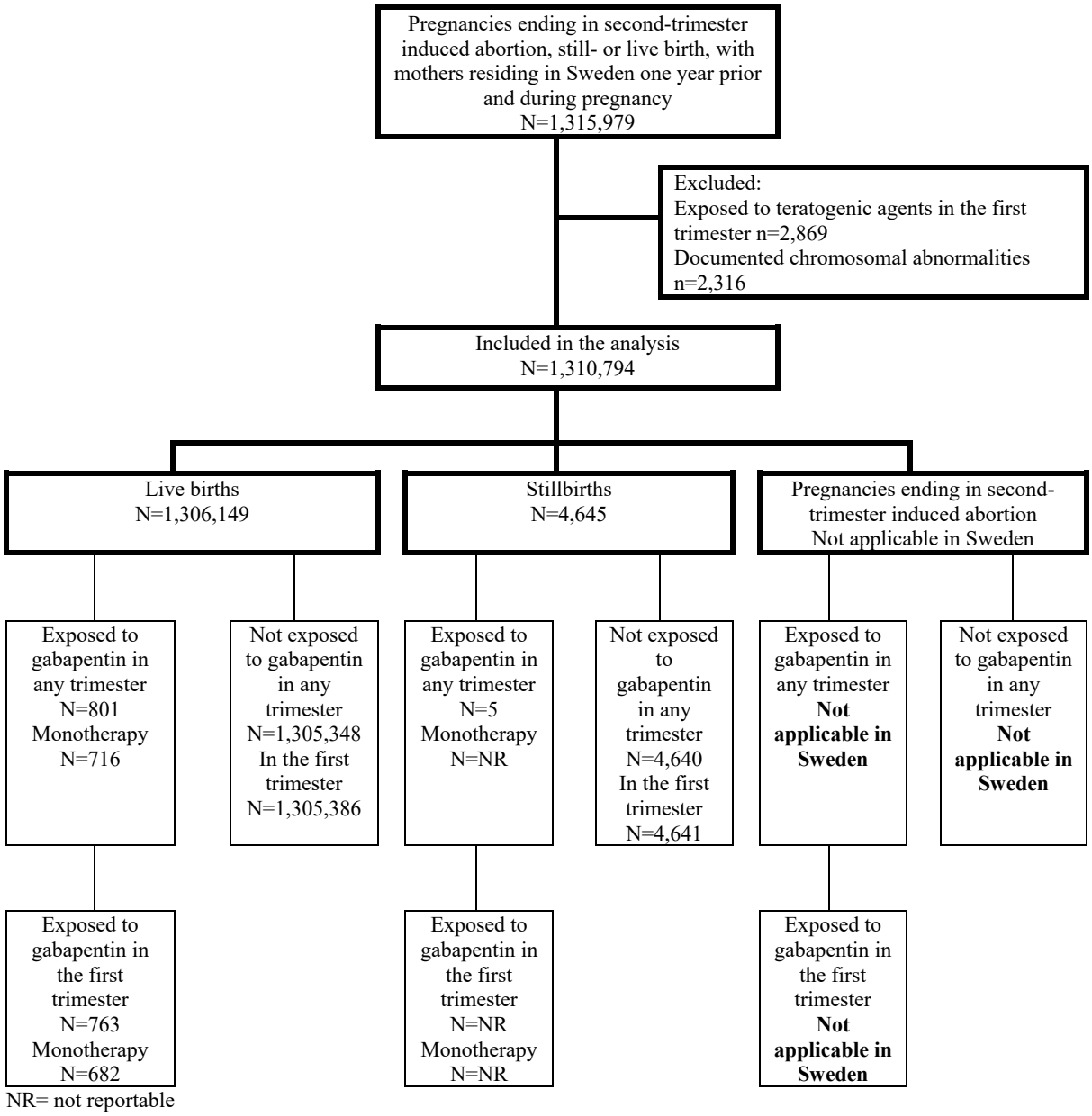
NR= not reportable

Figure 3. Identification of the study population, Norway, Jan 2005- Dec 2015



a Masked
b Pregnancy losses before week 22 were excluded (N=1,949).

Figure 4. Identification of the study population, Sweden, Jul 2006 to 31 Dec 2018



NR= not reportable

10.2. Descriptive data

The descriptive characteristics of the live/stillbirths according to prenatal exposure to gabapentin are shown in Table 4 for Denmark, Table 5 for Finland, Table 6 for Norway, and Table 7 for Sweden. The proportions of gabapentin-exposed births in any trimester in the study period were 0.06% in Denmark, 0.04% in Finland, 0.07% in Norway, and 0.06% in Sweden. The numbers of births exposed to any (poly- or monotherapy) gabapentin in any trimester were 460 in Denmark, 256 in Finland, 486 in Norway, and 806 in Sweden. Monotherapy accounted for most of the exposures both in the first trimester and any trimester (Appendix 4, Supplementary descriptive tables**)**. The gabapentin-exposed births had higher than the unexposed births prevalence of maternal smoking in pregnancy, maternal obesity, Caesarean delivery, and indicators of psychiatric comorbidity across all countries (Table 4-Table 7).

In Denmark, 26.5% of births with any exposure to gabapentin vs 12.3% of births without exposure to gabapentin or other AEDs were from mothers smoking in pregnancy; 24.1% vs 12.1%, respectively, were from mothers with BMI ≥30.0 kg/m^2; and 35.7% vs 22.0%, respectively, had a record of Caesarean delivery. In the 12 months pre-LMP, in Denmark, 25.7% of any gabapentin-exposed births vs 0.9% births with no exposure to gabapentin or other AED had a diagnostic record of neuropathic pain, and 25.0% vs 3.2% had a diagnostic record of other pain. The exact prevalence of epilepsy among gabapentin-exposed births cannot be reported because of data protection regulations; 0.2% of AED-unexposed births had a record of epilepsy diagnosis. The most prevalent co-medications in any trimester among the gabapentin-exposed births were antiinfectives for systemic use (62.0%), analgesics (61.3%), mood and anxiety disorders medication (36.7%), antidepressants (33.9%), and NSAIDs (33.9%); among births with no exposure to gabapentin or other AED the prevalence of co-medications was meaningfully lower for antiinfectives for systemic use (44.0%), analgesics (5.7%), mood and anxiety disorders medication (5.6%), antidepressants (3.7%), and NSAIDs (6.6%). The use of hypnotics and antipsychotics was more prevalent among gabapentin-exposed births vs births-unexposed to AEDs (8.0% vs 0.7% and 4.1% vs 0.4%, respectively).

In Finland, 36.3% of births with any exposure to gabapentin vs 14.9% of births without exposure to gabapentin or other AED were from mothers smoking in pregnancy; 16.0% vs 11.7%, respectively, were from mothers with BMI ≥ 30.0 kg/m^2; and 28.1% vs 16.7% had a record of Caesarean delivery. In the 12 months pre-LMP, in Finland, 12.1% of any gabapentin-exposed births vs 0.3% of births with no exposure to gabapentin or other AED had epilepsy diagnostic record, 24.2% vs 1.3% had diagnosis of neuropathic pain, 63.3% vs 11.5% had diagnosis of other pain. The most prevalent co-medications in any trimester among gabapentin-exposed births were antiinfectives for systemic use (58.6%), analgesics (64.1%), antidepressants (40.2%), and NSAIDs (41.8%); among births with no exposure to gabapentin or other AED the prevalence of co-medications was meaningfully lower for antiinfectives for systemic use (36.9%), analgesics (11.4%), antidepressants (4.6%), and NSAIDs (10.4%). The use of hypnotics and antipsychotics was more prevalent among gabapentin-exposed births vs births-unexposed to AEDs (11.3% vs 0.9% and 12.9% vs 0.7%, respectively).

In Norway, 23.0% of births with any exposure to gabapentin vs 9.7% of births with no exposure to gabapentin or other AED were from mothers smoking in pregnancy; 10.7% vs 4.9%, respectively, were from mothers with BMI ≥30.0 kg/m^2; and 31.7% vs 16.8%, respectively, had a record of Caesarean delivery. In the 12 months pre-LMP, in Norway, 4.7% of any gabapentin-exposed births vs 0.4% of births with no exposure to gabapentin or other AED had epilepsy diagnostic record, 8.2% vs 0.4% had diagnostic record of neuropathic pain, 55.6% vs 10.5% had diagnostic record of other pain. The most prevalent co-medications in any trimester among gabapentin-exposed births were antiinfectives for systemic use (44.0%), analgesics (50.8%), mood and anxiety disorders medication (14.0%), antidepressants (22.2%), and NSAIDs (39.1%); among births with no exposure to gabapentin or other AED the prevalence of co-medications was meaningfully lower for antiinfectives for systemic use (29.5%), analgesics (8.1%), mood and anxiety disorders medication (1.4%), antidepressants (0.8%), and NSAIDs (8.7%). The use of hypnotics and antipsychotics was also more prevalent among gabapentin-exposed births vs births-unexposed to AEDs (15.4% vs 1.5% and 8.8% vs 0.9%, respectively).

In Sweden, 19.4% of births with any exposure to gabapentin vs 5.5% of births with no exposure to gabapentin or other AED were from mothers smoking in pregnancy; 22.7% vs 12.3% were from mothers with BMI ≥30.0 kg/m^2; and 32.0% vs 17.7% had a record of Caesarean delivery. In the 12 months pre-LMP, in Sweden, 2.4% any gabapentin-exposed births vs <0.1% births without exposure to gabapentin or other AED had epilepsy diagnostic record, 27.8% vs 1.4% had diagnostic record of neuropathic pain, 25.8% vs 3.6% had diagnostic record of other pain. The most prevalent co-medications in any trimester among gabapentin-exposed births were antiinfectives for systemic use (48.8%), analgesics (71.6%), antidepressants (39.1%), and NSAIDs (32.3%); among births with no exposure to gabapentin or other AED the prevalence of co-medications was meaningfully lower for antiinfectives for systemic use (29.0%), analgesics (9.8%), antidepressants (5.2%), and NSAIDs (4.3%). The use of hypnotics and antipsychotics was also more prevalent among gabapentin-exposed births vs births-unexposed to AEDs (27.0% vs 2.3% and 6.5% vs 0.4%, respectively).

Similar pattern of higher prevalence of redeeming the prescriptions for antidepressants, hypnotics, and analgesics among birth with prenatal exposure to gabapentin vs comparators was observed across all countries.

Table 4. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Denmark.

Characteristics	Any exposure, any trimester, N=460	Monotherapy, any trimester, N=403	Any exposure, first trimester, N=442	Monotherapy, first trimester, N=389	No exposure during pregnancy, N=784,221	All pregnancies, N=789,578
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Calendar year of delivery						
2005	12 (2.6)	9 (2.2)	12 (2.7)	9 (2.3)	63,550 (8.1)	63,840 (8.1)
2006	9 (2.0)	9 (2.2)	8 (1.8)	8 (2.1)	64,164 (8.2)	64,473 (8.2)
2007	24 (5.2)	23 (5.7)	20 (4.5)	19 (4.9)	63,440 (8.1)	63,800 (8.1)
2008	20 (4.3)	16 (4.0)	20 (4.5)	16 (4.1)	64,186 (8.2)	64,548 (8.2)
2009	15 (3.3)	13 (3.2)	14 (3.2)	12 (3.1)	61,998 (7.9)	62,356 (7.9)
2010	31 (6.7)	24 (6.0)	30 (6.8)	23 (5.9)	62,428 (8.0)	62,827 (8.0)
2011	27 (5.9)	25 (6.2)	26 (5.9)	24 (6.2)	58,014 (7.4)	58,399 (7.4)
2012	37 (8.0)	33 (8.2)	37 (8.4)	33 (8.5)	56,873 (7.3)	57,296 (7.3)
2013	40 (8.7)	34 (8.4)	39 (8.8)	33 (8.5)	55,031 (7.0)	55,487 (7.0)
2014	51 (11.1)	41 (10.2)	50 (11.3)	41 (10.5)	56,119 (7.2)	56,604 (7.2)
2015	54 (11.7)	49 (12.2)	54 (12.2)	50 (12.9)	57,400 (7.3)	57,879 (7.3)
2016	62 (13.5)	55 (13.6)	58 (13.1)	53 (13.6)	60,650 (7.7)	61,177 (7.7)
2017	78 (17.0)	72 (17.9)	74 (16.7)	68 (17.5)	60,368 (7.7)	60,892 (7.7)
Age at the first day of LMP, years						
<25	56 (12.2)	50 (12.4)	52 (11.8)	47 (12.1)	102,766 (13.1)	103,522 (13.1)
25-34	280 (60.9)	241 (59.8)	273 (61.8)	236 (60.7)	532,882 (68.0)	536,380 (67.9)
35+	124 (27.0)	112 (27.8)	117 (26.5)	106 (27.2)	148,173 (18.9)	149,275 (18.9)
Missing	0	0	0	0	400 (0.1)	401 (0.1)
Parity						
Nulliparous	186 (40.4)	154 (38.2)	180 (40.7)	150 (38.6)	358,599 (45.7)	361,252 (45.8)
Parous[a]	274 (59.6)	249 (61.8)	262 (59.3)	239 (61.4)	425,622 (54.3)	428,326 (54.2)
Partner status						
Not cohabiting[b]	239 (52.0)	207 (51.4)	229 (51.8)	201 (51.7)	325,285 (41.5)	328,044 (41.5)
Cohabiting	221 (48.0)	196 (48.6)	213 (48.2)	188 (48.3)	458,936 (58.5)	461,534 (58.5)
Smoking during pregnancy						
Non-smoker	326 (70.9)	288 (71.5)	313 (70.8)	275 (70.7)	672,295 (85.7)	676,245 (85.6)
Smoker	122 (26.5)	103 (25.6)	118 (26.7)	103 (26.5)	96,405 (12.3)	97,667 (12.4)
Missing	12 (2.6)	12 (3.0)	11 (2.5)	11 (2.8)	15,521 (2.0)	15,666 (2.0)
Body mass index, kg/m2						
<18.5	27 (5.9)	25 (6.2)	26 (5.9)	24 (6.2)	33,957 (4.3)	34,200 (4.3)
18.5-< 25	209 (45.4)	187 (46.4)	199 (45.0)	179 (46.0)	468,941 (59.8)	471,637 (59.7)
25-< 30	96 (20.9)	81 (20.1)	94 (21.3)	79 (20.3)	159,567 (20.3)	160,810 (20.4)

Table 4. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Denmark.

Characteristics	Any exposure, any trimester, N=460	Monotherapy, any trimester, N=403	Any exposure, first trimester, N=442	Monotherapy, first trimester, N=389	No exposure during pregnancy, N=784,221	All pregnancies, N=789,578
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
≥ 30	111 (24.1)	96 (23.8)	107 (24.2)	94 (24.2)	94,629 (12.1)	95,558 (12.1)
Missing	17 (3.7)	14 (3.5)	16 (3.6)	13 (3.3)	27,127 (3.5)	27,373 (3.5)
Caesarean delivery	164 (35.7)	135 (33.5)	153 (34.6)	126 (32.4)	172,633 (22.0)	174,172 (22.1)
Multiple gestation	6 (1.3)	<5	6 (1.4)	<5	32,004 (4.1)	32,208 (4.1)
Girls	198 (43.0)	175 (43.4)	188 (42.5)	167 (42.9)	381,634 (48.7)	384,163 (48.7)
Stillbirth	<5	<5	<5	<5	2,931 (0.4)	2,959 (0.4)
Epilepsy	<5	0	<5	0	314 (0.0)	1,623 (0.2)
Birth weight, median (quartiles), grams	3,360 (3,020-3,760)	3,370 (3,024-3,764)	3,360 (3,020-3,760)	3,370 (3,025-3,760)	3,500 (3,150-3,850)	3,500 (3,150-3,850)
Gestational age, median (quartiles), weeks	39 (38-40)	39 (38-40)	39 (38-40)	39 (38-40)	40 (38-40)	40 (38-40)
Head circumference, median (quartiles), cm	35 (33-36)	35 (34-36)	35 (34-36)	35 (34-36)	35 (34-36)	35 (34-36)
Neuropathic pain	118 (25.7)	98 (24.3)	116 (26.2)	97 (24.9)	6,769 (0.9)	7,026 (0.9)
Other pain	115 (25.0)	99 (24.6)	113 (25.6)	98 (25.2)	25,144 (3.2)	25,611 (3.2)
Migraine or other headache syndromes	53 (11.5)	45 (11.2)	50 (11.3)	43 (11.1)	16,865 (2.2)	17,231 (2.2)
Other neurologic disorders	289 (62.8)	250 (62.0)	281 (63.6)	246 (63.2)	59,230 (7.6)	61,203 (7.8)
Depression	150 (32.6)	126 (31.3)	146 (33.0)	123 (31.6)	37,916 (4.8)	39,519 (5.0)
Bipolar disorder	0	0	0	0	136 (0.0)	232 (0.0)
Alcohol abuse or dependence	<5	<5	<5	<5	497 (0.1)	530 (0.1)
Drug abuse or dependence	26 (5.7)	21 (5.2)	24 (5.4)	20 (5.1)	2,866 (0.4)	3,011 (0.4)
Hypertension	23 (5.0)	17 (4.2)	23 (5.2)	17 (4.4)	11,893 (1.5)	12,108 (1.5)
Haematological diseases	11 (2.4)	10 (2.5)	11 (2.5)	10 (2.6)	2,891 (0.4)	2,941 (0.4)
Diabetes	9 (2.0)	9 (2.2)	8 (1.8)	8 (2.1)	11,790 (1.5)	11,899 (1.5)
Asthma	46 (10.0)	39 (9.7)	44 (10.0)	38 (9.8)	33,347 (4.3)	33,728 (4.3)
Liver diseases	0	0	0	0	285 (0.0)	287 (0.0)
Renal impairment	<5	<5	<5	<5	1,133 (0.1)	1,148 (0.1)
Rheumatic diseases	7 (1.5)	6 (1.5)	7 (1.6)	6 (1.5)	2,438 (0.3)	2,474 (0.3)
Obesity	116 (25.2)	101 (25.1)	112 (25.3)	99 (25.4)	98,917 (12.6)	99,897 (12.7)
Disorders of female pelvic organs/genital tract	<5	<5	<5	<5	2,830 (0.4)	2,860 (0.4)
Thyroid disorders	12 (2.6)	9 (2.2)	11 (2.5)	8 (2.1)	13,994 (1.8)	14,109 (1.8)
Infections	119 (25.9)	97 (24.1)	114 (25.8)	94 (24.2)	119,475 (15.2)	120,544 (15.3)

Table 4. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Denmark.

Characteristics	Any exposure, any trimester, N=460	Monotherapy, any trimester, N=403	Any exposure, first trimester, N=442	Monotherapy, first trimester, N=389	No exposure during pregnancy, N=784,221	All pregnancies, N=789,578
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Antiepileptic drugs other than exposure-first trimester	53 (11.5)	0	53 (12.0)	0	0	422 (0.1)
Antidepressants-first trimester	150 (32.6)	114 (28.3)	147 (33.3)	114 (29.3)	27,241 (3.5)	28,654 (3.6)
Hypnotics-first trimester	31 (6.7)	25 (6.2)	31 (7.0)	25 (6.4)	4,743 (0.6)	5,024 (0.6)
Anxiolytics-first trimester	18 (3.9)	14 (3.5)	17 (3.8)	13 (3.3)	3,758 (0.5)	4,100 (0.5)
Antipsychotics-first trimester	19 (4.1)	15 (3.7)	19 (4.3)	16 (4.1)	2,782 (0.4)	3,301 (0.4)
Analgesics-first trimester	264 (57.4)	229 (56.8)	257 (58.1)	224 (57.6)	34,346 (4.4)	35,295 (4.5)
Antihypertensives-first trimester	19 (4.1)	14 (3.5)	19 (4.3)	14 (3.6)	7,206 (0.9)	7,357 (0.9)
Non-steroidal anti-inflammatory drugs-first trimester	150 (32.6)	133 (33.0)	147 (33.3)	133 (34.2)	46,819 (6.0)	47,521 (6.0)
Drugs for peptic ulcer/gastroesophageal reflux-first trimester	80 (17.4)	71 (17.6)	79 (17.9)	71 (18.3)	21,099 (2.7)	21,514 (2.7)
Folic acid-first trimester	10 (2.2)	5 (1.2)	10 (2.3)	5 (1.3)	2,361 (0.3)	3,367 (0.4)
Drugs for in-vitro fertilization-first trimester	26 (5.7)	24 (6.0)	25 (5.7)	23 (5.9)	74,452 (9.5)	74,898 (9.5)
Thyroid hormones-first trimester	10 (2.2)	7 (1.7)	9 (2.0)	6 (1.5)	14,069 (1.8)	14,176 (1.8)
Systemic corticosteroids-first trimester	11 (2.4)	10 (2.5)	11 (2.5)	10 (2.6)	8,033 (1.0)	8,122 (1.0)
Antiinfectves for systemic use-first trimester	210 (45.7)	183 (45.4)	203 (45.9)	177 (45.5)	204,876 (26.1)	206,710 (26.2)
Antiepileptic drugs other than exposure-any	57 (12.4)	0	57 (12.9)	<5	0	469 (0.1)
Antidepressants-any	156 (33.9)	118 (29.3)	152 (34.4)	117 (30.1)	29,073 (3.7)	30,545 (3.9)
Hypnotics-any	37 (8.0)	31 (7.7)	36 (8.1)	30 (7.7)	5,452 (0.7)	5,763 (0.7)
Anxiolytics-any	18 (3.9)	14 (3.5)	17 (3.8)	13 (3.3)	4,445 (0.6)	4,853 (0.6)
Antipsychotics-any	19 (4.1)	15 (3.7)	19 (4.3)	16 (4.1)	3,009 (0.4)	3,550 (0.4)
Analgesics-any	282 (61.3)	247 (61.3)	270 (61.1)	237 (60.9)	44,449 (5.7)	45,530 (5.8)
Antihypertensives-any	28 (6.1)	23 (5.7)	26 (5.9)	21 (5.4)	11,191 (1.4)	11,394 (1.4)
Non-steroidal anti-inflammatory drugs-any	156 (33.9)	137 (34.0)	151 (34.2)	135 (34.7)	51,376 (6.6)	52,121 (6.6)
Drugs for peptic ulcer/gastroesophageal reflux-any	101 (22.0)	90 (22.3)	100 (22.6)	91 (23.4)	36,335 (4.6)	36,930 (4.7)

Table 4. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Denmark.

Characteristics	Any exposure, any trimester, N=460	Monotherapy, any trimester, N=403	Any exposure, first trimester, N=442	Monotherapy, first trimester, N=389	No exposure during pregnancy, N=784,221	All pregnancies, N=789,578
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Folic acid-any	12 (2.6)	6 (1.5)	11 (2.5)	5 (1.3)	2,779 (0.4)	3,902 (0.5)
Drugs for in-vitro fertilization-any	28 (6.1)	24 (6.0)	27 (6.1)	23 (5.9)	76,441 (9.7)	76,908 (9.7)
Thyroid hormones-any	12 (2.6)	9 (2.2)	10 (2.3)	7 (1.8)	15,992 (2.0)	16,114 (2.0)
Systemic corticosteroids-any	14 (3.0)	12 (3.0)	14 (3.2)	12 (3.1)	9,633 (1.2)	9,746 (1.2)
Antiinfectves for systemic use-any	285 (62.0)	249 (61.8)	273 (61.8)	239 (61.4)	345,093 (44.0)	347,913 (44.1)
Psychotic disorders	21 (4.6)	18 (4.5)	21 (4.8)	19 (4.9)	4,623 (0.6)	5,256 (0.7)
Mood and anxiety disorders	169 (36.7)	139 (34.5)	165 (37.3)	138 (35.5)	44,024 (5.6)	46,030 (5.8)
Number of hospitalizations, median (quartiles)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-0)
Number of specialist outpatient visits at hospitals, median (quartiles)	2 (0-6)	2 (0-7)	3 (0-6)	2 (0-7)	0 (0-1)	0 (0-1)
Sleep disorders	46 (10.0)	36 (8.9)	45 (10.2)	35 (9.0)	8,910 (1.1)	9,464 (1.2)
Eating disorders	6 (1.3)	<5	5 (1.1)	<5	2,420 (0.3)	2,634 (0.3)
ADHD, autism and intellectual disability	10 (2.2)	9 (2.2)	9 (2.0)	9 (2.3)	2,298 (0.3)	2,458 (0.3)
History of suicide attempt	0	0	0	0	201 (0.0)	214 (0.0)

a. Unknown parity information was counted into the category Parous

b. Unknown cohabiting information was counted into the category Not cohabiting.

Numbers are n (%) unless specified otherwise

Table 5. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Finland.

Characteristics		Any exposure, any trimester, N = 256	Monotherapy, any trimester, N = 191	Any exposure, first trimester, N = 241	Monotherapy, first trimester, N = 184	No exposure to gabapentin or other AED, N = 640,381	All births, N = 646,189
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Calendar year of delivery	2006	21 (8.2)	16 (8.4)	21 (8.7)	16 (8.7)	57,163 (8.9)	57,515 (8.9)
	2007	7 (2.7)	<5	7 (2.9)	<5	58,369 (9.1)	58,771 (9.1)
	2008	11 (4.3)	8 (4.2)	11 (4.6)	8 (4.3)	58,201 (9.1)	58,641 (9.1)
	2009	16 (6.2)	14 (7.3)	16 (6.6)	14 (7.6)	58,918 (9.2)	59,438 (9.2)
	2010	16 (6.2)	5-8 (2.6-4.2)	13 (5.4)	4-7 (2.2-3.8)	59,808 (9.3)	60,372 (9.3)
	2011	32 (12.5)	19 (9.9)	28 (11.6)	18 (9.8)	60,331 (9.4)	60,912 (9.4)
	2012	19 (7.4)	17 (8.9)	18 (7.5)	17 (9.2)	59,297 (9.3)	59,893 (9.3)
	2013	22 (8.6)	19 (9.9)	22 (9.1)	19 (10.3)	58,851 (9.2)	59,459 (9.2)
	2014	30 (11.7)	26 (13.6)	29 (12.0)	25 (13.6)	57,651 (9.0)	58,211 (9.0)
	2015	47 (18.4)	33 (17.3)	45 (18.7)	32 (17.4)	56,894 (8.9)	57,540 (8.9)
	2016	35 (13.7)	30 (15.7)	31 (12.9)	27 (14.7)	54,898 (8.6)	55,437 (8.6)
Age at the first day of LMP, years	<20	8 (3.1)	5 (2.6)	7 (2.9)	5 (2.7)	23,294 (3.6)	23,539 (3.6)
	20-34	196 (76.6)	144 (75.4)	183 (75.9)	138 (75.0)	516,930 (80.7)	521,583 (80.7)
	35-45	52 (20.3)	42 (22.0)	51 (21.2)	41 (22.3)	99,848 (15.6)	100,754 (15.6)
	>45	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	309 (0.0)	313 (0.0)
Parity	Nulliparous	107 (41.8)	86 (45.0)	103 (42.7)	84 (45.7)	267,313 (41.7)	269,992 (41.8)
	Parous	149 (58.2)	105 (55.0)	138 (57.3)	100 (54.3)	373,068 (58.3)	376,197 (58.2)
Partner status	Cohabiting	202 (78.9)	155 (81.2)	188 (78.0)	148 (80.4)	577,030 (90.1)	581,859 (90.0)
	Not cohabiting	38 (14.8)	23 (12.0)	37 (15.4)	23 (12.5)	33,220 (5.2)	33,850 (5.2)
	Other/missing	16 (6.2)	13 (6.8)	16 (6.6)	13 (7.1)	30,131 (4.7)	30,480 (4.7)
Smoking during pregnancy	No	155 (60.5)	126 (66.0)	144 (59.8)	120 (65.2)	528,944 (82.6)	532,853 (82.5)
	Yes	93 (36.3)	61-64 (31.9-33.5)	89 (36.9)	60-63 (32.6-34.2)	95,558 (14.9)	97,308 (15.1)
	Missing	8 (3.1)	<5	8 (3.3)	<5	15,879 (2.5)	16,028 (2.5)
Body mass index, kg/m2	<18.5	9 (3.5)	5 (2.6)	9 (3.7)	5 (2.7)	13,651 (2.1)	13,793 (2.1)
	18.5-<25.0	138 (53.9)	104 (54.5)	130 (53.9)	101 (54.9)	396,129 (61.9)	399,267 (61.8)
	25.0-<30.0	59 (23.0)	40 (20.9)	54 (22.4)	38 (20.7)	133,661 (20.9)	135,012 (20.9)
	≥30.0	41 (16.0)	34 (17.8)	39 (16.2)	32 (17.4)	74,622 (11.7)	75,632 (11.7)
	Missing	9 (3.5)	8 (4.2)	9 (3.7)	8 (4.3)	22,318 (3.5)	22,485 (3.5)
Caesarean delivery	Yes	72 (28.1)	56 (29.3)	71 (29.5)	55 (29.9)	106,993 (16.7)	108,220 (16.7)
Multiple gestation	Yes	10 (3.9)	8 (4.2)	10 (4.1)	8 (4.3)	18,377 (2.9)	18,521 (2.9)
Girls	Yes	134 (52.3)	100 (52.4)	129 (53.5)	98 (53.3)	313,040 (48.9)	315,906 (48.9)

Table 5. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Finland.

Characteristics		Any exposure, any trimester, N = 256	Monotherapy, any trimester, N = 191	Any exposure, first trimester, N = 241	Monotherapy, first trimester, N = 184	No exposure to gabapentin or other AED, N = 640,381	All births, N = 646,189
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Birth weight, median (quartiles), grams	Median (Q1-Q3)	3,246.00 (2,932.00-3,662.50)	3,260.00 (2,922.50-3,679.00)	3,272.00 (2,935.00-3,680.00)	3,271.00 (2,916.50-3,730.00)	3,525.00 (3,190.00-3,856.00)	3,525.00 (3,190.00-3,855.00)
Gestational age, median (quartiles), weeks	Median (Q1-Q3)	39.0 (38.0-40.0)	39.00 (38.0-40.0)	39.00 (38.0-40.0)	39.00 (38.0-40.0)	40.00 (39.0-40.0)	40.00 (39.0-40.0)
Head circumference, median (quartiles), cm	Median (Q1-Q3)	34.5 (33.5-35.0)	34.5 (33.5-35.5)	34.5 (33.5-35.0)	34.5 (33.5-35.4)	35.0 (34.0-36.0)	35.0 (34.0-36.0)
Stillbirth		<5	<5	<5	<5	1,929 (0.3)	1,957 (0.3)
Epilepsy (12m)		31 (12.1)	10 (5.2)	29 (12.0)	10 (5.4)	1,865 (0.3)	4,653 (0.7)
Neuropathic pain (12m)		62 (24.2)	52 (27.2)	56 (23.2)	48 (26.1)	8,487 (1.3)	8,858 (1.4)
Other pain		162 (63.3)	123 (64.4)	150 (62.2)	118 (64.1)	73,800 (11.5)	75,517 (11.7)
Migraine or other headache syndromes		52 (20.3)	38 (19.9)	47 (19.5)	36 (19.6)	18,822 (2.9)	19,358 (3.0)
Other neurologic disorders		171 (66.8)	128 (67.0)	159 (66.0)	123 (66.8)	59,726 (9.3)	61,976 (9.6)
Depression		118 (46.1)	79 (41.4)	113 (46.9)	78 (42.4)	38,383 (6.0)	40,092 (6.2)
Bipolar disorder		7 (2.7)	<5	6 (2.5)	<5	827 (0.1)	1,191 (0.2)
Alcohol abuse or dependence		5 (2.0)	<5	5 (2.1)	<5	959 (0.1)	1,082 (0.2)
Drug abuse or dependence		19 (7.4)	10 (5.2)	19 (7.9)	10 (5.4)	1,181 (0.2)	1,445 (0.2)
Hypertension		41 (16.0)	27 (14.1)	38 (15.8)	27 (14.7)	13,471 (2.1)	13,948 (2.2)
Haematological diseases		6 (2.3)	5 (2.6)	6 (2.5)	5 (2.7)	2,654 (0.4)	2,699 (0.4)
Diabetes		<5	<5	<5	<5	7,206 (1.1)	7,315 (1.1)
Asthma		60 (23.4)	41 (21.5)	58 (24.1)	41 (22.3)	42,353 (6.6)	43,014 (6.7)
Liver diseases		<5	<5	<5	0 (0.0)	330 (0.1)	340 (0.1)
Renal impairment		<5	<5	<5	<5	1,959 (0.3)	2,003 (0.3)
Rheumatic diseases		<5	<5	<5	<5	3,272 (0.5)	3,324 (0.5)
Obesity		41 (16.0)	34 (17.8)	39 (16.2)	32 (17.4)	74,828 (11.7)	75,843 (11.7)
Disorders of female pelvic organs/genital tract		30 (11.7)	22 (11.5)	28 (11.6)	21 (11.4)	40,499 (6.3)	40,997 (6.3)
Thyroid disorders		14 (5.5)	10 (5.2)	13 (5.4)	9 (4.9)	17,986 (2.8)	18,271 (2.8)
Infections		87 (34.0)	66 (34.6)	83 (34.4)	64 (34.8)	93,866 (14.7)	95,093 (14.7)
Antidepressants		103 (40.2)	67 (35.1)	97 (40.2)	65 (35.3)	29,177 (4.6)	30,645 (4.7)
Hypnotics		29 (11.3)	17 (8.9)	25 (10.4)	15 (8.2)	5,488 (0.9)	5,906 (0.9)
Antipsychotics		33 (12.9)	22 (11.5)	29 (12.0)	22 (12.0)	4,183 (0.7)	4,967 (0.8)
Analgesics		164 (64.1)	124 (64.9)	150 (62.2)	117 (63.6)	72,716 (11.4)	74,449 (11.5)

Table 5. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Finland.

Characteristics		Any exposure, any trimester, N = 256	Monotherapy, any trimester, N = 191	Any exposure, first trimester, N = 241	Monotherapy, first trimester, N = 184	No exposure to gabapentin or other AED, N = 640,381	All births, N = 646,189
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Antihypertensives		44 (17.2)	33 (17.3)	42 (17.4)	32 (17.4)	12,869 (2.0)	13,298 (2.1)
Non-steroidal anti-inflammatory drugs		107 (41.8)	83 (43.5)	98 (40.7)	79 (42.9)	66,292 (10.4)	67,689 (10.5)
Drugs for peptic ulcer/gastroesophageal reflux		64 (25.0)	44 (23.0)	59 (24.5)	42 (22.8)	33,663 (5.3)	34,343 (5.3)
Folic acid		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drugs for in-vitro fertilization		8 (3.1)	8 (4.2)	7 (2.9)	7 (3.8)	21,545 (3.4)	21,700 (3.4)
Thyroid hormones		15 (5.9)	10 (5.2)	14 (5.8)	9 (4.9)	23,188 (3.6)	23,545 (3.6)
Systemic corticosteroids		19 (7.4)	14 (7.3)	16 (6.6)	12 (6.5)	9,651 (1.5)	9,851 (1.5)
Antiinfectives for systemic use		150 (58.6)	107 (56.0)	137 (56.8)	102 (55.4)	236,267 (36.9)	239,109 (37.0)
Antidepressants (first tri)		92 (35.9)	59 (30.9)	88 (36.5)	58 (31.5)	26,751 (4.2)	28,123 (4.4)
Hypnotics (first tri)		23 (9.0)	12 (6.3)	20 (8.3)	11 (6.0)	5,015 (0.8)	5,394 (0.8)
Antipsychotics (first tri)		29 (11.3)	19 (9.9)	26 (10.8)	19 (10.3)	3,627 (0.6)	4,336 (0.7)
Analgesics (first tri)		134 (52.3)	102 (53.4)	127 (52.7)	100 (54.3)	42,360 (6.6)	43,618 (6.8)
Antihypertensives (first tri)		36 (14.1)	26 (13.6)	35 (14.5)	25 (13.6)	8,375 (1.3)	8,713 (1.3)
Non-steroidal anti-inflammatory drugs (first tri)		94 (36.7)	75 (39.3)	87 (36.1)	73 (39.7)	61,703 (9.6)	63,013 (9.8)
Drugs for peptic ulcer/gastroesophageal reflux (first tri)		46 (18.0)	31 (16.2)	43 (17.8)	30 (16.3)	18,111 (2.8)	18,572 (2.9)
Folic acid (first tri)		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Drugs for in-vitro fertilization (first tri)		8 (3.1)	8 (4.2)	7 (2.9)	7 (3.8)	21,540 (3.4)	21,695 (3.4)
Thyroid hormones (first tri)		11 (4.3)	7 (3.7)	11 (4.6)	7 (3.8)	18,994 (3.0)	19,296 (3.0)
Systemic corticosteroids (first tri)		13 (5.1)	8 (4.2)	10 (4.1)	6 (3.3)	7,208 (1.1)	7,355 (1.1)
Antiinfectves for systemic use (first tri)		117 (45.7)	83 (43.5)	108 (44.8)	80 (43.5)	151,998 (23.7)	153,978 (23.8)
Number of hospitalizations, median (quartiles)	Median (Q1-Q3)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-1.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)
Number of specialist outpatient visits at hospitals, median (quartiles)	Median (Q1-Q3)	3.00 (1.00-9.00)	3.00 (1.00-8.50)	3.00 (1.00-9.00)	3.00 (1.00-8.25)	0.00 (0.00-1.00)	0.00 (0.00-1.00)
Number of visits in primary care, median (quartiles)*	Median (Q1-Q3)	0.00 (0.00-9.00)	1.00 (0.00-9.00)	0.00 (0.00-9.00)	0.50 (0.00-9.00)	0.00 (0.00-0.00)	0.00 (0.00-0.00)

Table 5. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Finland.

Characteristics		Any exposure, any trimester, N = 256	Monotherapy, any trimester, N = 191	Any exposure, first trimester, N = 241	Monotherapy, first trimester, N = 184	No exposure to gabapentin or other AED, N = 640,381	All births, N = 646,189
		n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Psychotic disorders		37 (14.5)	27 (14.1)	35 (14.5)	27 (14.7)	5,149 (0.8)	5,944 (0.9)
Mood and anxiety disorder (12m)		136 (53.1)	90 (47.1)	129 (53.5)	88 (47.8)	43,108 (6.7)	45,303 (7.0)
Sleep disorders		52 (20.3)	25 (13.1)	49 (20.3)	25 (13.6)	9,670 (1.5)	10,610 (1.6)
Eating disorders		12 (4.7)	8 (4.2)	11 (4.6)	8 (4.3)	1,928 (0.3)	2,214 (0.3)
ADHD, autism and intellectual disability		<5	<5	<5	<5	509 (0.1)	557 (0.1)
History of suicide attempt		0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	7 (0.0)	8 (0.0)
Numbers are n (%) unless specified otherwise *Finland only)							

Table 6. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Norway.

Characteristics	Exposure to gabapentin					
	Any exposure, any trimester N=486	Monotherapy, any trimester N=407	Any exposure, first trimester N=359	Monotherapy, first trimester N=308	No exposure during pregnancy N=654,734	All pregnancies N=659,320
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Perinatal characteristics						
Calendar year of delivery						
2005	10 (2.1)	9 (2.2)	7 (1.9)	6 (1.9)	56,886 (8.7)	57,160 (8.7)
2006	15 (3.1)	13 (3.2)	12 (3.3)	10 (3.2)	58,539 (8.9)	58,875 (8.9)
2007	17 (3.5)	13 (3.2)	15 (4.2)	11 (3.6)	58,491 (8.9)	58,846 (8.9)
2008	19 (3.9)	12 (2.9)	14 (3.9)	7 (2.3)	60,551 (9.2)	60,968 (9.2)
2009	37 (7.6)	32 (7.9)	26 (7.2)	24 (7.8)	61,919 (9.5)	62,357 (9.5)
2010	47 (9.7)	37 (9.1)	35 (9.7)	28 (9.1)	61,486 (9.4)	61,897 (9.4)
2011	60 (12.3)	47 (11.5)	38 (10.6)	32 (10.4)	60,177 (9.2)	60,630 (9.2)
2012	75 (15.4)	61 (15.0)	57 (15.9)	46 (14.9)	60,178 (9.2)	60,665 (9.2)
2013	62 (12.8)	53 (13.0)	50 (13.9)	47 (15.3)	58,839 (9.0)	59,305 (9.0)
2014	80 (16.5)	72 (17.7)	61 (17.0)	55 (17.9)	58,894 (9.0)	59,360 (9.0)
2015	64 (13.2)	58 (14.3)	44 (12.3)	42 (13.6)	58,774 (9.0)	59,257 (9.0)
Age at LMP, years						

Table 6. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Norway.

Characteristics	Exposure to gabapentin					
	Any exposure, any trimester N=486	Monotherapy, any trimester N=407	Any exposure, first trimester N=359	Monotherapy, first trimester N=308	No exposure during pregnancy N=654,734	All pregnancies N=659,320
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
<20	9 (1.9)	7 (1.7)	6 (1.7)	4 (1.3)	19,969 (3.0)	20,119 (3.1)
20-34	352 (72.4)	295 (72.5)	255 (71.0)	221 (71.8)	532,985 (81.4)	536,622 (81.4)
35-45	125 (25.7)	105 (25.8)	98 (27.3)	83 (26.9)	101,477 (15.5)	102,275 (15.5)
>45	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	303 (0.0)	304 (0.0)
Parity						
Nulliparous	184 (37.9)	155 (38.1)	137 (38.2)	118 (38.3)	276,892 (42.3)	278,951 (42.3)
Parous	302 (62.1)	252 (61.9)	222 (61.8)	190 (61.7)	377,842 (57.7)	380,369 (57.7)
Partner status						
Cohabiting	424 (87.2)	357 (87.7)	310 (86.4)	266 (86.4)	606,716 (92.7)	610,643 (92.6)
Not cohabiting	62 (12.8)	50 (12.3)	49 (13.6)	42 (13.6)	48,018 (7.3)	48,677 (7.4)
Smoking during pregnancy						
Yes	112 (23.0)	88 (21.6)	89 (24.8)	74 (24.0)	63,439 (9.7)	64,362 (9.8)
No	306 (63.0)	263 (64.6)	223 (62.1)	193 (62.7)	476,560 (72.8)	479,546 (72.7)
Missing	68 (14.0)	56 (13.8)	47 (13.1)	41 (13.3)	114,735 (17.5)	115,412 (17.5)
Body mass index, kg/m2						
<18.5	11 (2.3)	10 (2.5)	9 (2.5)	8 (2.6)	10,983 (1.7)	11,064 (1.7)
18.5-25.0	131 (27.0)	105 (25.8)	100 (27.9)	82 (26.6)	171,383 (26.2)	172,594 (26.2)
25.0-30.0	67 (13.8)	59 (14.5)	44 (12.3)	40 (13.0)	49,825 (7.6)	50,237 (7.6)
>=30.0	52 (10.7)	47 (11.5)	37 (10.3)	34 (11.0)	31,839 (4.9)	32,174 (4.9)
missing	225 (46.3)	186 (45.7)	169 (47.1)	144 (46.8)	390,704 (59.7)	393,251 (59.6)
Caesarean delivery	154 (31.7)	133 (32.7)	107 (29.8)	94 (30.5)	109,803 (16.8)	110,931 (16.8)
Multiple gestation	25 (5.1)	22 (5.4)	25 (7)	23 (7.5)	22,395 (3.4)	22,523 (3.4)
Girls	233 (47.9)	197 (48.4)	172 (47.9)	151 (49.0)	318,639 (48.7)	320,885 (48.7)
Birth weight, median (quartiles), grams	3,370 (3,033-3,740)	3,365 (3,010-3,745)	3,360 (3,023-3,720)	3,345 (3,008-3,718)	3,526 (3,175-3,870)	3,525 (3,175-3,870)
Gestational age, median (quartiles), days	276 (267-284)	275 (266-283)	275 (266-284)	275 (266-284)	280 (273-286)	280 (273-286)
Head circumference, median (quartiles), cm	35 (34-36)	35 (34-36)	35 (34-36)	35 (34-36)	35 (34-36)	35 (34-36)
Stillbirth	1 (0.2)	1 (0.2)	1 (0.3)	1 (0.3)	2,486 (0.4)	2,508 (0.4)
Indication for Gabapentin use						
Epilepsy	23 (4.7)	8 (2.0)	20 (5.6)	6 (1.9)	2,546 (0.4)	4,586 (0.7)
Neuropathic pain	40 (8.2)	35 (8.6)	33 (9.2)	30 (9.7)	2,717 (0.4)	2,826 (0.4)
Other pain	270 (55.6)	226 (55.5)	211 (58.8)	183 (59.4)	68,868 (10.5)	70,155 (10.6)

Table 6. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Norway.

Characteristics	Exposure to gabapentin					
	Any exposure, any trimester N=486	Monotherapy, any trimester N=407	Any exposure, first trimester N=359	Monotherapy, first trimester N=308	No exposure during pregnancy N=654,734	All pregnancies N=659,320
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Morbidities other than indications for Gabapentin use						
Migraine or other headache syndromes	63 (13.0)	54 (13.3)	52 (14.5)	47 (15.3)	16,545 (2.5)	16,886 (2.6)
Other neurologic disorders	290 (59.7)	235 (57.7)	221 (61.6)	187 (60.7)	74,424 (11.4)	76,413 (11.6)
Depression	137 (28.2)	112 (27.5)	109 (30.4)	93 (30.2)	23,047 (3.5)	24,153 (3.7)
Bipolar disorder	2 (0.4)	1 (0.2)	1 (0.3)	0 (0.0)	412 (0.1)	648 (0.1)
Alcohol abuse or dependence	4 (0.8)	3 (0.7)	4 (1.1)	3 (1.0)	323 (0.0)	346 (0.1)
Drug abuse or dependence	1 (0.2)	0 (0.0)	1 (0.3)	0 (0.0)	559 (0.1)	613 (0.1)
Hypertension	33 (6.8)	25 (6.1)	24 (6.7)	20 (6.5)	6,644 (1.0)	6,802 (1.0)
Haematological diseases	3 (0.6)	3 (0.7)	2 (0.6)	2 (0.6)	1,024 (0.2)	1,046 (0.2)
Diabetes	18 (3.7)	15 (3.7)	11 (3.1)	9 (2.9)	6,736 (1.0)	6,809 (10.0)
Asthma	42 (8.6)	37 (9.1)	26 (7.2)	23 (7.5)	26,037 (4.0)	26,422 (4.0)
Liver diseases	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	108 (0.0)	109 (0.0)
Renal impairment	1 (0.2)	1 (0.2)	0 (0.0)	0 (0.0)	463 (0.1)	470 (0.1)
Rheumatic diseases	4 (0.8)	4 (1.0)	4 (1.1)	4 (1.3)	762 (0.1)	774 (0.1)
Obesity	55 (11.3)	50 (12.3)	40 (11.1)	37 (12.0)	32,399 (4.9)	32,748 (5)
Disorders of female pelvic organs genital tract	6 (1.2)	6 (1.5)	6 (1.7)	6 (1.9)	7,834 (1.2)	7,925 (1.2)
Thyroid disorders	18 (3.7)	17 (4.2)	12 (3.3)	12 (3.9)	14,731 (2.2)	14,926 (2.3)
Infections	218 (44.9)	188 (46.2)	152 (42.3)	131 (42.5)	173,759 (26.5)	175,487 (26.6)
Concomitant medications, any trimester						
Antidepressants	108 (22.2)	84 (20.6)	80 (22.3)	65 (21.1)	5,168 (0.8)	5,657 (0.9)
Hypnotics	75 (15.4)	56 (13.8)	55 (15.3)	41 (13.3)	9,696 (1.5)	10,236 (1.6)
Anxiolytics	68 (14.0)	49 (12.0)	54 (15.0)	42 (13.6)	9,286 (1.4)	9,973 (1.5)
Antipsychotics	43 (8.8)	35 (8.6)	29 (8.1)	24 (7.8)	6,089 (0.9)	6,576 (1.0)
Analgesics	247 (50.8)	209 (51.4)	169 (47.1)	149 (48.4)	52,788 (8.1)	53,901 (8.2)
Antihypertensives	42 (8.6)	33 (8.1)	31 (8.6)	24 (7.8)	8,856 (1.4)	9,038 (1.4)
Non-steroidal anti-inflammatory drugs	190 (39.1)	158 (38.8)	125 (34.8)	109 (35.4)	57,139 (8.7)	57,986 (8.8)
Drugs for peptic ulcer/gastroesophageal reflux	64 (13.2)	52 (12.8)	48 (13.4)	40 (13.0)	15,952 (2.4)	16,228 (2.5)
Folic acid	20 (4.1)	14 (3.4)	16 (4.5)	11 (3.6)	5,344 (0.8)	6,090 (0.9)
Drugs for in-vitro fertilization	24 (4.9)	24 (5.9)	20 (5.6)	20 (6.5)	28,001 (4.3)	28,204 (4.3)
Thyroid hormones	17 (3.5)	16 (3.9)	14 (3.9)	14 (4.5)	12,891 (2.0)	13,062 (2.0)

Table 6. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Norway.

Characteristics	Exposure to gabapentin					
	Any exposure, any trimester N=486	Monotherapy, any trimester N=407	Any exposure, first trimester N=359	Monotherapy, first trimester N=308	No exposure during pregnancy N=654,734	All pregnancies N=659,320
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Systemic corticosteroids	34 (7.0)	28 (6.9)	25 (7.0)	22 (7.1)	9,596 (1.5)	9,737 (1.5)
Antiinfectves for systemic use	214 (44.0)	178 (43.7)	147 (40.9)	126 (40.9)	193,052 (29.5)	194,806 (29.5)
Concomitant medications, first trimester						
Antidepressants	82 (16.9)	63 (15.5)	71 (19.8)	58 (18.8)	4,074 (0.6)	4,473 (0.7)
Hypnotics	61 (12.6)	45 (11.1)	49 (13.6)	36 (11.7)	7,111 (1.1)	7,546 (1.1)
anxiolytics	54 (11.1)	39 (9.6)	46 (12.8)	37 (12.0)	6,495 (1.0)	7,007 (1.1)
Antipsychotics	26 (5.3)	21 (5.2)	22 (6.1)	19 (6.2)	3,988 (0.6)	4,357 (0.7)
Analgesics	203 (41.8)	172 (42.3)	163 (45.4)	143 (46.4)	35,824 (5.5)	36,688 (5.6)
Antihypertensives	31 (6.4)	24 (5.9)	26 (7.2)	21 (6.8)	5,122 (0.8)	5,248 (0.8)
Non-steroidal anti-inflammatory drugs	149 (30.7)	121 (29.7)	115 (32.0)	98 (31.8)	38,518 (5.9)	39,161 (5.9)
Drugs for peptic ulcer/gastroesophageal reflux	42 (8.6)	33 (8.1)	34 (9.5)	27 (8.8)	10,149 (1.6)	10,343 (1.6)
Folic acid	13 (2.7)	9 (2.2)	12 (3.3)	9 (2.9)	3,184 (0.5)	3,754 (0.6)
Drugs for in-vitro fertilization	19 (3.9)	19 (4.7)	16 (4.5)	16 (5.2)	23,728 (3.6)	23,897 (3.6)
Thyroid hormones	13 (2.7)	13 (3.2)	12 (3.3)	12 (3.9)	11,276 (1.7)	11,424 (1.7)
Systemic corticosteroids	28 (5.8)	22 (5.4)	21 (5.8)	18 (5.8)	6,650 (1.0)	6,762 (1.0)
Antiinfectves for systemic use	142 (29.2)	118 (29.0)	102 (28.4)	87 (28.2)	121,722 (18.6)	122,918 (18.6)
Maternal markers of health care use						
Number of hospitalizations, median (quartiles)	0 (0-0)	0 (0-0)	-	-	0 (0-0)	0 (0-0)
Number of specialist outpatient visits at hospitals, median (quartiles)	0 (0-3)	0 (0-3)	-	-	0 (0-0)	0 (0-0)
Maternal mental health						
Psychotic disorders	42 (8.6)	30 (7.4)	32 (8.9)	23 (7.5)	4,844 (0.7)	5,366 (0.8)
Mood and anxiety disorders other than depression or bipolar disorder	179 (36.8)	137 (33.7)	142 (39.6)	116 (37.7)	29,021 (4.4)	30,501 (4.6)
Sleep disorders	99 (20.4)	76 (18.7)	80 (22.3)	63 (20.5)	14,088 (2.2)	14,905 (2.3)
Eating disorders and personality disorders	5 (1.0)	5 (1.2)	5 (1.4)	5 (1.6)	1,693 (0.3)	1,798 (0.3)
ADHD autism and intellectual disability	9 (1.9)	4 (1.0)	9 (2.5)	5 (1.6)	2,295 (0.4)	2,395 (0.4)

Table 7. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Sweden

Characteristic	Gabapentin, any trimester N=806	Gabapentin monotherapy, any trimester N=720	Gabapentin, first trimester N=767	Gabapentin monotherapy, first trimester N=686	Unexposed (not gabapentin, lamotrigine, pregabalin, other AED), any trimester N=1,301,450	All births N=1,310,794
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Perinatal characteristics						
Calendar year of delivery						
2006	16 (2.0)	15 (2.1)	16 (2.1)	15 (2.2)	47,448 (3.6)	47,643 (3.6)
2007	21 (2.6)	18 (2.5)	20 (2.6)	17 (2.5)	98,653 (7.6)	99,104 (7.6)
2008	30 (3.7)	22 (3.1)	27 (3.5)	19 (2.8)	100,522 (7.7)	101,048 (7.7)
2009	22 (2.7)	19 (2.6)	21 (2.7)	18 (2.6)	101,761 (7.8)	102,393 (7.8)
2010	43 (5.3)	41 (5.7)	42 (5.5)	40 (5.8)	106,643 (8.2)	107,358 (8.2)
2011	30 (3.7)	25 (3.5)	27 (3.5)	22 (3.2)	103,590 (8.0)	104,273 (8.0)
2012	36 (4.5)	31 (4.3)	33 (4.3)	29 (4.2)	104,399 (8.0)	105,160 (8.0)
2013	60 (7.4)	55 (7.6)	60 (7.8)	55 (8.0)	104,465 (8.0)	105,219 (8.0)
2014	77 (9.6)	68 (9.4)	71 (9.3)	63 (9.2)	106,315 (8.2)	107,166 (8.2)
2015	87 (10.8)	78 (10.8)	82 (10.7)	75 (10.9)	106,310 (8.2)	107,200 (8.2)
2016	120 (14.9)	107 (14.9)	115 (15.0)	103 (15.0)	108,642 (8.3)	109,599 (8.4)
2017	147 (18.2)	130 (18.1)	137 (17.9)	120 (17.5)	106,012 (8.1)	107,008 (8.2)
2018	117 (14.5)	111 (15.4)	116 (15.1)	110 (16.0)	106,690 (8.2)	107,623 (8.2)
Age at LMP, years						
<20	NR	NR	NR	NR	15,141 (1.2)	15,264 (1.2)
20-34	553 (68.6)	492 (68.3)	528 (68.8)	471 (68.7)	994,379 (76.4)	1,001,455 (76.4)
35-45	245 (30.4)	221 (30.7)	232 (30.2)	209 (30.5)	290,279 (22.3)	292,409 (22.3)
>45	NR	NR	NR	NR	1,649 (0.1)	1,664 (0.1)
Parity						
Nulliparous	312 (38.7)	280 (38.9)	302 (39.4)	271 (39.5)	558,980 (43.0)	563,344 (43.0)
Parous	494 (61.3)	440 (61.1)	465 (60.6)	415 (60.5)	742,469 (57.0)	747,449 (57.0)
Partner status						
Cohabiting	676 (83.9)	607 (84.3)	646 (84.2)	580 (84.5)	1,161,211 (89.2)	1,168,814 (89.2)
Not cohabiting	34 (4.2)	27 (3.8)	31 (4.0)	25 (3.6)	23,887 (1.8)	24,329 (1.9)
Other/missing	96 (11.9)	86 (11.9)	90 (11.7)	81 (11.8)	116,352 (8.9)	117,651 (9.0)
Smoking during pregnancy						

Table 7. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Sweden

Characteristic	Gabapentin, any trimester N=806	Gabapentin monotherapy, any trimester N=720	Gabapentin, first trimester N=767	Gabapentin monotherapy, first trimester N=686	Unexposed (not gabapentin, lamotrigine, pregabalin, other AED), any trimester N=1,301,450	All births N=1,310,794
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Yes	156 (19.4)	132 (18.3)	146 (19.0)	122 (17.8)	72,102 (5.5)	73,675 (5.6)
No	606 (75.2)	549 (76.3)	581 (75.7)	527 (76.8)	1,163,449 (89.4)	1,170,700 (89.3)
Missing	44 (5.5)	39 (5.4)	40 (5.2)	37 (5.4)	65,899 (5.1)	66,419 (5.1)
Body mass index, kg/m2						
<18.5	18 (2.2)	18 (2.5)	17 (2.2)	17 (2.5)	28,897 (2.2)	29,115 (2.2)
18.5-<25.0	331 (41.1)	297 (41.3)	314 (40.9)	284 (41.4)	718,962 (55.2)	723,223 (55.2)
25.0-<30.0	211 (26.2)	182 (25.3)	200 (26.1)	171 (24.9)	306,575 (23.6)	308,941 (23.6)
>=30.0	183 (22.7)	165 (22.9)	177 (23.1)	159 (23.2)	160,028 (12.3)	161,842 (12.3)
Missing	63 (7.8)	58 (8.1)	59 (7.7)	55 (8.0)	86,988 (6.7)	87,673 (6.7)
Caesarean delivery	258 (32.0)	228 (31.7)	241 (31.4)	212 (30.9)	230,153 (17.7)	232,594 (17.7)
Multiple gestation	28 (3.5)	24 (3.3)	28 (3.7)	24 (3.5)	36,957 (2.8)	37,232 (2.8)
Girls	395 (49.0)	348 (48.3)	370 (48.2)	327 (47.7)	632,285 (48.6)	636,896 (48.6)
Birth weight, median (quartiles), grams	3,371 (2,976-3,750)	3,378 (2,979-3,748)	3,380 (2,984-3,755)	3,380 (2,985-3,750)	3,540 (3,195-3,882)	3,540 (3,195-3,880)
Gestational age, median (quartiles), weeks	39 (38-40)	39 (38-40)	39 (38-40)	39 (38-40)	40 (39-41)	40 (39-41)
Head circumference, median (quartiles), cm	35 (34-36)	35 (34-36)	35 (34-36)	35 (34-36)	35 (34-36)	35 (34-36)
Stillbirth	5 (0.6)	NR	NR	NR	4,609 (0.4)	4,645 (0.4)
Indication for gabapentin use (not mutually exclusive)						
Epilepsy	19 (2.4)	6 (0.8)	16 (2.1)	5 (0.7)	516 (0.0)	2,613 (0.2)
Neuropathic pain	224 (27.8)	189 (26.3)	217 (28.3)	182 (26.5)	18,398 (1.4)	19,094 (1.5)
Other pain	208 (25.8)	179 (24.9)	196 (25.6)	168 (24.5)	46,422 (3.6)	47,444 (3.6)
Morbidities other than indications for gabapentin use						
Migraine or other headache syndromes	82 (10.2)	68 (9.4)	78 (10.2)	65 (9.5)	21,786 (1.7)	22,359 (1.7)
Other neurologic disorders	578 (71.7)	508 (70.6)	555 (72.4)	488 (71.1)	152,221 (11.7)	157,095 (12.0)
Depression	334 (41.4)	279 (38.8)	325 (42.4)	272 (39.7)	81,975 (6.3)	85,554 (6.5)
Bipolar disorder	10 (1.2)	NR	10 (1.3)	NR	1,651 (0.1)	2,679 (0.2)

Table 7. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Sweden

Characteristic	Gabapentin, any trimester N=806	Gabapentin monotherapy, any trimester N=720	Gabapentin, first trimester N=767	Gabapentin monotherapy, first trimester N=686	Unexposed (not gabapentin, lamotrigine, pregabalin, other AED), any trimester N=1,301,450	All births N=1,310,794
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Alcohol abuse or dependence	11 (1.4)	9 (1.3)	11 (1.4)	9 (1.3)	2,063 (0.2)	2,258 (0.2)
Drug abuse or dependence	56 (6.9)	40 (5.6)	54 (7.0)	38 (5.5)	5,474 (0.4)	6,075 (0.5)
Hypertension	43 (5.3)	34 (4.7)	42 (5.5)	33 (4.8)	16,617 (1.3)	17,020 (1.3)
Haematological diseases	7 (0.9)	6 (0.8)	6 (0.8)	5 (0.7)	6,314 (0.5)	6,392 (0.5)
Diabetes	16 (2.0)	16 (2.2)	15 (2.0)	15 (2.2)	10,710 (0.8)	10,846 (0.8)
Asthma	108 (13.4)	97 (13.5)	101 (13.2)	90 (13.1)	60,046 (4.6)	60,945 (4.6)
Liver diseases	NR	NR	NR	NR	476 (0.0)	485 (0.0)
Renal impairment	NR	NR	NR	NR	3,411 (0.3)	3,472 (0.3)
Rheumatic diseases	10 (1.2)	7 (1.0)	10 (1.3)	7 (1.0)	5,210 (0.4)	5,307 (0.4)
Obesity	190 (23.6)	172 (23.9)	184 (24.0)	166 (24.2)	161,955 (12.4)	163,805 (12.5)
Disorders of female pelvic organs/genital tract	137 (17.0)	112 (15.6)	131 (17.1)	108 (15.7)	124,827 (9.6)	126,003 (9.6)
Thyroid disorders	57 (7.1)	51 (7.1)	53 (6.9)	47 (6.9)	48,398 (3.7)	48,904 (3.7)
Infections	157 (19.5)	127 (17.6)	150 (19.6)	122 (17.8)	129,266 (9.9)	130,782 (10.0)
Concomitant medications during any trimester						
Antidepressants	315 (39.1)	268 (37.2)	301 (39.2)	256 (37.3)	67,346 (5.2)	70,575 (5.4)
Hypnotics	218 (27.0)	178 (24.7)	207 (27.0)	169 (24.6)	29,920 (2.3)	32,304 (2.5)
Antipsychotics	52 (6.5)	32 (4.4)	48 (6.3)	28 (4.1)	4,632 (0.4)	5,576 (0.4)
Analgesics	577 (71.6)	515 (71.5)	554 (72.2)	494 (72.0)	127,493 (9.8)	130,422 (9.9)
Antihypertensives	62 (7.7)	52 (7.2)	61 (8.0)	52 (7.6)	26,060 (2.0)	26,573 (2.0)
Non-steroidal anti-inflammatory drugs	260 (32.3)	234 (32.5)	251 (32.7)	226 (32.9)	55,732 (4.3)	56,900 (4.3)
Drugs for peptic ulcer/gastroesophageal reflux	189 (23.4)	167 (23.2)	181 (23.6)	160 (23.3)	65,108 (5.0)	66,368 (5.1)
Folic acid	114 (14.1)	87 (12.1)	106 (13.8)	80 (11.7)	34,914 (2.7)	38,706 (3.0)
Drugs for in-vitro fertilization	56 (6.9)	51 (7.1)	55 (7.2)	50 (7.3)	86,298 (6.6)	86,778 (6.6)
Thyroid hormones	69 (8.6)	60 (8.3)	63 (8.2)	55 (8.0)	76,669 (5.9)	77,406 (5.9)
Systemic corticosteroids	62 (7.7)	51 (7.1)	59 (7.7)	48 (7.0)	26,861 (2.1)	27,268 (2.1)
Antiinfectves for systemic use	393 (48.8)	342 (47.5)	368 (48.0)	322 (46.9)	376,970 (29.0)	380,703 (29.0)
Concomitant medications during first trimester						

Table 7. Baseline characteristics of livebirths and stillbirths according to exposure to gabapentin, Sweden

Characteristic	Gabapentin, any trimester N=806	Gabapentin monotherapy, any trimester N=720	Gabapentin, first trimester N=767	Gabapentin monotherapy, first trimester N=686	Unexposed (not gabapentin, lamotrigine, pregabalin, other AED), any trimester N=1,301,450	All births N=1,310,794
	n (%)	n (%)	n (%)	n (%)	n (%)	n (%)
Antidepressants	300 (37.2)	254 (35.3)	289 (37.7)	245 (35.7)	61,991 (4.8)	65,080 (5.0)
Hypnotics	193 (23.9)	156 (21.7)	185 (24.1)	150 (21.9)	22,478 (1.7)	24,601 (1.9)
Antipsychotics	45 (5.6)	29 (4.0)	42 (5.5)	26 (3.8)	4,148 (0.3)	5,021 (0.4)
Analgesics	515 (63.9)	459 (63.8)	500 (65.2)	445 (64.9)	75,142 (5.8)	77,392 (5.9)
Antihypertensives	37 (4.6)	30 (4.2)	36 (4.7)	29 (4.2)	11,032 (0.8)	11,353 (0.9)
Non-steroidal anti-inflammatory drugs	245 (30.4)	219 (30.4)	236 (30.8)	211 (30.8)	52,182 (4.0)	53,281 (4.1)
Drugs for peptic ulcer/gastroesophageal reflux	149 (18.5)	132 (18.3)	143 (18.6)	127 (18.5)	40,573 (3.1)	41,478 (3.2)
Folic acid	87 (10.8)	65 (9.0)	84 (11.0)	63 (9.2)	23,898 (1.8)	27,236 (2.1)
Drugs for in-vitro fertilization	53 (6.6)	48 (6.7)	52 (6.8)	47 (6.9)	85,026 (6.5)	85,488 (6.5)
Thyroid hormones	54 (6.7)	48 (6.7)	49 (6.4)	43 (6.3)	64,221 (4.9)	64,836 (4.9)
Systemic corticosteroids	52 (6.5)	43 (6.0)	50 (6.5)	41 (6.0)	20,437 (1.6)	20,753 (1.6)
Antiinfectves for systemic use	278 (34.5)	241 (33.5)	265 (34.6)	230 (33.5)	220,719 (17.0)	223,134 (17.0)
Maternal markers of health care use						
Number of hospitalizations, median (quartiles)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-1)	0 (0-0)	0 (0-0)
Number of specialist outpatient visits at hospitals, median (quartiles)	2 (1-5)	2 (0-5)	2 (1-5)	2 (0-5)	0 (0-1)	0 (0-1)
Number of visits in primary care, median (quartiles)*	. (.-.)	. (.-.)	. (.-.)	. (.-.)	. (.-.)	. (.-.)
Maternal mental health (to the extent measured)						
Psychotic disorders	52 (6.5)	34 (4.7)	49 (6.4)	31 (4.5)	4,537 (0.3)	5,605 (0.4)
Mood- and anxiety disorders other than depression or bipolar disorder	406 (50.4)	337 (46.8)	388 (50.6)	323 (47.1)	103,572 (8.0)	108,118 (8.2)
Sleep disorders	209 (25.9)	171 (23.8)	198 (25.8)	161 (23.5)	33,762 (2.6)	36,325 (2.8)
Eating disorders and personality disorders	43 (5.3)	31 (4.3)	41 (5.3)	30 (4.4)	4,432 (0.3)	5,185 (0.4)
ADHD, autism and intellectual disability	74 (9.2)	59 (8.2)	72 (9.4)	58 (8.5)	8,154 (0.6)	9,001 (0.7)
History of suicide attempt	18 (2.2)	10 (1.4)	18 (2.3)	10 (1.5)	2,259 (0.2)	2,495 (0.2)

Numbers are n (%) unless specified otherwise
Counts of 1, 2, 3, or 4 are not disclosed, and is replaced by NR in the table.
* Finland only

10.3. Outcome data

Table 8 provides reportable prevalence of major congenital malformations overall and by EUROCAT category, before any trimming has been applied, and combined across the four study countries (Denmark, Finland, Norway, and Sweden). The prevalence of any major congenital malformation was 4.83% for gabapentin-exposed births, 6.4% for pregabalin-exposed births, 5.27% for lamotrigine-exposed births, 5.55% for pregabalin and/or lamotrigine-exposed births, and 4.19% among births unexposed to gabapentin, active comparators and other AEDs. Specific major congenital malformation types were rare, even in the data combined across the four study countries, especially for gabapentin-exposed and the unexposed births. For malformations of nervous system the prevalences were 0.28% for gabapentin-exposed births, 0.23% for pregabalin-exposed births, 0.18% for lamotrigine-exposed births, the prevalence was non-reportable for pregabalin and/or lamotrigine-exposed births and was 0.13% for births unexposed to gabapentin, active comparators and other AEDs. For genital malformations, the prevalences were 0.34% for gabapentin-exposed births, 0.47% for pregabalin and/or lamotrigine-exposed births, and 0.40% for births unexposed to gabapentin, active comparators and other AEDs; the prevalences were non-reportable for births exposed to pregabalin and separately to lamotrigine. The limb malformations prevalences were the same among gabapentin-exposed births (1.01%) and births unexposed to gabapentin, active comparators and other AEDs.

Table 8. Prevalence of any and specific major congenital types combined across Denmark, Finland, Norway and Sweden.

Malformation type	**First-trimester exposure**									
	Gabapentin		**Pregabalin**		**Lamotrigine**		**Pregabalin or Lamotrigine**		**Unexposed**	
	N= 1,781		N=3,108		N= 9,883		N=12,876		N= 3,334,855	
	Cases	Prevalence (%)	Cases	Prevalence (%)	Cases	Prevalence (%)	Cases	Prevalence (%)	Cases	Prevalence (%)
Any major congenital malformation	**86**	**4.83**	**199**	**6.4**	**521**	**5.27**	**715**	**5.55**	**139,787**	**4.19**
Nervous system	5	0.28	7	0.23	18	0.18	NR	NR	4,425	0.13
Eye	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Ear, face and neck	0	0	NR	NR	6	0.06	8	0.06	2,149	0.06
Congenital heart defects	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Respiratory	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Oro-facial clefts	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Digestive system	5	0.28	11	0.35	35	0.35	NR	NR	8,310	0.25
Abdominal wall defects	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Urinary	NR	NR	NR	NR	NR	NR	NR	NR	NR	NR
Genital	6	0.34	NR	NR	NR	NR	61	0.47	13,455	0.40
Limb	18	1.01	NR	NR	121	1.22	156	1.21	33,607	1.01
Other anomalies/syndromes	16	0.9	NR	NR	72	0.73	101	0.78	16,171	0.48

NR = non-reportable because of counts 1-4 in one participating country or across all participating countries per study protocol, Section 9.11. Estimates of association are based on observed counts.

Table 9 shows prevalence of major congenital malformations overall and by the EUROCAT category. The prevalence of any major congenital malformations ranged from 2.31% in Norway to 5.35% in Finland.

Table 9. Prevalence (%) of major congenital malformations among live and stillbirths, by country.

EUROCAT major congenital malformation category	Denmark	Finland	Norway	Sweden
Any malformation	4.11	5.35	2.31	4.65
Nervous system	0.16	0.20	0.08	0.11
Eye	0.14	0.28	0.02	0.21
Ear, face and neck	0.04	0.16	0.02	0.05
Congenital heart defects	1.06	2.20	0.99	1.77
Respiratory	0.06	0.06	0.03	0.04
Oro-facial clefts	0.17	0.22	0.17	0.17
Digestive system	0.27	0.30	0.15	0.27
Abdominal wall defects	0.03	0.05	0.04	0.03
Urinary	0.38	0.45	0.22	0.43
Genital	0.36	0.32	0.27	0.54
Limb	1.19	1.30	0.62	0.96
Other	0.62	0.61	0.20	0.50

Given a small study sample size, and the low prevalence of major congenital malformations, we could not perform stratified analyses by the categories of defined daily dose (DDD) of gabapentin (1,800 mg), i.e., by three categories of < 1.0, 1.0-2.0, and > 2.0 times the DDD in all countries. Instead, whenever feasible we conducted analyses by the number (1 vs > 1) of redeemed prescriptions for gabapentin. Table 10 shows the prevalence of major congenital malformations among livebirths and stillbirths exposed to gabapentin in first trimester by number of dispensings of gabapentin in Sweden, a country with the largest sample size among the four participating Nordic countries.

Table 10. Prevalence of major congenital malformations among livebirths and stillbirths exposed to gabapentin in first trimester and crude prevalence ratios vs. unexposed by number of dispensings of gabapentin, Sweden

Outcome	**Gabapentin 1 dispensing during the first trimester, first trimester**				**Gabapentin >1 dispensing during the first trimester, first trimester**			
Outcome	gabapentin 1 dispensing during the first trimester, first trimester				gabapentin >1 dispensing during the first trimester, first trimester			
	Cases	Births	Prevalence, %	Crude prevalence ratio (95% CI)	Cases	Births	Prevalence, %	Crude prevalence ratio (95% CI)
Any major malformation	17	380	4.5	0.96 (0.59-1.57)	25	387	6.5	1.39 (0.95-2.03)
Nervous system	0	380	0.0	NE	NR	387	NR	2.31 (0.33-16.34)
Eye	0	380	0.0	NE	NR	387	NR	1.26 (0.18-8.92)
Ear, face and neck	0	380	0.0	NE	0	387	0.0	NE
Congenital heart defects	7	380	1.8	1.04 (0.45-2.39)	10	387	2.6	1.46 (0.79-2.69)
Respiratory	0	380	0.0	NE	0	387	0.0	NE
Oro-facial clefts	NR	380	NR	1.56 (0.22-11.04)	0	387	0.0	NE
Digestive system	NR	380	NR	0.97 (0.14-6.85)	NR	387	NR	0.95 (0.13-6.73)
Abdominal wall defects	0	380	0.0	NE	0	387	0.0	NE
Urinary	NR	380	NR	NE	NR	387	NR	1.20 (0.30-4.79)
Genital	NR	380	NR	1.46 (0.47-4.50)	NR	387	NR	0.48 (0.07-3.38)
Limb	NR	380	NR	0.55 (0.14-2.20)	8	387	2.1	2.16 (1.09-4.29)
Other anomalies/syndromes	NR	380	NR	1.57 (0.51-4.85)	NR	387	NR	2.06 (0.78-5.46)

NE, not estimable; NR, not reportable

10.4. Main results

To control for confounding in this study, PS-adjusted estimates were calculated, with separate PS estimated for each exposure definition (first-trimester, any-trimester), contrast (gabapentin vs. comparator [unexposed to AED/pregabalin/lamotrigine/pregabalin or lamotrigine), and country. The covariables included in the PS models varied by country depending on data availability and the number of observations available for modelling. A full list of covariables included in the country-specific PS models and corresponding PS score distribution and SMD values for each covariable per contrast are presented in Appendix 4, Supplementary propensity score tables and Appendix 5, Supplementary descriptive figures.

Generally, cohabiting status, smoking, BMI≥30 kg/m^2, depression, drug abuse or dependence, hypertension, asthma, neurological disorders, the use of antidepressants, hypnotics, anxiolytics, antipsychotics, analgesics, antihypertensives, and non-steroidal anti-inflammatory drugs were the covariables most frequently unbalanced prior to adjustment between gabapentin-exposed births and births with no exposure to gabapentin and AEDs (Table 4-Table 7). In each country, similar covariables were unbalanced for the same contrast in first-trimester pregnancy exposure as in any-trimester pregnancy exposure to gabapentin.

For the contrast of gabapentin-exposed births vs births with no exposure to gabapentin and AEDs, after PS computation, stratification and trimming, all covariables had SMD ≤ 0.1 in all four Nordic countries (Appendix 4, Supplementary propensity score tables).

After PS computation, stratification and trimming, the covariables with SMD between 0.1 and 0.2 (upper cut-off for the covariables to be deemed balanced[41]) in Denmark were calendar year, smoking status, disorders of female pelvic organs/genital tract, antidepressants, and drugs for in-vitro fertilization and for peptic ulcer/gastroesophageal reflux in first trimester for the contrast gabapentin-exposed births vs pregabalin-exposed births in first trimester and age group; age group, folic acid and systemic corticosteroids use in first trimester for the contrast gabapentin-exposed births vs lamotrigine-exposed births in first trimester. For the contrast gabapentin-exposed births vs pregabalin-exposed births any time in pregnancy, these covariables were calendar year, marital status, parity, rheumatic diseases, disorders of pelvic organs/genital tract, antidepressants, hypnotics, drugs for peptic ulcer/gastroesophageal reflux, drugs for in-vitro fertilization, and systemic corticosteroids. For the contrast of gabapentin-exposed births vs lamotrigine-exposed births any time in pregnancy, rheumatic diseases, folic acid and systemic corticosteroids use showed SMD between 0.1 and 0.2.

In Finland, these covariables were calendar year of delivery/pregnancy termination for gabapentin-exposed births vs lamotrigine-exposed births in first trimester and calendar year, age at LMP, cohabiting status, and number of outpatient visits termination for monotherapy gabapentin-exposed births vs lamotrigine-exposed births in first trimester.

In Norway, these covariables were other neurologic disorders, drugs for peptic ulcer/gastroesophageal reflux in first trimester for gabapentin-exposed births vs pregabalin-exposed births in first trimester.

In Sweden, there were two covariables with SMD≥0.2 for the contrast of gabapentin-exposed vs lamotrigine exposed births in first trimester (alcohol and drug abuse had SMD=0.20 and sleep disorders and hypnotics use had SMD=0.21; Appendix 4, Supplementary propensity score tables, Supplemental table 7-Sweden). The covariables with SMD between 0.1 and 0.2 in Sweden were calendar year, use of analgesics and antiinfectives in first trimester for the contrast gabapentin-exposed births vs pregabalin-exposed births in first trimester and calendar year of delivery, maternal age, migraine or other headache syndromes, infections, drugs for peptic ulcer/gastroesophageal reflux, systemic corticosteroids, number of outpatient visits, and smoking during pregnancy for gabapentin-exposed births vs lamotrigine-exposed births in first trimester. For gabapentin-exposed births vs lamotrigine-exposed births any time in pregnancy, SMD for calendar year, cohabiting/partner status, diabetes, infections, other pain, sleep disorders and hypnotics, drugs for peptic ulcer/gastroesophageal reflux, smoking in pregnancy, alcohol or drug abuse were between 0.1 and 0.2.

In general, we observed similar patterns for the same covariables across four Nordic countries. After PS computation, stratification and trimming, no covariables had SMD above the balance cut-off of 0.2 across all participating Nordic countries for the main analyses

except for the contrast of gabapentin-exposed vs lamotrigine exposed births in first trimester in Sweden.

10.5. Outcomes

10.5.1. Birth outcomes

Table 11 shows country-specific crude and PS-adjusted prevalence ratios for any major congenital malformations for any first-trimester gabapentin exposure vs the prespecified comparators. The aPRs (95% CI) vs the unexposed were 0.70 (0.43-1.16) in Denmark, 0.68 (0.37-1.25) in Finland, 1.97 (1.17-3.33) in Norway, and 0.98 (0.72-1.32) in Sweden. Compared with crude estimates, adjustment resulted in attenuation of all estimates when the AED-unexposed or pregabalin was the comparator.

Based on 86 events among 1,781 births gabapentin-exposed in first trimester across four Nordic countries, fixed effect meta-analysis for any major congenital malformation showed aPR 0.99 (95 % CI: 0.80-1.23). Taking into account zero exposed events, MH meta-analysis for any major congenital malformation resulted in aPR (95% CI) of 0.95 (0.77-1.17) (Table 11). Similar pooled PR estimate (1.03, 95% CI: 0.82-1.30) was obtained for gabapentin monotherapy exposure in the first trimester (based on 77 events among 1,540 births exposed to gabapentin monotherapy in four Nordic countries) (Appendix 5, Supplementary forest plots Mantel-Haenszel meta-analyses malformations). Pooled fixed effect estimates for any major congenital malformation contrasting gabapentin-exposed births with active comparators-exposed births in first trimester were 0.67 (95% CI: 0.51-0.87), 1.14 (95% CI: 0.90-1.43), and 0.86 (95% CI: 0.69-1.08) for pregabalin, lamotrigine, and pregabalin and/or lamotrigine, respectively. Pooled MH adjusted estimates were similar to the pooled fixed effect adjusted estimates for any major congenital malformation comparing gabapentin-exposed births with active comparators-exposed births in first trimester (Table 11).

For gabapentin-exposed in first trimester vs unexposed to gabapentin and other AEDs births, the pooled fixed effect aPRs were based on a small number of events and were 2.30 (95% CI: 0.83-6.36) for nervous system malformations, 1.12 (95% CI: 0.80-1.58) for congenital heart defects, 3.99 (95% CI: 0.51-31.41) for respiratory malformations, 1.15 (95% CI: 0.47-2.79) for digestive system malformations, 10.52 (95% CI: 2.45-45.17) for abdominal wall defects, 1.42 (95% CI: 0.86-2.34) for other malformations (Appendix 5, Supplementary forest plots fixed effect meta-analyses malformations, Figure 50.2).

Results for the specific major congenital malformation types are provided in country-specific supplemental output (Appendix 4, Supplementary major congenital malformation tables). Some, but not all country-specific results were indicative of a potential association of gabapentin exposure in first trimester with cardiac malformations. Pooled adjusted estimate for an association with cardiac malformations was 1.12 (0.80-1.58) (Appendix 5, Supplementary forest plots fixed effect meta-analyses malformations, Figure 50.2). Most estimates, however, were close to the null value of 1.0 and for crude PRs suggesting an association, PS adjustment resulted in estimates' attenuation.

The aPRs were attenuated towards the null value in the analyses comparing the risk of site-specific malformations among gabapentin-exposed births vs births exposed to active comparators. Specifically, in analyses of gabapentin-exposed in first trimester births vs pregabalin-exposed in first trimester births the pooled fixed effect aPRs were 0.65 (95% CI: 0.14-3.03) for nervous system malformations, 0.57 (95% CI: 0.32-1.02) for congenital heart defects, NE for respiratory malformations, 0.58 (95% CI: 0.17-1.90) for digestive system malformations, NE for abdominal wall defects, 0.68 (95% CI: 0.31-1.49) for other malformations (Appendix 5, Supplementary forest plots fixed effect meta-analyses malformations, Figure 52.2). Generally, the same shift towards the null value was observed in the analyses comparing gabapentin-exposed births vs other active comparators (lamotrigine, lamotrigine and/or pregabalin).

Table 11. Country-specific and combined crude and propensity score adjusted prevalence ratios of any major congenital malformations in first trimester gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Any major congenital malformations	Cases, n	Total, n	Prevalence (%)	Cases, n	Total, n	Prevalence (%)	Crude Prevalence Ratio (95% CI)	**PS-Adjusted Prevalence Ratio (95% CI)**	**MH Adjusted Pooled Prevalence Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	15	414	3.62	30,078	736,843	4.08	0.89 (0.54-1.46)	**0.70 (0.43-1.16)**	-
Finland	12	241	4.98	34,146	640,717	5.33	0.93 (0.52-1.66)	**0.68 (0.37-1.25)**	-
Norway	17	359	4.74	15,098	655,385	2.30	2.11 (1.26-3.53)	**1.97 (1.17-3.33)**	-
Sweden	42	767	5.48	60,466	1,301,958	4.64	1.18 (0.87-1.59)	**0.98 (0.72-1.32)**	-
Meta-analysis	86	1,781	4.83	139,788	3,334,855	4.19	1.20 (0.97-1.48)	**0.99 (0.80-1.23)**	**0.95 (0.77-1.17)**
Gabapentin vs Pregabalin									
Denmark	15	387	3.88	32	410	7.80	0.50 (0.27-0.90)	**0.44 (0.20-0.96)**	-
Finland	12	241	4.98	68	951	7.15	0.68 (0.36-1.28)	**0.51 (0.25-1.04)**	-
Norway	15	333	4.50	8	242	3.31	1.38 (0.56-3.39)	**0.96 (0.28-3.24)**	-
Sweden	40	724	5.52	91	1,505	6.05	0.91 (0.63-1.32)	**0.78 (0.48-1.27)**	-
Meta-analysis	82	1,685	4.87	199	3,108	6.40	0.80 (0.61-1.04)	**0.65 (0.46-0.91)**	**0.67 (0.51-0.87)**
Gabapentin vs Lamotrigine									
Denmark	15	400	3.75	152	2,594	5.86	0.64 (0.38-1.08)	**0.93 (0.51-1.67)**	-
Finland	12	241	4.98	83	1,194	6.95	0.70 (0.38-1.31)	**0.65 (0.25-1.70)**	-
Norway	17	353	4.82	55	1,893	2.91	1.69 (0.94-3.03)	**2.10 (1.06-4.16)**	-
Sweden	41	743	5.52	231	4,202	5.50	1.00 (0.72-1.39)	**1.16 (0.60-2.23)**	-
Meta-analysis	85	1,737	4.89	521	9,883	5.27	0.95 (0.75-1.20)	**1.17 (0.83-1.65)**	**1.14 (0.90-1.43)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	15	374	4.01	182	2,978	6.11	0.66 (0.39-1.10)	**0.68 (0.38-1.23)**	-
Finland	12	241	4.98	153	2,168	7.06	0.69 (0.38-1.26)	**0.59 (0.31-1.13)**	-
Norway	15	327	4.59	63	2,128	2.96	1.58 (0.86-2.89)	**1.88 (0.96-3.70)**	-
Sweden	39	704	5.54	317	5,602	5.66	0.98 (0.70-1.36)	**0.90 (0.59-1.36)**	-
Meta-analysis	81	1,646	4.92	715	12,876	5.55	0.92 (0.73-1.16)	**0.88 (0.67-1.16)**	**0.86 (0.69-1.08)**

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded. Cases represent the crude number of any major congenital malformation included in the analysis. Total represents the total number of newborns at risk (first trimester exposed births). Prevalence = Cases/Total. Crude Prevalence Ratio is presented based on Pooled Crude results of fixed meta-analyses. PS-Adjusted = Propensity score adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. NR = nonreportable or potentially NR due to the possibility of estimating a low number of individuals (<5) in other cells; some data may be reported with the final draft. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases.

Table 12 shows country-specific crude and PS-adjusted prevalence ratios for stillbirth for any gabapentin exposure any time during gestation vs the prespecified comparators. Prevalence of stillbirth among gabapentin-exposed births was around the expected 0.5% in the population.[48] Adjusted PR (95% CI) for gabapentin-exposed births vs births unexposed to gabapentin and other AEDs were 1.45 (0.36-5.91) in Denmark, 1.77 (0.43-7.33) in Finland, 0.43 (0.06-3.06) in Norway, and 1.29 (0.52-3.17) in Sweden. The number of observations in all groups was low. PS-adjusted analyses resulted in modest or no attenuation of crude measures of association for this outcome for all comparators used.

Pooled adjusted estimate for gabapentin-exposed births vs unexposed births was 1.24 (95% CI: 0.66-2.34) using fixed effects meta-analysis and 1.14 (95% CI: 0.62-2.12) using MH approach. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs (95% CIs) were 1.07 (0.40-2.87), 1.69 (0.67-4.27), and 1.68 (0.76-3.73) for pregabalin, lamotrigine and pregabalin or lamotrigine, respectively. MH pooled aPRs (95% CIs) were 1.23 (0.57-2.68), 0.83 (0.38-1.84), and 1.54 (0.75-3.14) for contrasts with births exposed to pregabalin, lamotrigine, and pregabalin or lamotrigine, respectively.

Table 12. Country-specific and combined crude and propensity score adjusted prevalence ratios of stillbirth in gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Stillbirth	Cases, n	Total, n	Prevalence (%)	Cases, n	Total, n	Prevalence (%)	Crude Prevalence Ratio (95% CI)	**PS-Adjusted Prevalence Ratio (95% CI)**	**MH Adjusted Pooled Prevalence Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	<5	430	NR	2,490	736,596	0.34	NR	**1.45 (0.36-5.91)**	-
Finland	<5	256	NR	1,929	640,381	0.30	2.61 (0.65-10.49)	**1.77 (0.43-7.33)**	-
Norway	NR	486	0.21	2,486	654,734	0.38	0.54 (0.08-3.83)	**0.43 (0.06-3.06)**	-
Sweden	5	806	0.62	4,609	1,301,450	0.35	1.75 (0.73-4.20)	**1.29 (0.52-3.17)**	-
Meta-analysis	10	1,978	0.51	11,520	3,333,161	0.35	1.60 (0.86-2.98)	**1.24 (0.66-2.34)**	**1.14 (0.62-2.12)**
Gabapentin vs Pregabalin									
Denmark	<5	401	NR	<5	415	NR	NR	**NE**	-
Finland	<5	256	NR	<5	975	NR	2.55 (0.42-15.35)	**1.66 (0.26-10.58)**	-
Norway	NR	436	0.23	5	310	1.61	0.14 (0.02-1.21)	**0.20 (0.02-1.87)**	-
Sweden	5	762	0.66	9	1,553	0.58	1.13 (0.38-3.36)	**1.41 (0.35-5.60)**	-
Meta-analysis	NR	1,855	NR	NR	3,253	NR	1.06 (0.48-2.38)	**1.07 (0.40-2.87)**	**1.23 (0.57-2.68)**
Gabapentin vs Lamotrigine									
Denmark	<5	416	NR	13	2,713	0.48	NR	**0.53 (0.08-3.75)**	-
Finland	<5	256	NR	<5	1,249	NR	2.45 (0.45-13.46)	**0.64 (0.06-6.84)**	-
Norway	NR	478	0.21	8	2,155	0.37	0.56 (0.07-4.49)	**0.98 (0.12-8.26)**	-
Sweden	NR	781	NR	16	4,403	0.36	1.41 (0.47-4.20)	**5.56 (1.44-21.56)**	-
Meta-analysis	NR	1,931	NR	NR	10,520	NR	1.28 (0.62-2.67)	**1.69 (0.67-4.27)**	**0.83 (0.38-1.84)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	<5	388	NR	14	3,102	0.45	NR	**0.98 (0.15-6.41)**	-
Finland	<5	256	NR	7	2,251	0.31	2.52 (0.52-12.22)	**1.28 (0.23-7.12)**	-
Norway	NR	429	0.23	13	2,457	0.53	0.44 (0.06-3.36)	**0.91 (0.12-7.09)**	-
Sweden	NR	741	NR	24	5,846	0.41	1.31 (0.46-3.78)	**2.53 (0.77-8.31)**	-
Meta-analysis	9	1,814	0.50	58	13,656	0.42	1.27 (0.63-2.58)	**1.68 (0.76-3.73)**	**1.54 (0.75-3.14)**

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded. Cases represent the crude number of any major congenital malformation included in the analysis. Cases represent the crude number of any stillbirth included in the analysis. Total represents the total number of newborns at risk (first trimester exposed births). Prevalence= Cases/Total. PS-Adjusted = Propensity score adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. NR = nonreportable or potentially NR due to the possibility of estimating a low number of individuals (<5) in other cells; some data may be reported with the final draft. NE = non-estimable due to 0 cases in one or more cells. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases.

Table 13 shows country-specific crude and PS-adjusted prevalence ratios for low birth weight for any gabapentin exposure any time during gestation vs the prespecified comparators. The aPRs (95% CI) for gabapentin-exposed births vs births unexposed to gabapentin and other AEDs were 1.13 (0.73-1.74) in Denmark, 1.53 (0.96-2.43) in Finland, 1.19 (0.87-1.63) in Norway, and 1.15 (0.87-1.51) in Sweden. Adjustment resulted in estimates' attenuation when gabapentin was compared against unexposed or against pregabalin and/or lamotrigine (combined).

Pooled adjusted estimate for low birth weight comparing gabapentin-exposed births vs unexposed births was 1.21 (1.02-1.44) using fixed effects meta-analysis and 1.25 (1.07-1.46) using MH meta-analysis. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs (95% CIs) were 1.25 (0.92-1.70), 1.15 (0.87-1.51), and 1.14 (0.91-1.44) for pregabalin, lamotrigine, and pregabalin or lamotrigine, respectively. MH pooled aPRs (95% CIs) for low birth weight 1.18 (0.94-1.47), 1.18 (0.99-1.41), and 1.16 (0.98-1.38) for contrasts with births exposed to pregabalin, lamotrigine, and pregabalin or lamotrigine, respectively.

Table 13. Country-specific and combined crude and propensity score adjusted prevalence ratios of low birth weight in gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Low birth weight	Cases, n	Total, n	Prevalence (%)	Cases, n	Total, n	Prevalence (%)	Crude Prevalence Ratio (95% CI)	**PS-Adjusted Prevalence Ratio (95% CI)**	**MH Adjusted Pooled Prevalence Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	20	412	4.85	19,348	685,284	2.82	1.72 (1.12-2.64)	**1.13 (0.73-1.74)**	-
Finland	26	254	10.24	26,412	637,861	4.14	2.64 (1.67-4.17)	**1.53 (0.96-2.43)**	-
Norway	44	485	9.07	32821	654,274	5.02	1.81 (1.33-2.46)	**1.19 (0.87-1.63)**	-
Sweden	59	801	7.37	52,695	1,296,841	4.06	1.81 (1.38-2.38)	**1.15 (0.87-1.51)**	-
Meta-analysis	149	1,952	7.63	131,276	3,274,260	4.01	1.89 (1.60-2.25)	**1.21 (1.02-1.44)**	**1.25 (1.07-1.46)**
Gabapentin vs Pregabalin									
Denmark	18	385	4.68	22	381	5.77	0.81 (0.44-1.49)	**0.68 (0.26-1.79)**	-
Finland	26	254	10.24	54	971	5.56	1.94 (1.14-3.31)	**1.43 (0.76-2.70)**	-
Norway	41	435	9.43	25	308	8.12	1.16 (0.71-1.91)	**1.28 (0.64-2.56)**	-
Sweden	55	757	7.27	106	1,544	6.87	1.06 (0.75-1.49)	**1.25 (0.79-1.96)**	-
Meta-analysis	140	1,831	7.65	207	3,204	6.46	1.16 (0.92-1.46)	**1.25 (0.92-1.70)**	**1.29 (1.03-1.61)**
Gabapentin vs Lamotrigine									
Denmark	20	398	5.03	114	2,506	4.55	1.10 (0.69-1.76)	**0.68 (0.26-1.79)**	-
Finland	26	254	10.24	70	1,243	5.63	1.91 (1.13-3.25)	**1.99 (1.04-3.78)**	-
Norway	44	477	9.22	127	2,155	5.89	1.57 (1.08-2.26)	**1.15 (0.75-1.78)**	-
Sweden	59	777	7.59	223	4,387	5.08	1.49 (1.10-2.03)	**1.00 (0.60-1.68)**	-
Meta-analysis	149	1,906	7.82	534	10,291	5.19	1.48 (1.22-1.80)	**1.15 (0.87-1.51)**	**1.18 (0.99-1.41)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	18	372	4.84	135	2,865	4.71	1.03 (0.63-1.66)	**0.82 (0.43-1.54)**	-
Finland	26	254	10.24	127	2,241	5.67	1.90 (1.16-3.12)	**1.58 (0.92-2.72)**	-
Norway	41	428	9.58	152	2,455	6.19	1.55 (1.07-2.23)	**1.15 (0.76-1.74)**	-
Sweden	55	737	7.46	323	5,822	5.55	1.35 (1.00-1.82)	**1.13 (0.78-1.65)**	-
Meta-analysis	140	1,791	7.82	737	13,383	5.51	1.41 (1.16-1.71)	**1.14 (0.91-1.44)**	**1.16 (0.98-1.38)**

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded. Cases represent the crude number of any major congenital malformation included in the analysis. Cases represent the crude number of any low birth weight included in the analysis. Total represents the total number of newborns at risk (first trimester exposed births). Prevalence= Cases/Total. PS-Adjusted = Propensity score adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases.

Table 14 shows country-specific crude and PS-adjusted prevalence ratios for preterm birth for any gabapentin exposure any time during gestation vs the prespecified comparators. The aPRs (95% CI) for gabapentin-exposed births vs births unexposed to gabapentin and other AEDs were 1.31 (0.96-1.78) in Denmark, 1.26 (0.66-2.39) in Finland, 1.17 (0.89-1.54) in Norway, and 1.07 (0.84-1.35) in Sweden. Associations were attenuated when gabapentin-exposed births were compared with lamotrigine-exposed births and births exposed to pregabalin and/or lamotrigine.

Pooled adjusted estimate for preterm birth comparing gabapentin-exposed births vs unexposed births was 1.16 (1.00-1.35) using fixed effects meta-analysis and 1.18 (1.03-1.36) using MH meta-analysis approach. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs (95% CIs) were 1.11 (0.85-1.45), 0.98 (0.78-1.25), and 0.94 (0.77-1.15) for pregabalin, lamotrigine, and pregabalin and/or lamotrigine-exposed births, respectively. MH pooled aPRs (95% CIs) for low birth weight 1.14 (0.94-1.40), 1.05 (0.90-1.23), and 0.95 (0.82-1.11) for contrasts with births exposed to pregabalin, lamotrigine, and pregabalin and/or lamotrigine, respectively.

Table 14. Country-specific and combined crude and propensity score adjusted prevalence ratios of preterm birth in gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Preterm birth	Cases, n	Total, n	Prevalence (%)	Cases, n	Total, n	Prevalence (%)	Crude Prevalence Ratio (95% CI)	**PS-Adjusted Prevalence Ratio (95% CI)**	**MH Adjusted Pooled Prevalence Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	38	412	9.22	31,983	685,284	4.67	1.98 (1.46-2.68)	**1.31 (0.96-1.78)**	-
Finland	13	254	5.12	17,613	638,452	2.76	1.90 (1.01-3.59)	**1.26 (0.66-2.39)**	-
Norway	54	481	11.23	42,934	650,872	6.60	1.70 (1.30-2.23)	**1.17 (0.89-1.54)**	-
Sweden	78	801	9.74	73,464	1,296,841	5.66	1.72 (1.37-2.16)	**1.07 (0.84-1.35)**	-
Meta-analysis	183	1,948	9.39	165,994	3,271,449	5.07	1.78 (1.54-2.07)	**1.16 (1.00-1.35)**	**1.18 (1.03-1.36)**
Gabapentin vs Pregabalin									
Denmark	36	385	9.35	36	381	9.45	0.99 (0.63-1.54)	**0.68 (0.26-1.79)**	-
Finland	13	254	5.12	27	972	2.78	1.89 (0.90-3.96)	**1.82 (0.81-4.10)**	-
Norway	50	431	11.60	39	307	12.70	0.91 (0.61-1.37)	**1.29 (0.73-2.27)**	-
Sweden	72	757	9.51	177	1,544	11.46	0.83 (0.63-1.10)	**0.96 (0.67-1.37)**	-
Meta-analysis	171	1,827	9.36	279	3,204	8.71	0.93 (0.76-1.13)	**1.11 (0.85-1.45)**	**1.14 (0.94-1.40)**
Gabapentin vs Lamotrigine									
Denmark	36	398	9.05	212	2,506	8.46	1.07 (0.76-1.50)	**0.83 (0.53-1.31)**	-
Finland	13	254	5.12	44	1,245	3.53	1.47 (0.72-3.03)	**1.84 (0.75-4.52)**	-
Norway	54	473	11.42	175	2,145	8.16	1.40 (1.02-1.92)	**1.03 (0.70-1.52)**	-
Sweden	76	777	9.78	358	4,387	8.16	1.20 (0.93-1.55)	**1.02 (0.67-1.57)**	-
Meta-analysis	179	1,902	9.41	789	10,283	7.67	1.23 (1.04-1.45)	**0.98 (0.78-1.25)**	**1.05 (0.90-1.23)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	34	372	9.14	246	2,865	8.59	1.06 (0.76-1.50)	**0.80 (0.52-1.24)**	-
Finland	13	254	5.12	73	2,244	3.25	1.60 (0.81-3.18)	**1.64 (0.79-3.39)**	-
Norway	50	424	11.79	214	2,444	8.76	1.35 (0.98-1.85)	**1.07 (0.74-1.53)**	-
Sweden	71	737	9.63	525	5,822	9.02	1.07 (0.83-1.38)	**0.85 (0.63-1.16)**	-
Meta-analysis	168	1,787	9.4	1,058	13,375	7.91	1.17 (0.99-1.38)	**0.94 (0.77-1.15)**	**0.95 (0.82-1.11)**

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded. Cases represent the crude number of any major congenital malformation included in the analysis. Cases represent the crude number of any stillbirth included in the analysis. Total represents the total number of newborns at risk (first trimester exposed births). Prevalence= Cases/Total. PS-Adjusted = Propensity score adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases.

Table 15 shows country-specific crude and PS-adjusted prevalence ratios for SGA for any gabapentin exposure any time during gestation vs the prespecified comparators. The aPRs (95% CI) for gabapentin-exposed births vs births unexposed to gabapentin and other AEDs were 0.97 (0.49-1.95) in Denmark, 1.52 (0.81-2.87) in Finland, 0.87 (0.43-1.73) in Norway, and 1.09 (0.72-1.64) in Sweden.

Pooled adjusted estimate for being born small for gestational age comparing gabapentin-exposed births vs unexposed births was 1.10 (0.83-1.46) using fixed effects meta-analysis and similar using MH meta-analysis approach. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs (95% CIs) were) 1.12 (0.73-1.72) , 1.19 (0.77-1.85), and 1.14 (0.80-1.63) vs pregabalin-, lamotrigine-, and pregabalin- and/or lamotrigine-exposed births, respectively. MH pooled aPRs (95% CIs) for being born small for gestational age were slightly shifted towards the null value: 1.08 (0.75-1.57), 1.06 (0.77-1.46), and 1.09 (0.80-1.49) for contrasts with births exposed to pregabalin, lamotrigine, and pregabalin and/or lamotrigine, respectively.

Table 15. Country-specific and combined crude and propensity score adjusted prevalence ratios of small for gestational age in gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Small for gestational age	Cases, n	Total, n	Prevalence (%)	Cases, n	Total, n	Prevalence (%)	Crude Prevalence Ratio (95% CI)	**PS-Adjusted Prevalence Ratio (95% CI)**	**MH Adjusted Pooled Prevalence Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	8	412	1.94	11,169	685,284	1.63	1.19 (0.60-2.37)	**0.97 (0.49-1.95)**	-
Finland	12	251	4.78	13,771	625,840	2.20	2.25 (1.21-4.19)	**1.52 (0.81-2.87)**	-
Norway	8	468	1.71	10450	637,889	1.64	1.04 (0.53-2.07)	**0.87 (0.43-1.73)**	-
Sweden	23	773	2.98	26,768	1,258,601	2.13	1.40 (0.93-2.09)	**1.09 (0.72-1.64)**	-
Meta-analysis	51	1,904	2.68	62,158	3,207,614	1.94	1.43 (1.08-1.88)	**1.10 (0.83-1.46)**	**1.11 (0.84-1.46)**
Gabapentin vs Pregabalin									
Denmark	6	385	1.56	7	381	1.84	0.85 (0.29-2.50)	**0.55 (0.13-2.25)**	-
Finland	12	251	4.78	38	952	3.99	1.22 (0.60-2.46)	**1.24 (0.58-2.64)**	-
Norway	8	418	1.91	5	294	1.70	1.13 (0.37-3.42)	**1.66 (0.48-5.72)**	-
Sweden	21	731	2.87	55	1,499	3.67	0.78 (0.48-1.28)	**1.09 (0.58-2.02)**	-
Meta-analysis	47	1,785	2.63	105	3,126	3.36	0.92 (0.64-1.32)	**1.12 (0.73-1.72)**	**1.08 (0.75-1.57)**
Gabapentin vs Lamotrigine									
Denmark	8	398	2.01	42	2,506	1.68	1.20 (0.57-2.54)	**1.72 (0.69-4.29)**	-
Finland	12	251	4.78	34	1,225	2.78	1.77 (0.87-3.59)	**1.25 (0.45-3.45)**	-
Norway	8	460	1.74	25	2,101	1.19	1.46 (0.66-3.22)	**1.54 (0.62-3.82)**	-
Sweden	20	749	2.67	94	4,239	2.22	1.20 (0.75- 1.94)	**0.79 (0.38-1.65)**	-
Meta-analysis	48	1,858	2.58	195	10,071	1.94	1.34 (0.98-1.85)	**1.19 (0.77-1.85)**	**1.06 (0.77-1.46)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	6	372	1.61	49	2,865	1.71	0.94 (0.41-2.19)	**1.47 (0.56-3.83)**	-
Finland	12	251	4.78	72	2,203	3.27	1.50 (0.77-2.91)	**1.51 (0.75-3.05)**	-
Norway	8	411	1.95	30	2,388	1.26	1.55 (0.72-3.36)	**1.33 (0.56-3.17)**	-
Sweden	19	711	2.67	147	5,635	2.61	1.02 (0.64-1.64)	**0.84 (0.49-1.46)**	-
Meta-analysis	45	1,745	2.58	298	13,091	2.28	1.18 (0.86-1.63)	**1.14 (0.80-1.63)**	**1.09 (0.80-1.49)**

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded. Cases represent the crude number of any major congenital malformation included in the analysis. Cases represent the crude number of any stillbirth included in the analysis. Total represents the total number of newborns at risk. Prevalence= Cases/Total. PS-Adjusted = Propensity score adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. NR = NR due to the possibility of estimating a low number of individuals (<5) in other cells. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases.

Table 16 shows country-specific crude and PS-adjusted prevalence ratios for low (<7) five-minute Apgar score for any gabapentin exposure any time during gestation vs the prespecified comparators. The aPRs (95% CI) for gabapentin-exposed births vs births unexposed to gabapentin and other AEDs were 0.87 (0.32-2.35) in Denmark, 1.62 (0.94-2.80) in Finland, 0.68 (0.31-1.51) in Norway, and 1.00 (0.62-1.62) in Sweden.

Pooled adjusted estimate for low five-minute Apgar score comparing gabapentin-exposed births vs unexposed births was 1.09 (0.80-1.48) using fixed effects meta-analysis and nearly the same (1.05, 95 % CI: 0.78-1.42) using MH meta-analysis approach. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs (95% CIs) were 1.05 (0.69-1.61), 0.94 (0.59-1.48), and 0.99 (0.68-1.45) vs pregabalin, lamotrigine, and pregabalin and/or lamotrigine-exposed births, respectively. MH pooled aPRs were very similar in magnitude to fixed effect meta-analyses results with estimates close to the no-association (null) value of 1.0.

Table 16. Country-specific and combined crude and propensity score adjusted prevalence ratios of low Apgar score in gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Low Apgar score	Cases, n	Total, n	Prevalence (%)	Cases, n	Total, n	Prevalence (%)	Crude Prevalence Ratio (95% CI)	**PS-Adjusted Prevalence Ratio (95% CI)**	**MH Adjusted Pooled Prevalence Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	<5	412	NR	4,464	685,284	0.65	NR	**0.87 (0.32-2.35)**	-
Finland	14	254	5.51	12,878	638,452	2.02	2.83 (1.66-4.84)	**1.62 (0.94-2.80)**	-
Norway	7	485	1.44	11,215	653,994	1.71	0.84 (0.40-1.75)	**0.68 (0.31-1.51)**	-
Sweden	17	794	2.14	16,578	1,290,184	1.28	1.67 (1.04-2.67)	**1.00 (0.62-1.62)**	-
Meta-analysis	NR	1,945	NR	NR	3,267,914	NR	1.74 (1.28-2.35)	**1.09 (0.80-1.48)**	**1.05 (0.78-1.42)**
Gabapentin vs Pregabalin									
Denmark	<5	385	NR	8	381	2.10	<5	**0.34 (0.06-1.84)**	-
Finland	14	254	5.51	31	972	3.19	1.77 (0.93-3.37)	**1.69 (0.83-3.43)**	-
Norway	7	435	1.61	10	309	3.24	0.50 (0.19-1.29)	**2.06 (0.66-6.43)**	-
Sweden	15	750	2.00	48	1,531	3.14	0.64 (0.36-1.14)	**0.67 (0.36-1.28)**	-
Meta-analysis	NR	1,824	NR	NR	3,193	NR	0.84 (0.58-1.22)	**1.05 (0.69-1.61)**	**0.92 (0.63-1.34)**
Gabapentin vs Lamotrigine									
Denmark	<5	398	NR	37	2,506	1.48	NR	**0.75 (0.25-2.30)**	-
Finland	14	254	5.51	50	1,245	4.02	1.39 (0.76-2.56)	**1.09 (0.46-2.58)**	-
Norway	7	477	1.47	46	2,152	2.14	0.69 (0.31-1.51)	**0.90 (0.35-2.30)**	-
Sweden	17	770	2.21	100	4,358	2.29	0.96 (0.58-1.60)	**1.03 (0.47-2.28)**	-
Meta-analysis	NR	1,899	NR	NR	10,261	NR	0.98 (0.70-1.36)	**0.94 (0.59-1.48)**	**0.95 (0.67-1.34)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	<5	372	NR	44	2,865	1.54	NR	**0.80 (0.26-2.50)**	-
Finland	14	254	5.51	85	2,244	3.79	1.48 (0.83-2.64)	**1.36 (0.73-2.52)**	-
Norway	6	426	1.41	42	2,386	1.76	1.13 (0.45-2.80)	**0.75 (0.34-1.64)**	-
Sweden	15	730	2.05	143	5,781	2.47	0.83 (0.49-1.41)	**0.75 (0.40-1.41)**	-
Meta-analysis	NR	1,784	NR	NR	13,343	NR	0.96 (0.69-1.33)	**0.99 (0.68-1.45)**	**0.95 (0.68-1.32)**

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded. Cases represent the crude number of any major congenital malformation included in the analysis. Cases represent the crude number of any low Apgar score at 5 minutes included in the analysis. Total represents the total number of newborns at risk. Prevalence= Cases/Total. PS-Adjusted = Propensity score-adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. NR = nonreportable or potentially NR due to the possibility of estimating a low number of individuals (<5) in other cells; some data may be reported with the final draft. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases.MH = Mantel-Haenszel

Table 17 shows country-specific crude and PS-adjusted prevalence ratios for microcephaly for any gabapentin exposure any time during gestation vs the prespecified comparators. The aPRs (95% CI) for gabapentin-exposed births vs births unexposed to gabapentin and other AEDs were 0.87 (0.43-1.74) in Denmark, 0.89 (0.42-1.90) in Finland, 0.96 (0.53-1.73) in Norway, and 0.76 (0.38-1.52) in Sweden. Crude PRs were close to the null value of 1.00 for all contrasts, with wide 95% CIs.

Pooled adjusted estimate for microcephaly comparing gabapentin-exposed births vs unexposed births was 0.88 (0.62-1.23) using fixed effects meta-analysis and the same using MH meta-analysis approach; however, the precision was lacking due to small number of accrued events for both meta-analytic approaches. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aPRs (95% CIs) were 1.28 (0.77-2.14), 0.93 (0.59-1.47), and 0.88 (0.58-1.34) vs pregabalin, lamotrigine, and pregabalin and/or lamotrigine-exposed births, respectively. MH pooled aPRs gained very similar estimates.

Table 17. Country-specific and combined crude and propensity score adjusted prevalence ratios of microcephaly in gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Microcephaly	Cases, n	Total, n	Prevalence (%)	Cases, n	Total, n	Prevalence (%)	Crude Prevalence Ratio (95% CI)	**PS-Adjusted Prevalence Ratio (95% CI)**	**MH Adjusted Pooled Prevalence Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	8	412	1.94	13,162	685,284	1.92	1.01 (0.51-2.00)	**0.87 (0.43-1.74)**	-
Finland	7	239	2.93	15,221	609,072	2.50	1.16 (0.55-2.46)	**0.89 (0.42-1.90)**	-
Norway	11	461	2.39	15,613	634,171	2.46	0.97 (0.54-1.74)	**0.96 (0.53-1.73)**	-
Sweden	8	752	1.06	16,429	1,229,518	1.34	0.80 (0.40-1.59)	**0.76 (0.38-1.52)**	-
Meta-analysis	34	1,864	1.82	60,425	3,137,449	1.93	0.97 (0.69-1.35)	**0.88 (0.62-1.23)**	**0.90 (0.64-1.25)**
Gabapentin vs Pregabalin									
Denmark	7	385	1.82	10	381	2.62	0.69 (0.26-1.79)	**0.80 (0.27-2.37)**	-
Finland	7	239	2.93	34	931	3.65	0.78 (0.34-1.79)	**0.95 (0.40-2.23)**	-
Norway	10	412	2.43	9	298	3.02	0.80 (0.33-1.95)	**2.34 (0.83-6.62)**	-
Sweden	8	712	1.12	28	1,464	1.91	0.59 (0.27-1.28)	**1.17 (0.44-3.16))**	-
Meta-analysis	32	1,748	1.83	81	3,074	2.64	0.70 (0.46-1.08)	**1.28 (0.77-2.14)**	**1.20 (0.74-1.94)**
Gabapentin vs Lamotrigine									
Denmark	7	398	1.76	59	2,506	2.35	0.74 (0.34-1.62)	**0.92 (0.35-2.37)**	-
Finland	7	239	2.93	40	1,188	3.37	0.85 (0.38-1.93)	**1.81 (0.70-4.72)**	-
Norway	11	455	2.42	54	2,091	2.58	0.94 (0.49-1.78)	**0.90 (0.44-1.84)**	-
Sweden	7	728	0.96	58	4,131	1.40	0.68 (0.31-1.49)	**0.28 (0.08-1.00)**	-
Meta-analysis	32	1,820	1.76	211	9,916	2.13	0.81 (0.56-1.18)	**0.93 (0.59-1.47)**	**0.71 (0.49-1.03)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	6	372	1.61	67	2,865	2.34	0.69 (0.30-1.57)	**0.84 (0.33-2.12)**	-
Finland	7	239	2.93	74	2,145	3.45	0.83 (0.38-1.83)	**0.91 (0.40-2.10)**	-
Norway	10	407	2.46	62	2,381	2.60	0.94 (0.49-1.83)	**1.01 (0.49-2.07)**	-
Sweden	7	692	1.01	83	5,493	1.51	0.67 (0.31-1.44)	**0.70 (0.28-1.77)**	-
Meta-analysis	30	1,710	1.75	286	12,884	2.22	0.79 (0.54-1.15)	**0.88 (0.58-1.34)**	**0.89 (0.61-1.29)**

For analyses that use pregabalin as the comparator, pregnancies exposed to both gabapentin and lamotrigine in the same relevant exposure window were excluded. For analyses that use lamotrigine as the comparator, pregnancies exposed to both gabapentin and pregabalin in the same relevant exposure window were excluded. Cases represent the crude number of any major congenital malformation included in the analysis. Cases represent the crude number of any microcephaly included in the analysis. Total represents the total number of newborns at risk. Prevalence= Cases/Total. PS-Adjusted = Propensity score adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases.

10.5.2. Postnatal outcomes

Table 18 shows country-specific crude and PS-adjusted HRs for hyperkinetic disorders incl. ADHD among offspring for any gabapentin exposure any time during gestation vs the prespecified comparators. The aHR (95% CI) for gabapentin-exposed births vs births unexposed to gabapentin and other AEDs were 1.49 (0.79-2.81) in Denmark; 1.14 (0.54-2.44) in Finland; 0.89 (0.40-2.00) in Norway; and 1.03 (0.66-1.61) in Sweden. Adjustment for measured covariables resulted in estimates' attenuation across all countries.

Pooled aHR for hyperkinetic disorders incl. ADHD comparing gabapentin-exposed births vs unexposed births was 1.12 (95% CI: 0.82-1.51) using fixed effects meta-analysis and 1.11 (95% CI: 0.83-1.49) using MH meta-analysis approach. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aHRs (95% CIs) 1.05 (0.68-1.63), 0.91 (0.59-1.39), and 0.90 (0.61-1.33) vs pregabalin, lamotrigine, and pregabalin and/or lamotrigine-exposed births, respectively. MH pooled aHRs were similar to the results of the fixed-effects meta-analyses.

Table 18. Country-specific and combined crude and propensity score adjusted hazard ratios of hyperkinetic disorders incl. ADHD in gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Hyperkinetic disorders incl. ADHD	Cases, n	Person-years	Incidence Rate per 10,000 person-years	Cases, n	Person-years	Incidence Rate per 10,000 person-years	Crude Hazard Ratio (95% CI)	**PS-Adjusted Hazard Ratio (95% CI)**	**MH Adjusted Pooled Hazard Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	10	2,275.0	43.96	11,663	5,399,673.0	21.60	2.99 (1.59-5.62)	**1.49 (0.79-2.81)**	-
Finland	7	1,323.0	52.91	10,794	4,119,912.5	26.20	2.56 (1.21-5.44)	**1.14 (0.54-2.44)**	-
Norway	6	2,833.0	21.18	10,726	4,838,282.0	22.17	1.55 (0.69-3.48)	**0.89 (0.40-2.00)**	-
Sweden	21	4,071.0	51.60	27,636	9,157,771.0	30.20	2.73 (1.74-4.28)	**1.03 (0.66-1.61)**	-
Meta-analysis	44	10,502.0	41.90	60,819	23,515,639.0	25.86	2.55 (1.88-3.46)	**1.12 (0.82-1.51)**	**1.11 (0.83-1.49)**
Gabapentin vs Pregabalin									
Denmark	9	2,131.0	42.23	12	2,122.0	56.55	0.65 (0.27-1.60)	**1.30 (0.34-5.00)**	-
Finland	7	1,323.0	52.91	17	4,751.0	35.78	1.16 (0.46-2.91)	**1.68 (0.64-4.44)**	-
Norway	6	2,518.0	23.83	12	2,212.0	54.25	0.63 (0.25-1.60)	**1.25 (0.49-3.22)**	-
Sweden	19	3,852.0	49.30	85	10,147.0	83.80	0.48 (0.28-0.83)	**0.73 (0.39-1.37)**	-
Meta-analysis	41	9,824.0	41.73	126	19,232.0	65.52	0.62 (0.42-0.90)	**1.05 (0.68-1.63)**	**0.96 (0.65-1.42)**
Gabapentin vs Lamotrigine									
Denmark	10	2,180.0	45.87	59	17,326.0	34.05	1.63 (0.84-3.20)	**0.62 (0.24-1.57)**	-
Finland	7	1,323.0	52.91	31	7,075.4	43.81	1.21 (0.52-2.83)	**1.33 (0.50-3.56)**	-
Norway	6	2,789.0	21.51	46	14,581.0	31.55	0.97 (0.41-2.27)	**0.81 (0.30-2.17)**	-
Sweden	21	3,948.0	53.20	136	25,821.0	52.70	1.05 (0.66-1.69)	**0.96 (0.50-1.84)**	-
Meta-analysis	44	10,240.0	42.97	272	64,803.0	41.97	1.18 (0.85-1 .63)	**0.91 (0.59-1.39)**	**0.84 (0.60-1.16)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	9	2,043.0	44.05	70	19,321.0	36.23	1.41 (0.70-2.84)	**0.65 (0.23-1.80)**	-
Finland	7	1,323.0	52.91	48	11,947.6	40.18	1.17 (0.51-2.67)	**1.15 (0.46-2.87)**	-
Norway	6	2,483.0	24.16	58	16,728.0	34.67	0.99 (0.43-2.27)	**1.21 (0.50-2.94)**	-
Sweden	19	3,743.0	50.80	216	35,296.0	61.20	0.81 (0.50-1.31)	**0.80 (0.45-1.41)**	-
Meta-analysis	41	9,593.0	42.74	392	83,293.0	47.06	1.00 (0.72-1 .39)	**0.90 (0.61-1.33)**	**0.85 (0.61-1.18)**

Cases represent the crude number of any Hyperkinetic disorders including ADHD (attention deficit disorders) included in the analysis. Total person-years represents the total person-time at risk contributed by each liveborn infant. Incidence rate= Cases/Total person-years. PS-Adjusted = Propensity score adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases. NR = nonreportable or potentially NR due to the possibility of estimating a low number of individuals (<5) in other cells; some data may be reported with the final draft. NE = non-estimable due to 0 cases in one or more cells.

Table 19 shows country-specific crude and PS-adjusted HRs for pervasive developmental disorders including ASD among offspring for any gabapentin exposure any time during gestation vs the prespecified comparators. The aHR (95% CI) for gabapentin-exposed births vs births unexposed to gabapentin and other AEDs were 0.82 (0.31-2.21) in Denmark; 1.85 (0.58-5.85) in Finland; 1.46 (0.60-3.54) in Norway; and 0.78 (0.40-1.50) in Sweden. Adjustment resulted in estimates' attenuation in all four Nordic countries.

Pooled aHR for pervasive developmental disorders including ASD comparing gabapentin-exposed births vs unexposed births was 1.03 (0.67-1.58) using fixed effects meta-analysis. MH meta-analysis approach yielded similar pooled aHR. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aHRs (95% CIs) 1.27 (0.66-2.44), 0.90 (0.50-1.62), and 1.00 (0.60-1.66) vs pregabalin, lamotrigine, and pregabalin and/or lamotrigine-exposed births, respectively. MH pooled - aHRs were similar to the results of the fixed-effects meta-analyses.

Table 19. Country-specific and combined crude and propensity score adjusted hazard ratios of pervasive development disorders incl. ASD in gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Pervasive development disorders incl. ASD	Cases, n	Person-years	Incidence Rate per 10,000 person-years	Cases, n	Person-years	Incidence Rate per 10,000 person-years	Crude Hazard Ratio (95% CI)	**PS-Adjusted Hazard Ratio (95% CI)**	**MH Adjusted Pooled Hazard Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	<5	2,303.0	NR	9,312	5,403,154.0	17.23	NR	**0.82 (0.31-2.21)**	-
Finland	<5	1,322.8	NR	3,207	4,133,197.5	7.76	3.27 (1.05-10.19)	**1.85 (0.58-5.85)**	-
Norway	5	2,849.0	17.55	4,186	4,851,460.0	8.63	2.24 (0.93-5.39)	**1.46 (0.60-3.54)**	-
Sweden	9	4,071.0	22.10	15,277	9,157,771.0	16.70	2.00 (1.04-3.84)	**0.78 (0.40-1.50)**	-
Meta-analysis	21	10,546.0	19.91	31,982	23,545,582.0	13.58	2.01 (1.31-3.09)	**1.03 (0.67-1.58)**	**1.00 (0.65-1.53)**
Gabapentin vs Pregabalin									
Denmark	<5	2,156.0	NR	5	2,138.0	23.39	NR	**0.80 (0.17-3.66)**	-
Finland	<5	1,322.8	NR	6	4,774.7	12.57	1.67 (0.38-7.44)	**1.55 (0.35-6.88)**	-
Norway	5	2,535.0	19.73	2	2,234.0	8.95	2.23 (0.49-10.21)	**3.94 (0.73-21.28)**	-
Sweden	9	3,852.0	23.40	41	10,147.0	40.40	0.44 (0.20-0.97)	**0.71 (0.29-1.74)**	-
Meta-analysis	21	9,866.0	21.29	54	19,293.0	27.99	0.75 (0.42-1.34)	**1.27 (0.66-2.44)**	**1.10 (0.62-1.95)**
Gabapentin vs Lamotrigine									
Denmark	<5	2,208.0	NR	45	17,326.0	25.97	NR	**0.77 (0.24-2.43)**	-
Finland	<5	1,322.8	NR	14	7,101.0	19.72	1.20 (0.34-4.22)	**0.75 (0.16-3.51)**	-
Norway	5	2,806.0	17.82	25	14,636.0	17.08	1.11 (0.43-2.86)	**1.94 (0.63-5.98)**	-
Sweden	9	3,948.0	22.80	78	25,821.0	30.20	0.83 (0.42-1.65)	**0.59 (0.21-1.63)**	-
Meta-analysis	21	10,285.0	20.42	162	64,884.0	24.97	0.92 (0.59-1.46)	**0.90 (0.50- 1.62)**	**0.76 (0.48-1.22)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	<5	2,069.0	NR	50	19,333.0	25.86	NR	**0.92 (0.29-2.96)**	-
Finland	<5	1,322.8	NR	21	11,996.8	17.50	1.31 (0.38-4.47)	**0.84 (0.23-3.06)**	-
Norway	5	2,500.0	20.00	27	16,806.0	16.07	1.36 (0.53-3.46)	**2.46 (0.89-6.85)**	-
Sweden	9	3,743.0	24.00	117	35,296.0	33.10	0.74 (0.37-1.46)	**0.62 (0.28-1.36)**	-
Meta-analysis	21	9,635.0	21.80	215	83,432.0	25.77	0.94 (0.60-1.48)	**1.00 (0.60-1.66)**	**0.91 (0.58-1.44)**

Cases represent the crude number of any pervasive development disorders including ASD (autism spectrum disorder) included in the analysis. Total person-years represents the total person-time at risk contributed by each liveborn infant. Incidence rate= Cases/Total person-years. PS-Adjusted = Propensity score adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed cases. NR = nonreportable or potentially NR due to the possibility of estimating a low number of individuals (<5) in other cells; some data may be reported with the final draft NE = non-estimable due to 0 cases in one or more cells.

Table 20 shows country-specific crude and PS-adjusted HRs for learning disorders among offspring for any gabapentin exposure any time during gestation vs the prespecified comparators. The aHR (95% CI) for gabapentin-exposed births vs births unexposed to gabapentin and other AEDs were 0.95 (0.30-2.98) in Denmark, 1.06 (0.56-1.99) in Finland, 1.40 (0.72-2.73) in Norway, and 0.88 (0.48-1.59) in Sweden. Adjustment resulted in estimates' attenuation compared to crude estimates.

Pooled aHR for learning disorders including intellectual disability comparing gabapentin-exposed births vs unexposed births was 1.06 (0.75-1.49) using fixed effects meta-analysis. MH meta-analysis approach yielded similar pooled aHR. In analyses contrasting gabapentin-exposed births with active comparators, pooled fixed effect meta-analyses showed aHRs (95% CIs) 0.99 (0.62-1 .60), 0.84 (0.51-1.38), and 0.80 (0.52-1.22) vs pregabalin, lamotrigine, and pregabalin and/or lamotrigine-exposed births, respectively. MH pooled aHRs were similar to pooled fixed effect meta-analyses results.

Table 20. Country-specific and combined crude and propensity score adjusted hazard ratios of learning disorders including intellectual disability in gabapentin-exposed births vs. comparators

	Gabapentin			Comparator					
Learning disorders including intellectual disability	Cases, n	Person-years	Incidence Rate per 10,000 person-years	Cases, n	Person-years	Incidence Rate per 10,000 person-years	Crude Hazard Ratio (95% CI)	**PS-Adjusted Hazard Ratio (95% CI)**	**MH Adjusted Pooled Hazard Ratio (95% CI)**
Gabapentin vs Unexposed									
Denmark	<5	2,297.0	NR	5,172	5,412,708.0	9.56	NR	**0.95 (0.30-2.98)**	-
Finland	11	1,294.1	85.00	25,590	4,056,326.7	63.09	1.51 (0.81-2.82)	**1.06 (0.56-1.99)**	-
Norway	9	2,827.0	31.84	8,658	4,836,122.0	17.90	2.09 (1.08-4.04)	**1.40 (0.72-2.73)**	-
Sweden	11	4,071.0	27.00	16,568	9,157,771.0	18.10	2.21 (1.22-4.00)	**0.88 (0.48-1.59)**	-
Meta-analysis	NR	NR	NR	55,988	23,462,928.0	NR	1.87 (1.33-2.64)	**1.06 (0.75-1.49)**	**1.04 (0.74-1.46)**
Gabapentin vs Pregabalin									
Denmark	<5	2,150.0	NR	<5	2,130.0	NR	NR	**1.62 (0.22-12.06)**	-
Finland	11	1,294.1	85.00	36	4,703.3	76.54	1.17 (0.58-2.37)	**0.92 (0.41-2.06)**	-
Norway	9	2,512.0	35.83	8	2,218.0	36.07	1.06 (0.45-2.51)	**1.40 (0.52-3.75)**	-
Sweden	11	3,852.0	28.60	40	10,147.0	39.40	0.66 (0.32-1.38)	**0.80 (0.37-1.77)**	-
Meta-analysis	NR	9,808.0	NR	NR	19,198.0	NR	0.93 (0.61-1.43)	**0.99 (0.62-1.60)**	**0.94 (0.61-1.46)**
Gabapentin vs Lamotrigine									
Denmark	<5	2,202.0	NR	20	17,397.0	11.50	NR	**0.94 (0.15-5.86)**	-
Finland	11	1,294.1	85.00	75	6,949.7	107.92	0.84 (0.43-1.65)	**0.72 (0.31-1.69)**	-
Norway	9	2,784.0	32.33	47	14,576.0	32.24	1.10 (0.54-2.22)	**1.31 (0.60-2.89)**	-
Sweden	11	3,948.0	27.90	91	25,821.0	35.20	0.87 (0.46-1.64)	**0.51 (0.17-1.51)**	-
Meta-analysis	NR	NR	NR	233	64,744.0	35.99	0.95 (0.66-1.38)	**0.84 (0.51-1.38)**	**0.69 (0.48-1.00)**
Gabapentin vs Pregabalin or lamotrigine									
Denmark	<5	2,062.0	NR	23	19,397.0	11.86	NR	**0.50 (0.08-3.10**	-
Finland	11	1,294.1	85.00	113	11,768.7	96.02	0.92 (0.48-1.78)	**0.85 (0.41-1.75)**	-
Norway	9	2,483.0	36.00	55	16,842.0	33.00	1.23 (0.62-2.46)	**1.14 (0.51-2.54)**	-
Sweden	11	3,743.0	29.40	127	35,296.0	36.00	0.86 (0.46-1.61)	**0.62 (0.29-1.31)**	-
Meta-analysis	NR	NR	NR	318	83,192.0	38.22	1.01 (0.70-1.44)	**0.80 (0.52-1.22)**	**0.75 (0.53-1.08)**

Cases represent the crude number of any intellectual disability (mental retardation) included in the analysis. Total person-years represents the total person-time at risk contributed by each liveborn infant. Incidence rate= Cases/Total person-years. PS-Adjusted = Propensity score adjusted. Meta-analysis = Combination of country-specific crude and adjusted estimates of association for each prespecified contrast. MH = Mantel-Haenszel- Pooling method that allowed incorporation into combined estimates of associations while retaining information from strata with no exposed case. NR = nonreportable or potentially NR due to the possibility of estimating a low number of individuals (<5) in other cells; some data may be reported with the final draft

10.6. Other analyses

10.6.1. Sensitivity analyses

As monotherapy of gabapentin accounted for most of the exposure, results for monotherapy were similar, but less precise than those for any exposure (Appendix 5. Supplementary figures, Supplementary forest plots 16.4.2-16.4.5).

Sensitivity analysis including the 2nd trimester induced abortions in the analyses of pregnancies (available in Denmark, Finland, and Norway) produced very similar estimates as in the tables not including the 2nd trimester induced abortions since the inclusion of the 2nd trimester induced abortions added very few gabapentin-exposed pregnancies.

10.7. Adverse events / adverse reactions

This study includes data that already exist as structured data in an electronic database. In these data sources, it is not possible to link (i.e., establish whether causal relation was reported between) a particular product and medical event for any individual. Thus, the minimum criteria for reporting an adverse event (i.e., identifiable patient, identifiable reporter, a suspect product, and event) are not available and adverse events are not reportable as individual adverse event reports.

11. DISCUSSION

11.1. Key results

In this study, the proportion of gabapentin users in any trimester of a pregnancy ending in a live birth or stillbirth in the study period (2005-2015 for Denmark, Finland, and Norway, and 2006-2018 for Sweden) was 0.06% in Denmark, 0.04% in Finland, 0.07% in Norway, and 0.06% in Sweden. The gabapentin-exposed births had higher than unexposed births prevalence of maternal smoking in pregnancy, maternal obesity, Caesarean delivery, maternal psychiatric comorbidities and maternal history of use of psychiatric and other medications across all countries.

The main results of this study showed no increased risk (pooled aPR: 0.99, 95% CI: 0.80-1.23) of any major congenital malformations among live or stillborn offspring of women exposed to gabapentin in first pregnancy trimester compared to offspring unexposed to gabapentin and any AED. The analyses using the prespecified active comparators were broadly consistent with no association between prenatal gabapentin exposure and increased risk of major congenital malformations.

Pooled aPRs for specific malformations were imprecise and unstable due to the low number of events, but suggested that cardiac, nervous system, respiratory, digestive system malformations, and abdominal wall defects may be more prevalent among births gabapentin-exposed in first trimester vs births unexposed to gabapentin and other AED in first trimester. In addition to low precision, these estimates are subject to a chance finding due to multiple

comparisons. Pooled aPRs for site-specific malformations were shifted towards the null value in analyses using active comparators.

In the meta-analyses results for the remaining birth outcomes, comparing prenatal exposure to gabapentin any time during gestation vs no exposure to AED, we observed aPRs (95% CI) 1.24 (0.66-2.34 for stillbirth,) 1.21 (1.02-1.44) for low birth weight, 1.16 (1.00-1.35) for preterm birth, 1.10 (0.83-1.46) for SGA, 1.09 (0.80-1.48) for low Apgar score at 5 minutes, and 0.88 (0.62-1.23) for microcephaly for gabapentin-exposed compared with unexposed births. Analyses using lamotrigine and pregabalin and/or lamotrigine as an active comparator showed pooled aPRs close to unity; analyses using pregabalin as an active comparator showed no association of gabapentin exposure in pregnancy with stillbirth, SGA, low Apgar score at 5 minutes, and microcephaly, while the pooled aPRs (95% CI) for low birth weight and preterm birth in this analysis were 1.25 (0.92-1.70) and 1.11 (0.85-1.45).

For the postnatal neurodevelopmental outcomes, the risk of ADHD was not appreciably increased in gabapentin-exposed offspring compared to unexposed to AEDs (aHR: 1.12, 95% CI: 0.82-1.51), no association was observed when compared with active comparators (aHR: 1.05, 95% CI: 0.68-1.63 compared with pregabalin, 0.91 (0.59-1.39) compared with lamotrigine, and 0.90 (0.61-1.33) compared with lamotrigine or pregabalin). No increased risk of ASD and ID was observed in gabapentin-exposed offspring vs offspring unexposed to AEDs, pregabalin-exposed, lamotrigine-exposed, and lamotrigine and/or pregabalin-exposed offspring. Results of this study for postnatal neurodevelopmental outcomes following prenatal exposure to gabapentin were in line with results of another large Nordic register-based study of antiepileptic drugs in pregnancy (SCAN-AED) showing no association between prenatal exposure to gabapentin and increased risk of autism and intellectual disability.[15]

11.2. Limitations

Population-based healthcare registries in Nordic countries are a best available setting for examining the safety of medicines in pregnancy. Their most important strengths are the capture of all births and clinically relevant birth and postnatal outcomes; routine capture of prescription medications dispensings including capture of medication dispensed in pregnancy to women; extensive information about maternal and offspring health outcomes; and exact linkage between the maternal and the offspring records. Thus, unlike studies based on data from teratology information services, for example, there is no bias by self-referral, recall, or access to health care. Dispensations of medicines represent a better proxy of actual medicine intake than issued prescriptions, thus reducing misclassification of the actual medicine intake. Selection bias due to lack of data on all pregnancy outcomes in all countries cannot be ruled out.

Residual confounding, especially confounding by indication cannot be fully accounted for by the applied methods as indication is not available from the data sources. The indications for gabapentin and active comparators intersect but are not identical. Indications for gabapentin include epilepsy and peripheral neuropathic pain. Indications for pregabalin include neuropathic pain, and partial seizures. Indications for lamotrigine include epilepsy and

bipolar disorder. Differences in the leading indication for the active comparators vs gabapentin may result in residual confounding. The gabapentin-exposed births had higher than the unexposed births prevalence of maternal smoking in pregnancy, maternal obesity, Caesarean delivery, and indicators of psychiatric comorbidity across all countries. Since the gabapentin-exposed women may differ considerably from not only the unexposed but also the active comparators, the residual confounding due to uneven underreporting of confounders in gabapentin or comparator groups may have influenced the results. In support of possible residual confounding for the contrasts of gabapentin-exposed births vs active comparators, after PS stratification and trimming, antidepressant use, diabetes, infections, sleep disorders, the use of hypnotics, smoking in pregnancy, alcohol or drug abuse covariables (in various Nordic countries) had SMD between 0.1 and 0.2 and could not be double-adjusted for due to models' non-convergence.

Validity of routinely collected healthcare data in Nordic national registries has been found to be high in all countries.[29 49-63] In Denmark, the positive predictive value of diagnoses of cardiac malformations is 89%.[64] For drugs used chronically, there is also a high level of agreement between general practitioner and dispensing records.[65] An agreement between dispensing records and drug use reported in the standard medical antenatal records included in the birth register was 69% for antiepileptics in Sweden.[66]

Misclassification of all study variables based on routinely collected data cannot be ruled out. However, outcomes are likely to have high specificity, implying that relative measures of association are not expected to be biased by the misclassification of the outcome. Risks of the postnatal outcomes based on hospital diagnoses likely represent the most severe part of the disease spectrum as they have resulted in a hospital contact. Moreover, we had no data on primary care visits in this study in all participating countries but Finland.

Although non-differential misclassification of the binary outcome with regard to exposure is expected to lead to the dilution of the effect, given the high validity of data on the outcomes in this study, the observed null associations are unlikely to be explained away by the outcome misclassification.

Low precision of some estimates is a further limitation, especially in the contrasts involving active comparators.

11.3. Interpretation

The adjusted associations for prenatal exposure to gabapentin and most of the examined outcomes were consistent with no association. The association observed for a majority of the study outcomes was attenuated in response to increasing control of confounding via use of active comparators, indicating potential for residual confounding in the contrast of gabapentin-exposed births with AED-unexposed births.

The results of the present study ruled out larger than 1.5-fold increases in the prevalence of most birth outcomes or rates of postnatal neurodevelopmental outcomes associated with prenatal exposure to gabapentin in a relevant risk period. This is based on the upper limits of 95% confidence intervals. Multiple effect estimates in this study were imprecise due to the

low number of observed events (also consistent with known low use of gabapentin in pregnancy) and the results should be interpreted with caution.

11.4. Generalizability

The study was based on population-based nationwide routinely collected data from registries in Denmark, Finland, Norway, and Sweden, covering more than a 10-year period after introduction of gabapentin to the market. In the Nordic countries, >90% of the population is Caucasian, and thus the available data on other racial and ethnical groups are too limited to conduct stratified analyses, but based on biological plausibility, there is no reason to suspect non-generalizability of these results to other populations.

12. OTHER INFORMATION

Not applicable.

13. CONCLUSIONS

In this post-authorisation safety study based on routinely collected secondary population-based data from four Nordic countries, prenatal exposure to gabapentin was not associated with an increased risk of most adverse birth outcomes or postnatal neurodevelopmental outcomes. The weak associations observed for low birth weight and preterm birth may, at least partially, be due to residual confounding, although could not be ruled out completely.

14. REFERENCES

1. EMA. Neurontin [Available from: https://www.ema.europa.eu/documents/referral/neurontin-article-30-referral-annex-i-ii-iii_en.pdf accessed 26 July 2021.
2. Weston J, Bromley R, Jackson CF, et al. Monotherapy treatment of epilepsy in pregnancy: congenital malformation outcomes in the child. *Cochrane Database Syst Rev* 2016;11(11):CD010224. doi: 10.1002/14651858.CD010224.pub2 [published Online First: 2016/11/08]
3. Veroniki AA, Cogo E, Rios P, et al. Comparative safety of anti-epileptic drugs during pregnancy: a systematic review and network meta-analysis of congenital malformations and prenatal outcomes. *BMC Med* 2017;15(1):95. doi: 10.1186/s12916-017-0845-1 [published Online First: 2017/05/06]
4. Tomson T, Battino D, Perucca E. Teratogenicity of antiepileptic drugs. *Curr Opin Neurol* 2019;32(2):246-52. doi: 10.1097/WCO.0000000000000659 [published Online First: 2019/01/22]
5. Margulis AV, Hernandez-Diaz S, McElrath T, et al. Relation of in-utero exposure to antiepileptic drugs to pregnancy duration and size at birth. *PLoS One* 2019;14(8):e0214180. doi: 10.1371/journal.pone.0214180 [published Online First: 2019/08/06]
6. Hernandez-Diaz S, Smith CR, Shen A, et al. Comparative safety of antiepileptic drugs during pregnancy. *Neurology* 2012;78(21):1692-9. doi: 10.1212/WNL.0b013e3182574f39 [published Online First: 2012/05/04]
7. Källén B, Borg N, Reis M. The use of central nervous system active drugs during pregnancy. *Pharmaceuticals (Basel)* 2013;6(10):1221-86. doi: 10.3390/ph6101221
8. CDC. Update on Overall Prevalence of Major Birth Defects --- Atlanta, Georgia, 1978--2005 [Available from: https://www.cdc.gov/mmwr/preview/mmwrhtml/mm5701a2.htm accessed 26 July 2021.
9. Huybrechts KF, Broms G, Christensen LB, et al. Association Between Methylphenidate and Amphetamine Use in Pregnancy and Risk of Congenital Malformations: A Cohort Study From the International Pregnancy Safety Study Consortium. *JAMA Psychiatry* 2018;75(2):167-75. doi: 10.1001/jamapsychiatry.2017.3644 [published Online First: 2017/12/15]
10. Broe A, Damkier P, Pottegard A, et al. Congenital Malformations in Denmark: Considerations for the Use of Danish Health Care Registries. *Clin Epidemiol* 2020;12:1371-80. doi: 10.2147/CLEP.S278596 [published Online First: 2020/12/29]
11. Finnish Institute for Health and Welfare. Congenital Malformations 2017 [accessed 26 July 2021.
12. Agence Nationale de Sécurité du Médicament et des produits de santé (ANSM). Exposition in utero à l'acide valproïque et aux autres traitements de l'épilepsie et des troubles bipolaires et risqué de malformations congénitales majeures (MCM) en France 2017 [Available from: https://www.ameli.fr/content/rapport-exposition-utero-lacide-valproique-et-risque-de-malformations-congenitales-majeures accessed 26 July 2021.

13. Mostacci B, Poluzzi E, D'Alessandro R, et al. Adverse pregnancy outcomes in women exposed to gabapentin and pregabalin: data from a population-based study. *J Neurol Neurosurg Psychiatry* 2018;89(2):223-24. doi: 10.1136/jnnp-2017-316143 [published Online First: 2017/07/19]
14. Patorno E, Hernandez-Diaz S, Huybrechts KF, et al. Gabapentin in pregnancy and the risk of adverse neonatal and maternal outcomes: A population-based cohort study nested in the US Medicaid Analytic eXtract dataset. *PLoS Med* 2020;17(9):e1003322. doi: 10.1371/journal.pmed.1003322 [published Online First: 2020/09/02]
15. Bjørk M-H, Zoega H, Leinonen MK, et al. Association of Prenatal Exposure to Antiseizure Medication With Risk of Autism and Intellectual Disability. *JAMA Neurology* 2022 doi: 10.1001/jamaneurol.2022.1269
16. Bosco JL, Silliman RA, Thwin SS, et al. A most stubborn bias: no adjustment method fully resolves confounding by indication in observational studies. *J Clin Epidemiol* 2010;63(1):64-74. doi: 10.1016/j.jclinepi.2009.03.001 [published Online First: 2009/05/22]
17. Lund JL, Richardson DB, Sturmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. *Curr Epidemiol Rep* 2015;2(4):221-28. doi: 10.1007/s40471-015-0053-5 [published Online First: 2016/03/10]
18. Laugesen K, Ludvigsson JF, Schmidt M, et al. Nordic Health Registry-Based Research: A Review of Health Care Systems and Key Registries. *Clinical Epidemiology* 2021;Volume 13:533-54. doi: 10.2147/CLEP.S314959
19. European Surveillance of Congenital Anomalies EUROCAT 2021 [Available from: https://eu-rd-platform.jrc.ec.europa.eu/eurocat_en accessed 16 June 2021.
20. Sankilampi U, Hannila ML, Saari A, et al. New population-based references for birth weight, length, and head circumference in singletons and twins from 23 to 43 gestation weeks. *Ann Med* 2013;45(5-6):446-54. doi: 10.3109/07853890.2013.803739 [published Online First: 2013/06/19]
21. Glinianaia SV, SkjÆRven R, Magnus PER. Birthweight percentiles by gestational age in multiple births. *Acta Obstet Gynecol Scand* 2000;79(6):450-58. doi: 10.1034/j.1600-0412.2000.079006450.x
22. Dalsgaard S, Thorsteinsson E, Trabjerg BB, et al. Incidence Rates and Cumulative Incidences of the Full Spectrum of Diagnosed Mental Disorders in Childhood and Adolescence. *JAMA Psychiatry* 2020;77(2):155-64. doi: 10.1001/jamapsychiatry.2019.3523 [published Online First: 2019/11/21]
23. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *Eur J Epidemiol* 2014;29(8):541-49. doi: 10.1007/s10654-014-9930-3 [published Online First: 2014/06/27]
24. Ludvigsson JF, Otterblad-Olausson P, Pettersson BU, et al. The Swedish personal identity number: possibilities and pitfalls in healthcare and medical research. *Eur J Epidemiol* 2009;24(11):659-67. doi: 10.1007/s10654-009-9350-y [published Online First: 2009/06/09]
25. Lynge E, Sandegaard JL, Rebolj M. The Danish National Patient Register. *Scand J Public Health* 2011;39(7 Suppl):30-36. doi: 10.1177/1403494811401482 [published Online First: 2011/08/04]

26. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clin Epidemiol* 2015;7:449-90. doi: 10.2147/CLEP.S91125 [published Online First: 2015/11/26]
27. Wettermark B, Zoega H, Furu K, et al. The Nordic prescription databases as a resource for pharmacoepidemiological research--a literature review. *Pharmacoepidemiol Drug Saf* 2013;22(7):691-9. doi: 10.1002/pds.3457 [published Online First: 2013/05/25]
28. Johannesdottir SA, Chang ET, Mehnert F, et al. Nonsteroidal anti-inflammatory drugs and the risk of skin cancer: a population-based case-control study. *Cancer* 2012;118(19):4768-76. doi: 10.1002/cncr.27406 [published Online First: 2012/05/31]
29. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. *BMC Public Health* 2011;11(1):450. doi: 10.1186/1471-2458-11-450 [published Online First: 2011/06/11]
30. Mors O, Perto GP, Mortensen PB. The Danish Psychiatric Central Research Register. *Scand J Public Health* 2011;39(7 Suppl):54-7. doi: 10.1177/1403494810395825 [published Online First: 2011/08/04]
31. Helsedirektoratet. Norwegian Patient Registry 2019 [Available from: https://helsedirektoratet.no/english/norwegian-patient-registry accessed 11 April 2019.
32. Cnattingius S, Ericson A, Gunnarskog J, et al. A quality study of a medical birth registry. *Scand J Soc Med* 1990;18(2):143-8. doi: 10.1177/140349489001800209 [published Online First: 1990/06/01]
33. Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *Eur J Epidemiol* 2017;32(9):765-73. doi: 10.1007/s10654-017-0316-1 [published Online First: 2017/10/07]
34. Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. *Lancet* 2015;386(10006):1845-52. doi: 10.1016/s0140-6736(15)00045-8 [published Online First: 20150825]
35. Desai RJ, Rothman KJ, Bateman BT, et al. A Propensity-score-based Fine Stratification Approach for Confounding Adjustment When Exposure Is Infrequent. *Epidemiology* 2017;28(2):249-57. doi: 10.1097/EDE.0000000000000595 [published Online First: 2016/12/07]
36. Ehrenstein V, Sorensen HT, Bakketeig LS, et al. Medical databases in studies of drug teratogenicity: methodological issues. *Clin Epidemiol* 2010;2:37-43. [published Online First: 2010/09/25]
37. Rothman KJ, Greenland S. Planning Study Size Based on Precision Rather Than Power. *Epidemiology* 2018;29(5):599-603. doi: 10.1097/EDE.0000000000000876 [published Online First: 2018/06/19]
38. Rothman KJ. Episheet [Available from: http://krothman.hostbyet2.com/episheet.xls accessed 26 October 2019.
39. Wyss R, Girman CJ, LoCasale RJ, et al. Variable selection for propensity score models when estimating treatment effects on multiple outcomes: a simulation study. *Pharmacoepidemiol Drug Saf* 2013;22(1):77-85. doi: 10.1002/pds.3356
40. Patorno E, Bateman BT, Huybrechts KF, et al. Pregabalin use early in pregnancy and the risk of major congenital malformations. *Neurology* 2017;88(21):2020-25. doi: 10.1212/WNL.0000000000003959 [published Online First: 2017/04/28]

41. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med* 2009;28(25):3083-107. doi: 10.1002/sim.3697 [published Online First: 2009/09/17]
42. Nguyen TL, Collins GS, Spence J, et al. Double-adjustment in propensity score matching analysis: choosing a threshold for considering residual imbalance. *BMC Med Res Methodol* 2017;17(1):78. doi: 10.1186/s12874-017-0338-0 [published Online First: 2017/04/30]
43. Selmer R, Haglund B, Furu K, et al. Individual-based versus aggregate meta-analysis in multi-database studies of pregnancy outcomes: the Nordic example of selective serotonin reuptake inhibitors and venlafaxine in pregnancy. *Pharmacoepidemiol Drug Saf* 2016;25(10):1160-69. doi: 10.1002/pds.4033 [published Online First: 2016/05/20]
44. EUPAS27339 A Population-based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes [Available from: http://www.encepp.eu/encepp/viewResource.htm?id=36881 accessed 26 July 2021.
45. Rosen M. National Health Data Registers: a Nordic heritage to public health. *Scand J Public Health* 2002;30(2):81-5. doi: 10.1080/140349401753683444 [published Online First: 2002/05/25]
46. Ludvigsson JF, Haberg SE, Knudsen GP, et al. Ethical aspects of registry-based research in the Nordic countries. *Clin Epidemiol* 2015;7:491-508. doi: 10.2147/CLEP.S90589 [published Online First: 2015/12/10]
47. SDS. Hjemsendelse af analyseresultater. Retningslinjer for Sundhedsdatastyrelsens forskermaskine 2020 [Available from: https://sundhedsdatastyrelsen.dk/-/media/sds/filer/forskerservice/retningslinjer-for-hjemsendelse-af-analyseresultater_2018_07_03.pdf?la=da accessed 30 May 2022.
48. Lidegaard Ø, Krebs L, Petersen OBB, et al. Are the Danish stillbirth rates still record low? A nationwide ecological study. *BMJ open* 2020;10(12):e040716-e16. doi: 10.1136/bmjopen-2020-040716
49. Stegmayr B, Asplund K. Measuring stroke in the population: quality of routine statistics in comparison with a population-based stroke registry. *Neuroepidemiology* 1992;11(4-6):204-13. doi: 10.1159/000110933 [published Online First: 1992/01/01]
50. Lindblad U, Rastam L, Ranstam J, et al. Validity of register data on acute myocardial infarction and acute stroke: the Skaraborg Hypertension Project. *Scand J Soc Med* 1993;21(1):3-9. doi: 10.1177/140349489302100102 [published Online First: 1993/03/01]
51. Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. *Int J Epidemiol* 2000;29(3):495-502.
52. Linnersjo A, Hammar N, Gustavsson A, et al. Recent time trends in acute myocardial infarction in Stockholm, Sweden. *Int J Cardiol* 2000;76(1):17-21.
53. Hammar N, Alfredsson L, Rosen M, et al. A national record linkage to study acute myocardial infarction incidence and case fatality in Sweden. *Int J Epidemiol* 2001;30 Suppl 1:S30-4.
54. Ingelsson E, Arnlov J, Sundstrom J, et al. The validity of a diagnosis of heart failure in a hospital discharge register. *Eur J Heart Fail* 2005;7(5):787-91. doi: 10.1016/j.ejheart.2004.12.007

55. Appelros P, Terent A. Validation of the Swedish inpatient and cause-of-death registers in the context of stroke. *Acta Neurol Scand* 2011;123(4):289-93. doi: 10.1111/j.1600-0404.2010.01402.x
56. Andersson P, Londahl M, Abdon NJ, et al. The prevalence of atrial fibrillation in a geographically well-defined population in northern Sweden: implications for anticoagulation prophylaxis. *J Intern Med* 2012;272(2):170-6. doi: 10.1111/j.1365-2796.2012.02519.x
57. Sund R. Quality of the Finnish Hospital Discharge Register: a systematic review. *Scand J Public Health* 2012;40(6):505-15. doi: 10.1177/1403494812456637 [published Online First: 2012/08/18]
58. Furu K, Wettermark B, Andersen M, et al. The Nordic countries as a cohort for pharmacoepidemiological research. *Basic Clin Pharmacol Toxicol* 2010;106(2):86-94. doi: 10.1111/j.1742-7843.2009.00494.x [published Online First: 2009/12/08]
59. Langhoff-Roos J, Krebs L, Klungsoyr K, et al. The Nordic medical birth registers--a potential goldmine for clinical research. *Acta Obstet Gynecol Scand* 2014;93(2):132-7. doi: 10.1111/aogs.12302 [published Online First: 2013/11/19]
60. Artama M, Gissler M, Malm H, et al. Nationwide register-based surveillance system on drugs and pregnancy in Finland 1996-2006. *Pharmacoepidemiol Drug Saf* 2011;20(7):729-38. doi: 10.1002/pds.2159 [published Online First: 20110527]
61. Haukka J. Finnish health and social welfare registers in epidemiological research. *Norsk Epidemiologi* 2009;14(1) doi: 10.5324/nje.v14i1.284
62. Gissler M, Shelley J. Quality of data on subsequent events in a routine Medical Birth Register. *Med Inform Internet Med* 2002;27(1):33-8. doi: 10.1080/14639230110119234
63. Teperi J. Multi method approach to the assessment of data quality in the Finnish Medical Birth Registry. *J Epidemiol Community Health* 1993;47(3):242-7. doi: 10.1136/jech.47.3.242
64. Jepsen B, Jepsen P, Johnsen SP, et al. Validity of diagnoses of cardiac malformations in a Danish population-based hospital-discharge registry. *Int J Risk Saf Med* 2006;18 77–81.
65. Johannesdottir SA, Horvath-Puho E, Ehrenstein V, et al. Existing data sources for clinical epidemiology: The Danish National Database of Reimbursed Prescriptions. *Clin Epidemiol* 2012;4:303-13. doi: 10.2147/CLEP.S37587 [published Online First: 2012/12/04]
66. Stephansson O, Granath F, Svensson T, et al. Drug use during pregnancy in Sweden – assessed by the Prescribed Drug Register and the Medical Birth Register. *Clin Epidemiol* 2011;3:43-50. doi: 10.2147/CLEP.S16305

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Not applicable

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Signature

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Study Protocol

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Codes used to identify study variables

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