AARHUS UNIVERSITY
Department of Clinical Epidemiology
Aarhus University
Aarhus University Hospital
Olof Palmes Allé 43-45
8200 Aarhus N
DENMARK

EPID Research
Spektri, Duo Building
Metsänneidonkuja 6
FI-02130 Espoo
FINLAND

UNIVERSITY OF BERGEN
Department of Global Public Health and Primary Care
University of Bergen
Kalfarveien 31
5018 Bergen
NORWAY

Centre for Pharmacoepidemiology
Karolinska Institutet
Karolinska University Hospital
SE 171 76 Stockholm
SWEDEN

NON-INTERVENTIONAL (NI) FINAL STUDY REPORT

PASS information

Title	A Population-based Cohort Study of Pregabalin to Characterize Pregnancy Outcomes
Protocol number	A0081359
Version identifier of the final study report	1.0
Date	01 June 2020
EU Post Authorization Study (PAS) register number	EUPAS27339
Active substance	Pregabalin (ATC N03AX16)
Medicinal product	Lyrica® (pregabalin) and Pregabalin Pfizer
Product reference	EMEA/H/C/000546 (Lyrica) EMEA/H/C/003880 (Pregabalin Pfizer)
Procedure number	Not available
Marketing Authorization Holder (MAH)	Pfizer Europe MA EEIG Boulevard de la Plaine 17 1050 Brussels Belgium
Joint PASS	No
Research question and objectives	The study objectives are to: 1. Describe the use of pregabalin in pregnancy. 2. Estimate the risk of major congenital malformations, birth outcomes other than congenital malformations, and neurodevelopmental outcomes with the use of pregabalin.
Countries of study	Denmark, Finland, Norway, and Sweden

Authors	Gunnar Toft, PhD, DMSc Vera Ehrenstein, MPH, DSc Kofi Asomaning, PhD

Marketing Authorization Holder(s)

Marketing Authorization Holder(s)	**Pfizer Europe MA EEIG** Boulevard de la Plaine 17 1050 Brussels Belgium
Marketing Authorization Holder(s) contact person	Kofi Asomaning, PhD Director, Safety Surveillance Research Pfizer Inc. 500 Arcola Road Collegeville, PA 19426 USA

TABLE OF CONTENTS

1. ABSTRACT (STAND-ALONE DOCUMENT) 8
2. LIST OF ABBREVIATIONS 8
3. INVESTIGATORS 10
4. OTHER RESPONSIBLE PARTIES 11
5. MILESTONES 13
6. RATIONALE AND BACKGROUND 14
7. RESEARCH QUESTION AND OBJECTIVES 16
8. AMENDMENTS AND UPDATES 17
9. RESEARCH METHODS 17
9.1. Study design 17
9.2. Setting 18
9.3. Subjects 18
9.4. Variables 19
9.4.1. Outcomes 21
9.4.1.1. Primary outcomes (birth outcomes) 24
9.4.1.2. Secondary outcomes (postnatal neurodevelopmental outcomes) 24
9.4.1.3. Sensitivity analysis outcomes (major congenital malformations) 24
9.4.1.4. Other outcomes 24
9.4.2. Covariates 24
9.5. Data sources and measurement 25
9.6. Bias 28
9.7. Study Size 29
9.8. Data transformation 31
9.9. Statistical methods 31
9.9.1. Main summary measures 31
9.9.2. Main statistical methods 32
9.9.2.1. Calculation of prevalences of birth outcomes 32
9.9.2.2. Calculation of incidence rates of postnatal outcomes 32
9.9.2.3. Estimation of prevalence ratios and hazard ratios 33
9.9.2.4. Computation of propensity scores 33
9.9.2.5. Primary analyses 34

9.9.2.6. Descriptive analysis 34
9.9.2.7. Major congenital malformation outcomes 35
9.9.2.8. Birth outcomes other than major congenital malformations 35
9.9.2.9. Secondary analyses 35
9.9.3. Missing values 36
9.9.4. Sensitivity analyses 36
9.9.5. Amendments to the statistical analysis plan 36
9.9.6. Meta-analyses 37
9.10. Quality control 37
9.11. Protection of human subjects 38
10. RESULTS 39
10.1. Participants 39
10.2. Descriptive data 44
10.2.1. Baseline characteristics 44
10.2.2. Exposure data 44
10.3. Outcome data 45
10.4. Main results 45
10.5. Other analyses 60
10.5.1. Sensitivity analyses 60
10.6. Adverse events / adverse reactions 61
11. DISCUSSION 61
11.1. Key results 61
11.2. Limitations 63
11.3. Interpretation 64
11.4. Generalisability 64
12. OTHER INFORMATION 64
13. CONCLUSIONS 64
14. REFERENCES 65
15. LIST OF SOURCE TABLES AND FIGURES 69
16. APPENDICES 71
16.1. Appendix 1. Supplementary tables 71
16.1.1. Supplementary descriptive tables 71

16.1.2. Supplementary malformation tables....71
16.1.3. Supplementary birth outcomes and postnatal outcomes tables....71
16.2. Appendix 2. Supplementary figures....71
16.2.1. Supplementary descriptive figures....71
16.2.2. Supplementary forest plots Mantel-Haenszel meta-analyses malformations....71
16.2.3. Supplementary forest plots Mantel-Haenszel meta-analyses birth outcomes and postnatal outcomes....71
16.3. Appendix 3. Protocol....71
16.4. Appendix 4. Codes used to identify study variables....71

1. ABSTRACT (STAND-ALONE DOCUMENT)

Please refer to the stand-alone document.

2. LIST OF ABBREVIATIONS

Abbreviation	Definition
ADHD	Hyperkinetic disorders, including attention deficit disorders (ADHD)
AED	Antiepileptic drug
aPR	Adjusted prevalence ratio
ASD	Pervasive developmental disorders, including autism spectrum disorder (ASD)
ATC	Anatomical Therapeutic Chemical
BMI	Body mass index
CI	Confidence interval
DDD	Defined daily dose
DUS	Drug utilisation study
EMA	European Medicines Agency
ENCePP	European Network of Centers for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
EUROCAT	European Network of Congenital Anomaly Registers
GAD	General anxiety disorder
GPP	Good Pharmacoepidemiology Practice
HR	Hazard ratio
ICD-9	International Classification of Diseases, Ninth Revision
ICD-10	International Classification of Diseases, Tenth Revision

ID	Intellectual disability
IEC	Independent Ethics Committee
IQR	Interquartile range
IRB	Institutional Review Board
ISPE	International Society for Pharmacoepidemiology
KI	Karolinska Institutet
LMP	(first day of) Last Menstrual Period
MAH	Marketing Authorization Holder
MH	Mantel-Haenszel
NE	Non-estimable
NR	Non-reportable
NI	Non-interventional
PAS	Post-Authorisation Study
PASS	Post-Authorisation Safety Study
PR	Prevalence ratio
PS	Propensity score
RR	Risk ratio
SD	Standard deviation
SGA	Small for gestational age
SNRI	Serotonine norepinephrine reuptake inhibitor
SSRI	Selective Serotonin Reuptake Inhibitor
TIS	Teratology information services
US	United States
UK	United Kingdom

3. INVESTIGATORS

Principal Investigator(s) of the Protocol

Name, degree(s)	Title	Affiliation
Henrik T. Sørensen, MD, PhD, DMSc	Professor, Chair of Department	Department of Clinical Epidemiology Aarhus University Hospital Denmark
Vera Ehrenstein, MPH, DSc	Professor	Department of Clinical Epidemiology Aarhus University Hospital Denmark
Kofi Asomaning, PhD	Director, Safety Surveillance Research	Pfizer Inc. Collegeville, PA, USA

Lead Country Investigators of the Protocol

Name, degree(s)	Title	Affiliation
Gunnar Toft, PhD, DMSc	Associate Professor Coordinating Investigator	Department of Clinical Epidemiology Aarhus University Hospital Denmark
Pasi Korhonen, PhD	Senior Principal	EPID Research Oy Finland
Anne Kjersti Daltveit, MSc, PhD	Professor	Department of Global Public Health and Primary Care University of Bergen Norway
Helle Kieler, MD, PhD	Professor, Director of Centre for Pharmacoepidemiology	Centre for Pharmacoepidemiology Karolinska Institutet Sweden

4. OTHER RESPONSIBLE PARTIES

Responsible Party Name and Affiliation	Role in the study
Szimonetta Komjáthiné Szépligeti Department of Clinical Epidemiology Aarhus University Hospital Denmark	Data Analysis, Denmark and combined analysis
Fabian Hoti EPID Research Oy, Finland	Data Analysis, Finland
Saara Hetemäki EPID Research Oy, Finland	Project Management, Finland
Matti Rantanen EPID Research Oy, Finland	Data Analysis, Finland
Laura Saarelainen EPID Research Oy, Finland	Epidemiologist, Finland
Pia Vattulainen EPID Research Oy, Finland	Data Analysis, Finland
Ingvild Odsbu Centre for Pharmacoepidemiology Karolinska Institutet, Sweden	Project Management, Sweden
Pär Karlsson Centre for Pharmacoepidemiology Karolinska Institutet, Sweden	Data Analysis, Sweden
Anna Ingemarsdotter Centre for Pharmacoepidemiology Karolinska Institutet, Sweden	Project Management, Sweden
Johan Reutfors	Clinical Expert, Sweden

Centre for Pharmacoepidemiology Karolinska Institutet, Sweden	
Astrid Lunde Department of Global Public Health and Primary Care University of Bergen, Norway	Data Analysis, Norway
Tatiana Fomina Department of Global Public Health and Primary Care University of Bergen, Norway	Data Analysis, Norway

5. MILESTONES

Milestone	Planned date	Actual date	Comments
Start of data collection	30 December 2018	30 March 2019	Within 3 months of protocol endorsement by the EMA
End of data collection	28 February 2019	20 July 2019	Within 4 months of the start of data collection
Registration in the EU PAS register: EUPAS27339	30 November 2018	01 March 2019	Prior to start of data collection
Final report of study results	November 2019	01 June 2020	Within 1 year of the end of data collection

6. RATIONALE AND BACKGROUND

Pregabalin (Lyrica®) was approved in July 2004 by the European Medicines Agency (EMA) for the treatment of peripheral neuropathic pain and as an adjunctive therapy for adult patients with partial onset seizures. Subsequently, the marketing authorizations were expanded to include generalized anxiety disorder (GAD), in March 2006 and central neuropathic pain, in September 2006. Per current European Union (EU) label, "Lyrica should not be used during pregnancy unless clearly necessary (if the benefit to the mother clearly outweighs the potential risk to the fetus)."[1] Overall in Europe, pregabalin is prescribed to approximately 0.5 per thousand pregnant women in Europe, based on data from the United Kingdom (UK), France, and two regions of Italy and a study from Denmark,[2 3] but in several countries the use has risen during the last decade and in the UK the prevalence of pregabalin prescribing during pregnancy was > 2 per thousand pregnancies in 2015-2016.[2]

In the general population (including men and women of all ages), pregabalin is mostly used for neuropathic pain (18–98%) and least used for epilepsy (4–6%).[4] Use of pregabalin in a non-pregnant population, as assessed in a study in Sweden, is primarily for neuropathic pain (36%) and only 1.3% for epilepsy, with 40% of pregabalin initiators having no identifiable approved indication based on routine records,[5] and no data on indication from other sources are available. A study from two distinct United States (US) datasets reported prevalence of epilepsy indication of 5.5% and 6.7% of pregabalin use in pregnant women.[6] In the feasibility assessment for this study, based on available Danish data, 21% of pregnancies exposed to pregabalin in the first trimester had a known indication identifiable by a hospital diagnosis in the previous year. Those included epilepsy (4% of those with identifiable indication), neuropathic pain (72% of those with identifiable indication), or GAD (24% of those with identifiable indication). Frequency distributions were similar for pregnancies exposed to pregabalin at any trimester.

Evidence regarding pregabalin safety in pregnancy is limited. A recent study, using data from eight European Teratology Information Services (TIS), based on 164 pregabalin-exposed and 656 pregabalin-unexposed pregnancies, reported a 3-fold increased risk of any major non-chromosomal congenital malformation associated with first-trimester pregabalin exposure.[7] Major limitations of the analysis included lack of data on specific malformations, potential selection and detection bias due to self-referral, low precision, and confounding by indication. A subsequent study based on 477 pregabalin-exposed pregnancies among Medicaid beneficiaries in the US did not confirm the 3-fold increased risk but could not rule out a smaller effect. When all available evidence was combined, adjusted risk ratios (RRs) for any major malformation were 1.3 (95% confidence interval [CI] 0.8–2.2) for any first-trimester exposure to pregabalin and 1.0 (95% CI 0.7–1.5) for pregabalin monotherapy exposure in the first trimester compared with unexposed.[6] A recent Nordic study examining the risk of major malformations for different antiepileptic drugs (AEDs) found no clear evidence of an increased risk of any malformation for pregabalin compared with lamotrigine (RR 1.2, 95% CI 0.9–1.7).[8] A recent French study examining AED exposure relative to 23 major malformations reported an odds ratio of 5.8 (95% CI 1.6–14.9) based on only 4 exposed cases.[9] To extend the available evidence, safety of pregabalin use in pregnancy should be examined using outcomes other than malformations, including fetal growth

indicators and postnatal neurologic morbidity. A recent Swedish study based on a study population partially overlapping with the present study suggested that pregabalin-exposed pregnancies had a slightly shorter gestation and a slightly lower birth weight than lamotrigine-exposed pregnancies,[10] and an Italian study reported similar results and in addition suggested increased odds of spontaneous and induced abortions in pregabalin-exposed pregnancies compared with unexposed.[11]

To reduce confounding by indication in observational studies, risks in pregabalin-exposed pregnancies should be compared with risks in pregnancies among women with the same indication but treated with a different agent (active comparator). Pregabalin has several indications, and diagnoses given at medical encounters, available for this study, do not fully capture all relevant indications. Therefore, in this study, pregnancies exposed to pregabalin were compared with pregnancies exposed to medications with similar sets of indications. To the best of the investigators' knowledge, there is no single product with a set and distribution of indications identical to that of pregabalin. Based on their combined sets of indications, lamotrigine and duloxetine were identified as two active comparators with similar indications. Between 2004 and 2010, lamotrigine was the most commonly used AED in Europe, which provided an additional advantage of improving the precision of this study.[12] In Europe, lamotrigine, alone or in combination with other AEDs, is indicated for the treatment of epilepsy, partial and generalized seizures, including tonic-clonic seizures and the seizures associated with Lennox-Gastaut Syndrome in adults.[13] Lamotrigine is also indicated for the treatment of bipolar disorder.[13] Lamotrigine has not been associated with an increased risk of congenital malformations.[14] In the feasibility assessment for this study, based on available Danish data, the following distribution of known pregabalin indications were identified for pregnancies exposed to lamotrigine in the first trimester based on diagnosed diseases: epilepsy (79% of those with an identifiable indication), neuropathic pain (10% of those with an identifiable indication), or GAD (10% of those with an identifiable indication). Duloxetine is not an AED but an antidepressant that belongs to the serotonin-norepinephrine reuptake inhibitor (SNRI) drug family. Duloxetine has been approved in the EU since 2004 for treatment of GAD, depressive disorder, major diabetic neuropathies, and, since 2014, for treatment of neuralgia.[15] Available data, albeit sparse, do not suggest a clinically important increased risk associated with duloxetine use in pregnancy.[16-18]

This non-interventional study evaluated use and safety of pregabalin in pregnancy using data on all pregnancies identifiable from population-based registries in Denmark, Finland, Norway, and Sweden. Safety was measured by occurrence of major congenital malformations, birth outcomes, and selected neurodevelopmental postnatal outcomes. The primary analyses consisted of a comparison of pregabalin exposed vs. AED unexposed during the biologically relevant period of pregnancy for the development of the outcomes. To control for confounding by indication,[19] in addition to assessing the risk of study outcomes according to exposure to pregabalin during pregnancy, the study outcomes were also assessed among pregnancies exposed to lamotrigine (epilepsy) and duloxetine (neuropathic pain, GAD), agents with similar indications as pregabalin.

This non-interventional study is designated as a Post-Authorisation Safety Study (PASS) and is a commitment to the EMA.

7. RESEARCH QUESTION AND OBJECTIVES

The study objectives were to:

1. Describe the use of pregabalin in pregnancy
2. Estimate the risk of major congenital malformations, birth outcomes other than congenital malformations, and neurodevelopmental outcomes with the use of pregabalin.

The specific primary objectives of the study were to:

- Describe use of pregabalin, lamotrigine, and duloxetine during pregnancy overall, by trimester, and by calendar year of delivery in pregnancies ending in live births or stillbirths, as characterized by:
  - Prevalence of use (proportion of pregnancies with 1 or more dispensing of a given drug),
  - Distribution of therapeutic indications among the exposed pregnancies (epilepsy, GAD, neuropathic pain),
  - Cumulative dose, based on dispensing count and amount dispensed in each pregnancy;

- Describe the prevalence of (proportion of live or stillborn children with) major congenital malformations after first-trimester in utero exposure to pregabalin (yes/no); after first-trimester exposure to lamotrigine, after first-trimester exposure to duloxetine, after first-trimester exposure to lamotrigine or duloxetine, in pregnancies ending in live birth or stillbirth; in live or stillborn children unexposed to antiepileptics in the first trimester; and in the total population of live or stillborn children;

- Estimate the association between first-trimester exposure to pregabalin and prevalence of major congenital malformations, as compared with no first-trimester exposure to pregabalin or other AEDs, with first-trimester exposure to lamotrigine, with first-trimester exposure to duloxetine, and first-trimester exposure to lamotrigine or duloxetine, in live or stillborn children;

- Describe the prevalence of birth outcomes other than major congenital malformations (listed in Section 9.4.1.1) according to exposure (yes/no) to pregabalin any time during gestation, according to exposure to lamotrigine any time during gestation, according to any in utero exposure to duloxetine, according to any in utero exposure to lamotrigine or duloxetine, and in live or stillborn children unexposed in utero to antiepileptics;

- Estimate the association between any in utero exposure to pregabalin and the birth outcomes other than major congenital malformations, as compared with no exposure to pregabalin; any in utero exposure to lamotrigine; any in utero exposure to duloxetine; any in utero exposure to lamotrigine or duloxetine, and no in utero exposure to antiepileptics;

- Estimate, in a sensitivity analysis to evaluate potential impact of selection bias, the association between first-trimester exposure to pregabalin and prevalence of major congenital malformations, as compared with no first-trimester exposure to pregabalin or other AEDs; first-trimester exposure to lamotrigine; first-trimester exposure to duloxetine; and first-trimester exposure to lamotrigine or duloxetine, in pregnancies ending in livebirth, stillbirth, or 2nd trimester induced abortion (in Denmark, Finland, and Norway).

The specific secondary objectives of the study were to:

- Describe, in liveborn infants, the incidence rates of pre-specified postnatal neurodevelopmental outcomes (listed in Section 9.4.1.2) according to exposure (yes/no) to pregabalin any time during pregnancy, after any in utero exposure to lamotrigine, after any in utero exposure to duloxetine, and after any in utero exposure to lamotrigine or duloxetine;
- Estimate, in liveborn infants, the association between in utero exposure to pregabalin and the pre-specified postnatal neurodevelopmental outcomes, as compared with no in utero exposure to pregabalin; any in utero exposure to lamotrigine, any in utero exposure to duloxetine, and any in utero exposure to pregabalin or duloxetine.

The calculations of 'prevalence' and 'incidence rate' are further described in section 9.9.

8. AMENDMENTS AND UPDATES

None.

9. RESEARCH METHODS

The research was carried out as specified in the study protocol (Appendix 3. Protocol).

9.1. Study design

This PASS was a population-based cohort study based on routinely collected data from administrative and medical registers in four Nordic countries: Denmark, Finland, Norway, and Sweden. It included all identifiable pregnancies between 01 January 2005 and 31 December 2015 in Denmark, Finland, and Norway, and between 01 July 2006 and 31 December 2016 in Sweden. All liveborn children had an opportunity for at least 1 year of follow-up after birth in all countries, with actual follow-up varying slightly by country (Table 1). Each country has tax-supported universal health care; routine and prospectively collected data on outpatient dispensings, live births and stillbirths, 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).[20]

Population-based healthcare registries in Nordic countries are an optimal setting for examining the safety of medicines in pregnancy. Their most important strengths are capture of all births and, in some cases, clinically relevant birth and postnatal outcomes; routine capture of dispensings of prescription medications to pregnant women; extensive information

about maternal and offspring health outcomes; and exact linkage between the maternal and the offspring record. Thus, unlike studies based on data from TIS, for example, there is no risk of bias by self-referral, recall, or access to health care. Dispensings of medicines represent a better proxy of actual drug intake than issued prescriptions, thus reducing misclassification of the actual drug intake.

Because pregabalin is used to treat epilepsy, GAD, and neuropathic pain, the comparators were chosen to represent the background occurrence of the outcomes. This includes occurrence in unexposed pregnancies and in pregnancies exposed to lamotrigine and/or duloxetine representing medications that are considered relatively safe for use in pregnancy and have similar indications to pregabalin (epilepsy, GAD, neuropathic pain).

The outcomes chosen are standard outcomes used, as requested by the EMA, to evaluate safety of medication exposure for the offspring and are the outcomes examined in previous studies [6 7 12 14 16 18] (birth outcomes) as well as prespecified postnatal neurodevelopmental outcomes, detailed in section 9.4.

Because confounding by indication or severity of the underlying disease is likely to persist to some extent even when compared to an active comparators,[19] the amount of confounding may be inferred indirectly by examining whether estimates of association differ depending on the nature of the comparator.

9.2. Setting

This study was conducted using data from four Nordic countries: Denmark, Finland, Norway, and Sweden (listed alphabetically). In each country, all live births and stillbirths are recorded in the birth registries from gestational week 22 from July 2008 onwards. In addition, the Swedish birth register recorded live births and stillbirths born from gestational week 28 until July 2008). The start of the study period in each country was selected to ensure availability of pregabalin and the active comparators on the market and availability of data on outpatient dispensings for at least 12 months before the end of the earliest identified pregnancy. For example, a pregnancy ending at term with a live birth on 01 January 2005 in Denmark had prescription history from 01 January 2004, thus covering the 9 months of gestation and a 3-month period of preconception.

9.3. Subjects

The study population consisted of all pregnancies identified in the respective administrative registries from 01 January 2005 to 31 December 2015 in Denmark, Finland, and Norway and all pregnancies identified from 01 July 2006 to 31 December 2016 in Sweden. Singleton and multiple pregnancies ending in live births or stillbirths were identified in each country's birth registry. For the medication use analysis, the unit of observation was pregnancy; for the other outcomes, in the main analysis, the unit of observation was birth. Pregnancies ending in an abortive outcome were considered to contain a single fetus.

As all birth outcomes are presumed to have occurred as of the date of delivery, prevalence was used as a measure of occurrence of the birth outcomes.[20] To allow for

delayed reporting/diagnosis, diagnoses of congenital malformations were included if recorded until 1 year of age, according to the standard procedure used by the European Network of Congenital Anomaly Registers (EUROCAT).[21] Thus, malformations were identified through the end of 2015 in Finland; 2016 in Denmark and Norway; and through the end of 2017 in Sweden. In a sensitivity analysis, pregnancies ending in therapeutic 2nd trimester induced abortions were identified in Denmark, Finland, and Norway.[22] Such pregnancies could not be identified in Sweden. When possible, for malformations leading to pregnancy terminations it was important to identify pregnancy terminations due to malformations of the nervous system of the fetus, as nearly half of the pregnancies involving fetuses affected by nervous system malformations may be terminated.[22]

Stillbirth prevalence at birth among live and stillborn infants was described and compared among pregabalin-exposed and the comparators. For the birth outcomes other than congenital malformations or stillbirth, as specified below prevalence at birth among liveborn infants was described and compared. For postnatal neurodevelopmental outcomes, liveborn offspring of all pregabalin-exposed and the comparator pregnancies were followed from the date of birth until the earliest record of a given outcome of interest, emigration (except Norway, where emigration data are unavailable), death, or end of study (31 December 2017 in Sweden and Norway; 31 December 2016 in Denmark and Finland); for this analysis, children in Norway born before 2008 were excluded as the Patient Registry of Norway only had individual level data from 2008. Thus, for neurodevelopmental postnatal outcomes, liveborn children were followed up to a minimum of 1 year and a maximum of 10 years postnatally in Denmark, Finland, and Norway and up to a maximum of 11.5 years postnatally in Sweden.

Inclusion criteria
All pregnancies/births identified from 01 January 2005 through 31 December 2015 (both dates inclusive) in Denmark, Finland, and Norway and all pregnancies/births identified from 01 July 2006 through 31 December 2016 (both dates inclusive) in Sweden.

Exclusion criteria
Pregnancies meeting any of the following criteria were not included in the study:

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

2. Pregnancies carrying a fetus with a chromosomal abnormality diagnosis.

9.4. Variables

Exposures
For the purposes of timing of exposure, trimesters of pregnancy were defined as follows:

- First trimester: from last menstrual period ((first day of) 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).

Exposure during the first trimester
Pregabalin exposure in the first trimester was defined as at least one 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.

Comparators:
Unexposed to pregabalin during the first trimester comparator was defined as pregnancies without dispensing for pregabalin or other AEDs including lamotrigine, or duloxetine during the first trimester.

Lamotrigine exposure in the first trimester was defined by at least one 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.

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

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

For analyses that use lamotrigine as the comparator, pregnancies exposed to both pregabalin and lamotrigine in the first trimester were excluded. For analyses that use duloxetine as the comparator, pregnancies exposed to both pregabalin and duloxetine in the first trimester were excluded.

Exposure any time during pregnancy
Pregabalin exposure any time during pregnancy was defined by at least one dispensing of pregabalin during any trimester. Pregabalin monotherapy any time during pregnancy was defined as any-pregnancy exposure to pregabalin and no dispensing for any other AED during any trimester.

Comparators:
Unexposed to pregabalin during any trimester comparator was defined as pregnancies without dispensing for pregabalin or other AEDs including lamotrigine, or duloxetine during any trimester.

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

Duloxetine exposure any time during pregnancy was defined by at least one dispensing of duloxetine during any trimester. Duloxetine monotherapy any time during pregnancy was defined as any-pregnancy exposure to duloxetine and no dispensing for any AED during any trimester.

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

For analyses that use lamotrigine as the comparator, pregnancies exposed to both pregabalin and lamotrigine in any trimester were excluded. For analyses that use duloxetine as the comparator, pregnancies exposed to both pregabalin and duloxetine in any trimester were excluded.

Sensitivity analysis of different exposure definition for monotherapy

In a sensitivity analysis, monotherapy with pregabalin, lamotrigine, and/or duloxetine was defined by absence of other AED, selective serotonin reuptake inhibitors (SSRIs), or benzodiazepines.

9.4.1. Outcomes

This study describes use and assesses the safety of pregabalin use during pregnancy based on a series of birth and postnatal outcomes. For each outcome defined below, the population (denominator), period of pregnancy identification, and follow-up for outcome assessment are described in Table 1.

Table 1. Outcome-specific study population and follow-up for the primary analyses, secondary analyses, and sensitivity analyses

Outcome		Study population and period of pregnancy identification				Follow-up for outcome assessment
		Denmark	Finland	Norway	Sweden	
Primary analyses	Major congenital malformations (overall and specific)	Pregnancies ending in singleton/multiple live birth or stillbirth, 01Jan2005 - 31Dec2015 both inclusive			Pregnancies ending in singleton/multiple live birth or stillbirth 01Jul2006 - 31Dec2016 both inclusive	Prevalence at birth with outcomes identified at birth, and until the first birthday (inclusive) through 2015 in Finland; through 2016 in Denmark and Norway; and through 2017 in Sweden
	Stillbirth	Pregnancies ending in singleton/multiple live birth or stillbirth, 01Jan2005 - 31Dec2015 both inclusive			Pregnancies ending in singleton/multiple live birth or stillbirth 01Jul2006 - 31Dec2016 both inclusive	Prevalence at birth
	Low birth weight SGA[19] Preterm birth Low Apgar score at 5 minutes Microcephaly	Pregnancies ending in singleton/multiple live birth, 01Jan2005 - 31Dec2015 both inclusive			Pregnancies ending in singleton/multiple live birth 01Jul2006 - 31Dec2016 both inclusive	Prevalence at birth
Secondary analyses	Hyperkinetic disorders, including ADHD Pervasive developmental	Pregnancies ending in singleton/multiple live birth, 01Jan2005 - 31Dec2015 both inclusive		Pregnancies ending in singleton/multiple live birth, 01Jan2008 -	Pregnancies ending in singleton/multiple live birth 01Jul2006- 31Dec2016 both inclusive	Minimum 1 year postnatally. Maximum available postnatally, 31Dec2016 Denmark, Finland, Norway*; 31Dec2017 Sweden.

Table 1. Outcome-specific study population and follow-up for the primary analyses, secondary analyses, and sensitivity analyses

Outcome		Study population and period of pregnancy identification				Follow-up for outcome assessment
		Denmark	Finland	Norway	Sweden	
	disorders, including ASD			31Dec2015 both inclusive		
	Intellectual disabilities (including mental retardation)					
Sensitivity analyses	Major congenital malformations (overall and specific) including malformations identified prenatally	Pregnancies ending in singleton/multiple live birth, stillbirth, 01Jan2005 - 31Dec2015 both inclusive and				Prevalence at birth with outcomes identified prenatally, at birth, and until the first birthday (inclusive) through 2016 in Denmark and Norway and 31Dec2015 in Finland
		pregnancies ending in therapeutic 2nd trimester induced abortion, 01Jan2005-31Dec2015 both inclusive (Denmark, Norway) 1Jan2005-31Dec2012 (Finland)			None	

ADHD: Attention deficit hyperactivity disorder; ASD: autism spectrum disorder; SGA: Small for gestational age.
*The Patient Registry of Norway, the source of data for the postnatal outcomes, has data available from 2008.

9.4.1.1. Primary outcomes (birth outcomes)

- Major congenital malformations, overall and specific, according to the EUROCAT classification.[23]
- Stillbirth, as recorded in each country's birth registry.
- Low birth weight (birth weight < 2500 g).
- Small for gestational age (SGA), defined 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 standards.[24 25] SGA non-singleton gestations was excluded from the analysis, given the difficulty in interpretation.
- Preterm birth, defined as gestational age <37 weeks.
- Low Apgar score at 5 minutes, defined as a dichotomous variable (low 0-6 vs. not low 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 study population as the reference standard.

9.4.1.2. Secondary outcomes (postnatal neurodevelopmental outcomes)

- Attention deficit hyperactivity disorder (ADHD) defined as hyperkinetic disorders, including ADHD (identified via inpatient or outpatient hospital diagnosis or a medication proxy).
- Autism spectrum disorders (ASD) defined as pervasive developmental disorders, including ASD (identified via inpatient or outpatient hospital diagnosis).
- Intellectual disabilities (including mental retardation) (identified via inpatient or outpatient hospital diagnosis).

9.4.1.3. Sensitivity analysis outcomes (major congenital malformations)

- Major congenital malformations identified at live births or stillbirths or 2nd trimester abortions, and any specific outcomes as described in section 9.4.1.1 (Table 1 above for the following countries: Denmark, Finland, and Norway).

9.4.1.4. Other outcomes

- Major congenital malformations identified in the total study population of live births or stillbirths, to provide context.

9.4.2. Covariates

Characteristics of the study population included perinatal covariates of the pregnancy of interest and covariates of the mother. A full list of the study variables and their operational definitions are provided in Annex 3 of the study protocol.

Covariates considered for adjustment (inclusion in propensity score model) included:

- calendar year of delivery;
- age in years at LMP;

- marital/cohabiting status;
- smoking during pregnancy;
- obesity (body mass index (BMI) =>30 kg/m^2) or a hospital diagnosis of obesity;
- single or multiple gestation;
- hospital-recorded 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, obesity, disorders of female pelvic organs/genital tract, thyroid disorders, infections (infections was assessed in 90 days pre-LMP). In Finland, in addition to the hospital diagnoses, diagnoses from primary care are also available and was used;
- indicators of maternal healthcare utilization in the 12 months pre-LMP (number of inpatient and specialized 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).

Parity (number of live births and stillbirths prior to the on-study pregnancy), caesarean delivery, and child's sex was reported but was not used for adjustment, except for inclusion of parity in the propensity score (PS) model in Finland. In addition, indication for pregabalin use in the 12 months pre-LMP (epilepsy, neuropathic pain, GAD and related disorders) was reported descriptively but was not used for adjustment.

9.5. Data sources and measurement

Data sources used to construct the analysis data set for this study are presented in Table 2. Within each country, records from all registries are linkable at the individual level by a unique national person 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.

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 3. 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 covariates (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.)

Validity of routinely collected healthcare data in Nordic national registries has been found to be high in all countries.[26-41] In Denmark, the positive predictive value of diagnoses of cardiac malformations is 89%.[42] For drugs used chronically, there is also a high level of agreement between general practitioner and dispensing records.[43] 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.[44]

Table 2. National registries in Denmark, Finland, Norway, and Sweden and type of data available 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[45] Finnish Medical Birth Register* National Registry of Norway Swedish Total Population Register[46]
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[47 48] Finnish Register on Induced Abortions* Norwegian Register of Pregnancy Terminations (part of the Medical Birth Registry of Norway) Not available in Sweden
Exposure (for full list see section 9.4)	Maternal dispensings of pregabalin, lamotrigine, duloxetine	Danish National Health Services Prescription Database[49 50] Finnish Prescription Register[49] Norwegian Prescription Database[49] Swedish Prescribed Drug Register[49]

Table 2. National registries in Denmark, Finland, Norway, and Sweden and type of data available from each registry

Study variable/role	Type of data	Data source(s)
Outcome (for full list see section 9.4.1)	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 [33 51]
	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
	Neurodevelopmental outcomes	Danish National Patient Registry [47] Danish Psychiatric Central Research Register [52] Danish Psychiatric Central Register Danish National Health Services Prescription Database [49 50] Finnish Care Register for Health Care Finnish Register of Primary Health Care visits Finnish Prescription Register [49] Norwegian Patient Registry [53] Norwegian Prescription Database [49] Swedish National Patient Register [33 51]
Covariates (for full list see section 9.4.2)	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 [54] Swedish National Patient Register

Table 2. National registries in Denmark, Finland, Norway, and Sweden and type of data available from each registry

Study variable/role	Type of data	Data source(s)
	Maternal morbidity (including indication for pregabalin) Markers of health care utilization	Danish National Patient Registry [47] Danish National Health Services Prescription Database [49 50] Finnish Care Register for Health Care Finnish Register of Primary Health Care visits Finnish Special Reimbursement Register. Finnish Prescription Register [49] Norwegian Prescription Database [33] Norwegian Patient Registry [53] Swedish National Patient Register [33 51] Swedish Prescribed Drug Register [49]
	Maternal medications	Danish National Health Services Prescription Database [49 50] Finnish Prescription Register [49] Norwegian Prescription Database [49] Swedish Prescribed Drug Register [49]
Loss to follow-up	Death, emigration†	Danish Civil Danish Civil Registration System [45] Finnish Causes of Death Register Finnish Population Register Centre National Registry of Norway Swedish Cause of Death Register [55] 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 that may include confounding, information bias and selection bias. As with most pharmacoepidemiologic studies, confounding by indication may be introduced since epilepsy itself is known to be associated with adverse pregnancy outcomes.[56] Other sources of confounding include residual confounding by unmeasured characteristics and resulting from misclassification of confounders. Even though this study proposed to use not only unexposed pregnancies, but pregnancies exposed to medications with indications similar to pregabalin, those latter comparisons may still be confounded. Selection of an appropriate reference group is challenging since no single drug is known to have all the indications of pregabalin and the unexposed population is likely to be healthier than the exposed population. As suggested by the feasibility analyses (pilot data), the distribution of the indications for the comparator drugs are different from that of pregabalin and this could also result in

confounding. Furthermore, the validity of diagnostic codes used to identify GAD has not been studied in any of the registers; in fact, most patients who actually do have such a disorder do not get that specific diagnosis and may be assigned a less specific anxiety diagnosis instead. Assessing safety of pregabalin within each indication of use does not appear feasible as data on indication are only available for a minority of pregnancies according to the pilot data.

Information bias manifests as misclassification of exposure, outcome, or confounders. Dispensing records may not 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 can be 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 specialist care diagnoses, used in identifying indications, covariates, and outcomes, are imperfect measures of true events they purport to measure. Furthermore, as is common in such studies, malformations in pregnancies ending in spontaneous and first trimester induced abortions cannot be observed, resulting in underestimation of the number of cases. If such selective dropout (i.e., selection bias) is associated with pregabalin exposure, associations based on prevalent outcomes will be biased. Given its design of a fixed study period, the study will be unable to provide equal follow-up for live births regarding postnatal neurodevelopmental outcomes. 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. Due to the limitations of the measurement and case ascertainment, the study objective and analyses of postnatal outcomes were designated as secondary. Selection bias stemming from inclusion of all eligible pregnancies is of less concern in this study, as study entry for each woman is the estimated conception date of pregnancy and ends for each outcome of interest with the event (e.g., date of live birth, stillbirth). Not all liveborn infants will have follow-up into the school age, and the number of pregabalin-exposed pregnancies in the earlier study period may not be sufficient to yield stable estimates of association, as specified in the provided feasibility counts in the protocol Table 5.
Emigration data (censoring variable) are not available in the Swedish or the Norwegian datasets, however, the impact of this is likely to be negligible.

To reduce bias, we used PS stratification, which performs well when multiple outcomes are being examined.[57]

9.7. Study size

Table 3 shows estimated and actual number of pregnancies ending in live birth or stillbirth and pregnancies with exposures and indications potentially relevant for analysis.

Table 3. Estimated study population size before study start and actual numbers of pregnancies ending in live birth or stillbirth according to exposure categorization

	Denmark (2005-2015)		Finland (2005-2015)		Sweden (2006-2016)*		Norway 2005-2015)
	Estimated	**Actual**	**Estimated**	**Actual**	**Estimated**	**Actual**	**Actual**
Pregnancies ending in live birth/stillbirth	730,000	675,525	580,000	643,088	800,000	1,152,002	657,451
Pregnancies with dispensation of							
-Pregabalin, first trimester	200	320	700	935	400	1230	227
-Pregabalin, any time during pregnancy	350	325	900	965	800	1275	307
-Lamotrigine, first trimester	2000	2001	900	961	1300	2838	1688
-Lamotrigine, any time during pregnancy	2700	2101	1100	1012	1800	2991	1934
-Duloxetine, first trimester	400	764	500	709	500	1637	90
-Duloxetine, any time during pregnancy	800	780	600	718	1000	1660	102

*The larger study population compared to estimated study population in Sweden is mainly due to inclusion of 3 additional years in the study population (2006-2016) in addition to the originally proposed (2006-2013).

The estimated numbers of pregnancies ending in live or still birth for potentially analysis-relevant categories for Norway were unavailable at the time of the protocol writing. Based on the estimated numbers and on each country's population size, we conservatively estimated achievable size for this study to be more than 1000 pregnancies exposed to pregabalin during the first trimester.[23 58] The actual number exposed to pregabalin in first trimester was 2712.

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 application to its country-specific data custodian. 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 before the analysis. Data were cleaned and coded, and harmonized analytic datasets were prepared according to the specifications provided in Annex 3 of the protocol. All four countries used similar coding systems for medications, diagnoses, and procedures, and codes were shared whenever feasible. There was slight variation between country in the specific diagnostic or procedure codes, which was 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 'vendor organizing institution' (Aarhus University Hospital, Denmark). In addition, the marketing authorization holder (Pfizer) did not have access to any patient-level data. Aggregated data as specified in the protocol Annex 3 were provided to the Department of Clinical Epidemiology, Aarhus University Hospital for meta-analysis and reporting.

SAS version 9.3 or later and/or R version 3.1.1 or later were used for data management and analyses.

9.9. Statistical methods

For all data analyses, the birth (not the patient/mother) 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 GEE (generalized estimating equation) or robust variance estimates. The primary analyses were conducted in the following study population/analysis set: pregnancies ending in singleton/multiple live birth or stillbirth. The assessment of the outcomes stillbirth and major congenital malformations included stillbirths; the other primary outcomes assessment excluded stillbirths.

9.9.1. Main summary measures

- Pregabalin use in pregnancy was described as the number and proportion of pregnancies exposed in the first trimester, and in any trimester. Number and proportion of pregnancies with pregabalin monotherapy were reported. Use of lamotrigine and duloxetine was similarly described.

- Distributions of the covariates in the study population were tabulated according to pregabalin exposure categories: first trimester (exposed/unexposed); any trimester

(exposed/unexposed) and separately for the monotherapy subgroup. Categorical variables were summarized using frequencies and proportions; continuous variables using either mean and SD, or median and interquartile range (IQR) as appropriate.

- Distribution of maternal and offspring characteristics in the study population was tabulated according to pregabalin and the active comparator categories, as above. All descriptive tables were constructed including stillbirths.

- Crude prevalence of the major congenital malformations was reported according to first-trimester exposure to pregabalin (overall and in the subcategory of monotherapy) and each comparator (overall and in the subcategory of monotherapy for lamotrigine and duloxetine). Crude prevalence of the other birth outcomes was reported according to any trimester exposure to pregabalin and each comparator, in the same fashion.

9.9.2. Main statistical methods

All steps of the country-specific data analyses were conducted separately in each participating country according to the description below in this section including subsections. Each country generated a set of identical analytic tables, according to the table shells provided in Annex 3 of the protocol.

After conducting the country-specific data analyses, country-specific datasets containing crude and adjusted estimates of association were transferred to Aarhus University Hospital, Denmark, for meta-analyses.

9.9.2.1. Calculation of prevalences of birth outcomes

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 liveborn newborns.

9.9.2.2. Calculation of incidence rates of postnatal outcomes

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 infant. 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.

9.9.2.3. Estimation of prevalence ratios and hazard ratios

Crude and adjusted prevalence ratios (aPRs) and 95% Wald CIs for each birth outcome and a given population/contrast were estimated using log-binomial regression. Crude and adjusted incidence rate ratios and 95% Wald CIs were estimated using Cox's proportional-hazards regression for each postnatal outcome. Robust standard error estimates were used to account for dependent observations from pregnancies with more than one child in Denmark, Norway, and Finland, but not in Sweden. In Sweden, a sensitivity analysis was performed indicating: for the comparisons of pregabalin vs. unexposed, the change in CIs were less than 15%; unweighted analyses (among all comparisons): CI ratio varied from 0.97 to 1.11; weighted analyses (pregabalin vs. unexposed): CI ratio varied from 1.01 to 1.14; weighted analyses (pregabalin vs. other drugs): CI ratio varied from 0.58 to 2.08.

9.9.2.4. Computation of propensity scores

To account for confounding by the measured covariates, an adjusted analysis was conducted using PS stratification, following the approach by Patorno et al.[6] For each pregnancy, a PS was computed, using logistic regression, as the probability of being exposed to pregabalin vs. given comparator conditional on the measured covariates listed in Section 9.4.2 and Appendix 4. Codes used to identify study variables.[59]

PS was estimated for each pregnancy using a generic-outcome model, meaning that all prespecified covariates 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.[57] Furthermore, it is reasonable to assume in this study that all confounders distort the association in the same direction for all outcomes.

A separate PS was estimated for each study population and contrast. To summarize, the following sets of PS were estimated:

1. First-trimester pregabalin vs. first-trimester unexposed
2. First-trimester pregabalin vs. first-trimester lamotrigine
3. First-trimester pregabalin vs. first-trimester duloxetine
4. First-trimester pregabalin vs. first-trimester duloxetine or lamotrigine
5. First-trimester pregabalin monotherapy vs. first-trimester unexposed
6. First-trimester pregabalin monotherapy vs. first-trimester lamotrigine monotherapy
7. First-trimester pregabalin monotherapy vs. first-trimester duloxetine monotherapy
8. First-trimester pregabalin monotherapy vs. first-trimester duloxetine or lamotrigine monotherapy
9. Any-trimester pregabalin vs. any-trimester unexposed
10. Any-trimester pregabalin vs. any-trimester lamotrigine
11. Any-trimester pregabalin vs. any-trimester duloxetine
12. Any-trimester pregabalin vs. any-trimester duloxetine or lamotrigine
13. Any-trimester pregabalin monotherapy vs. unexposed
14. Any-trimester pregabalin monotherapy vs. any-trimester lamotrigine monotherapy
15. Any-trimester pregabalin monotherapy vs. any-trimester duloxetine monotherapy

16. Any-trimester pregabalin monotherapy vs. any-trimester duloxetine or lamotrigine monotherapy

After estimation of each PS, the following steps were taken in each country:

- A graph showing the distribution of PS of the exposed and unexposed pregnancies was produced and pregnancies with PS in non-overlapping areas were deleted (trimming).

- Based on the trimmed distributions, strata of PS were defined using boundaries of the pregabalin-exposed pregnancies. The number of strata was determined by the number of exposed pregnancies and varied across countries.

- All exposed and unexposed pregnancies 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 aPRs or adjusted hazards ratios were estimated using a weighted regression model.

Balance of the covariates following trimming and stratifications-strata specific weights was assessed in each country's dataset using standardized mean differences. Covariates with standardized mean differences <0.1 were considered balanced. No interactions were entered into the PS models. PS was estimated by an analyst in each country and the final PS models that achieved acceptable covariate balance were different in each country.

The crude and the adjusted country-specific estimates of association were reported separately and combined in a meta-analysis (described in Section 9.9.4).

9.9.2.5. Primary analyses

The primary analyses were conducted in the following study population/analysis set: pregnancies ending in singleton/multiple live birth or stillbirth. The assessment of the outcomes stillbirth and major congenital malformations included stillbirths; the other primary outcomes assessment excluded stillbirths.

9.9.2.6. Descriptive analysis

- Pregabalin use in pregnancy was described as the number and proportion of pregnancies exposed in the first trimester, and in any trimester. Number and proportion of pregnancies with pregabalin monotherapy was reported. Cumulative dose during first trimester and any trimester was described based

on the amount of dispensings during a relevant period. Use of lamotrigine and duloxetine was similarly described.

- Distributions of the characteristics of the study population was tabulated according to pregabalin exposure categories: first trimester (exposed/unexposed); any trimester (exposed/unexposed), and separately for the monotherapy subgroup. Categorical variables were summarized using frequencies and proportions; continuous variables using either mean and SD, or median and IQR as appropriate.

- Distribution of maternal and offspring characteristics in the study population was tabulated according to pregabalin and the active comparator categories, as above. All descriptive tables were constructed including stillbirths.

- Crude prevalence of the major congenital malformations was reported according to first-trimester exposure to pregabalin (overall and in the subcategory of monotherapy) and each comparator (overall for all comparators including not exposed and in the subcategory of monotherapy for lamotrigine and duloxetine). In addition, overall prevalence of malformations in the whole general population was presented. Crude prevalence of the other birth outcomes (stillbirth, low birth weight, SGA, preterm birth, low Apgar score at 5 minutes, and microcephaly) was reported according to any-trimester exposure to pregabalin and each comparator, in the same fashion.

9.9.2.7. Major congenital malformation outcomes

Major congenital malformations (any and each major malformation category - sample size permitting), among pregnancies ending in a live birth or a stillbirth pregnancy exposed to pregabalin during the first trimester were compared against each of the comparators estimating crude and aPRs in log-binomial regression.

9.9.2.8. Birth outcomes other than major congenital malformations

For birth outcomes other than major congenital malformations, any-trimester pregabalin-exposed pregnancies were compared against each of the comparators estimating crude and aPRs in log-binomial regression. Except for stillbirth, all remaining birth outcomes were assessed in pregnancies ending in a live birth.

9.9.2.9. Secondary analyses

The secondary analyses were conducted in the following study population/analysis set: pregnancies ending in singleton/multiple live birth. In these analyses, any-trimester pregabalin exposure was considered vs. each of the comparators as above. The monotherapy subset was examined, sample size permitting.

Incidence rates (number of events/person-time contributed by liveborn infants) of the postnatal neurodevelopmental outcomes were reported according to any

exposure to pregabalin and the predefined comparators. All incidence rates were reported for any pregabalin therapy and the subset with pregabalin monotherapy.

For the postnatal neurodevelopmental outcomes, exposure was defined at any time during pregnancy and the same comparators as above. Crude and PS-adjusted hazard ratios were estimated using Cox's proportional-hazards regression. If too few postnatal outcomes were observed to estimate association, the number of cases and crude rates were reported to the extent allowed by the data protection regulation.

9.9.3. Missing values

Missing data were treated as missing in the statistical models without attempts to impute missing values.

9.9.4. Sensitivity analyses

To reduce the potential bias in the analysis of congenital malformations from not including pregnancies terminated due to known malformations, a sensitivity analysis was conducted in the countries where this information was available (Denmark, Norway, and Finland). The sensitivity analyses were conducted in the following study population/analysis set: pregnancies ending in singleton/multiple live birth, stillbirth, or in therapeutic 2nd trimester induced abortion. The analyses in this population assessed the association of the first-trimester exposure to pregabalin and major congenital malformations, including all the comparators above. Separate descriptive tables were produced, and separate sets of PS were estimated as appropriate for each contrast in the sensitivity analyses.

In another sensitivity analysis, crude estimates of association for the birth outcomes were provided defining monotherapy of pregabalin, lamotrigine, and/or duloxetine by absence of other AED, SSRIs, or benzodiazepines. By comparing magnitude and direction of change in the estimates of association obtained in this analysis and those in the main analyses of monotherapy, it was possible to infer the direction and the amount of any potential unmeasured confounding, thus aiding interpretation of the results.[55]

All estimates of association were reported with Wald 95% CIs.

9.9.5. Amendments to the statistical analysis plan

Since any cell counts representing >0 and <5 individuals was not allowed to be presented from Denmark and Norway, due to data protection regulations, and several of the studied outcomes contained non-zero numbers <5, country-specific detailed output of the results have not been reported, but only the results of the meta-analysis are presented.

The traditional meta-analysis method proposed in the protocol, to combine country-specific results across countries for specific malformations, by default removes any estimate of effect that is zero, i.e., an analysis with zero exposed cases. For many specific malformations, and some of the birth outcomes and postnatal neurodevelopmental outcomes, no pregabalin-

exposed cases were observed, resulting in a relative estimate of effect being zero. By default, such observations are not included in the meta-analysis, potentially producing an upwards bias of the combined estimates.

To address this limitation, a post-hoc analysis was added that allowed inclusion of estimates of association stemming from analyses with zero exposed cases. Within each country, crude and PS-weighted 2x2 tables for each contrast/outcome were produced and results were pooled using a Mantel-Haenszel (MH) approach retaining information from strata with no exposed cases.

In addition, the following modifications were applied:

1) In Finland, a special reimbursement register was used as an additional data source (for better identification of mother's comorbidities).
2) In Finland, in addition to ICD-10 codes also ICD-9 codes were used to identify major congenital abnormalities.
3) Terminology updates for postnatal outcomes to reflect exact conditions included in ICD-10 coding.
4) To investigate further the observed increased risk of eye malformations in Sweden, the analysis was repeated with different follow-up times (2 years, 3 years, 4 years, and 5 years).

9.9.6. Meta-analyses

After the separate analyses in each participating country, aggregated level data on crude and adjusted estimates of association were transferred to Aarhus University Hospital, Denmark for meta-analyses. Because of similarities among the healthcare systems in the Nordic countries and the use of a common study protocol with well-defined selection of exposures, outcomes, and covariates, the research partners do not expect the associations between the exposures and outcomes to vary substantially between countries and therefore a fixed-effects meta-analysis was applied.[56] Country-specific crude and adjusted estimates of association for each prespecified contrast was combined in a meta-analysis.[57] For each outcome, the coordinating center at Aarhus University Hospital, Denmark used the inverse variance method in the fixed effects meta-analyses, which is weighting the country-specific estimates of association by the inverse of the within-country variances. Heterogeneity of the estimates was verified, and a random-effects meta-analysis was considered as an alternative should the estimates be found to vary significantly between countries. Results of the meta-analyses were presented using a standard forest plot, reporting the combined crude and adjusted point estimates, with 95% CIs.

9.10. Quality control

Data storage, management, and analyses were conducted according to each institution's standard procedures. At a minimum, all study documents (protocol, report, publications) are reviewed by the entire research team. A senior epidemiologist in each institution reviewed the report before submission to the sponsor. Clinical expertise was available for appropriate interpretation of results. Each institution followed its internal quality control procedures and ensured 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.

9.11. Protection of human subjects

Subject information and consent

Registry-based studies in the Nordic countries do not require patient consent. All parties ensured protection of patient personal data and did not include patient names on any sponsor forms, reports, publications, or in any other disclosures, except where required by laws. No individual-level data were transferred to Pfizer or between 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).[58 60] An 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 routine registries. An approval from the Danish Data Protection Agency, required for all studies, was obtained (2016-051-000001, serial number 544), recorded by Aarhus University.

In Finland, the protocol was subjected to the Ethics Committee of the Hospital District of Helsinki and Uusimaa for review and approval (HUS/887/2018). Ethical approval received 14 March 2018.

In Norway, the protocol was approved by the Regional Committee for Medical and Health Research Ethics (2017/1507/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 2015/1826-31/2, 2017/2238-32, 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, and results will be posted in the EU PAS register.

10. RESULTS

10.1. Participants

The total number of live births, stillbirths, and births ending in a 2nd trimester induced abortion included in the analyses in the study period (2005-2015 for Denmark, Finland, and Norway and 2006-2016 for Sweden) were 670,704 in Denmark, 649,483 in Finland, 661,179 in Norway, and 1,152,002 in Sweden. The distribution in each country of pregabalin exposure stratified by live birth, stillbirth, and pregnancies ending in 2nd trimester induced abortion is shown in Figure 1 - Figure 4.

Figure 1. Identification of the study population, Denmark

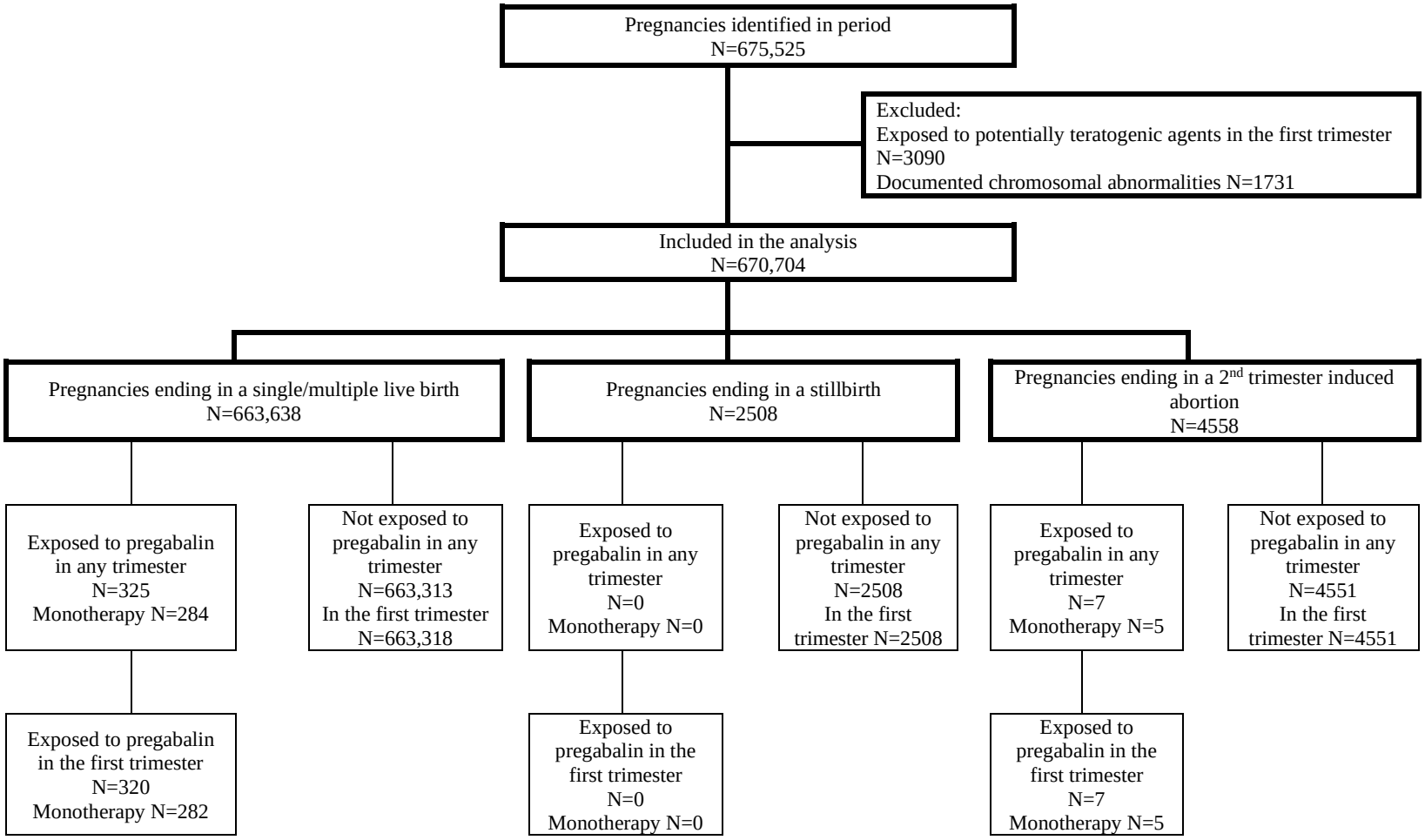
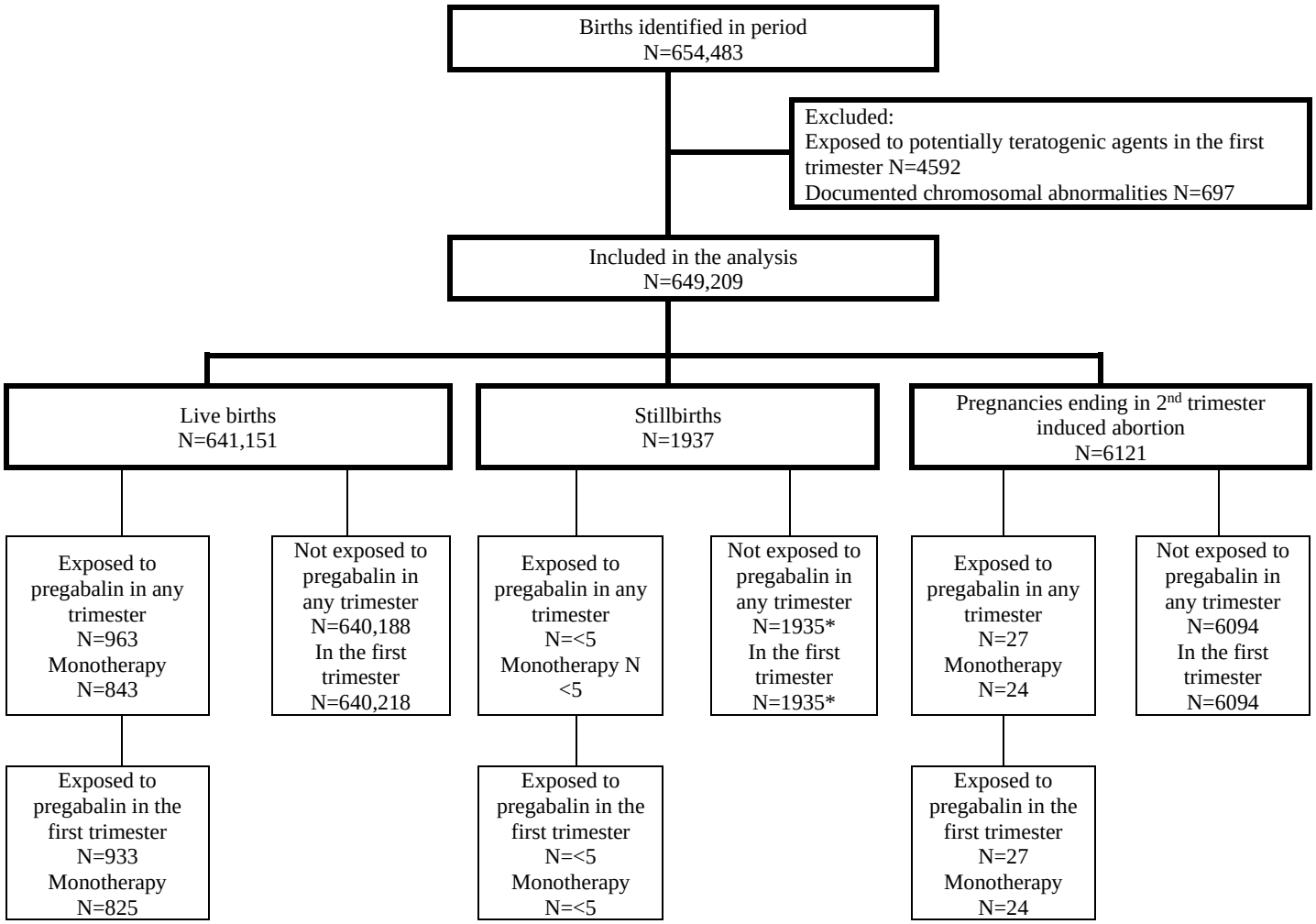
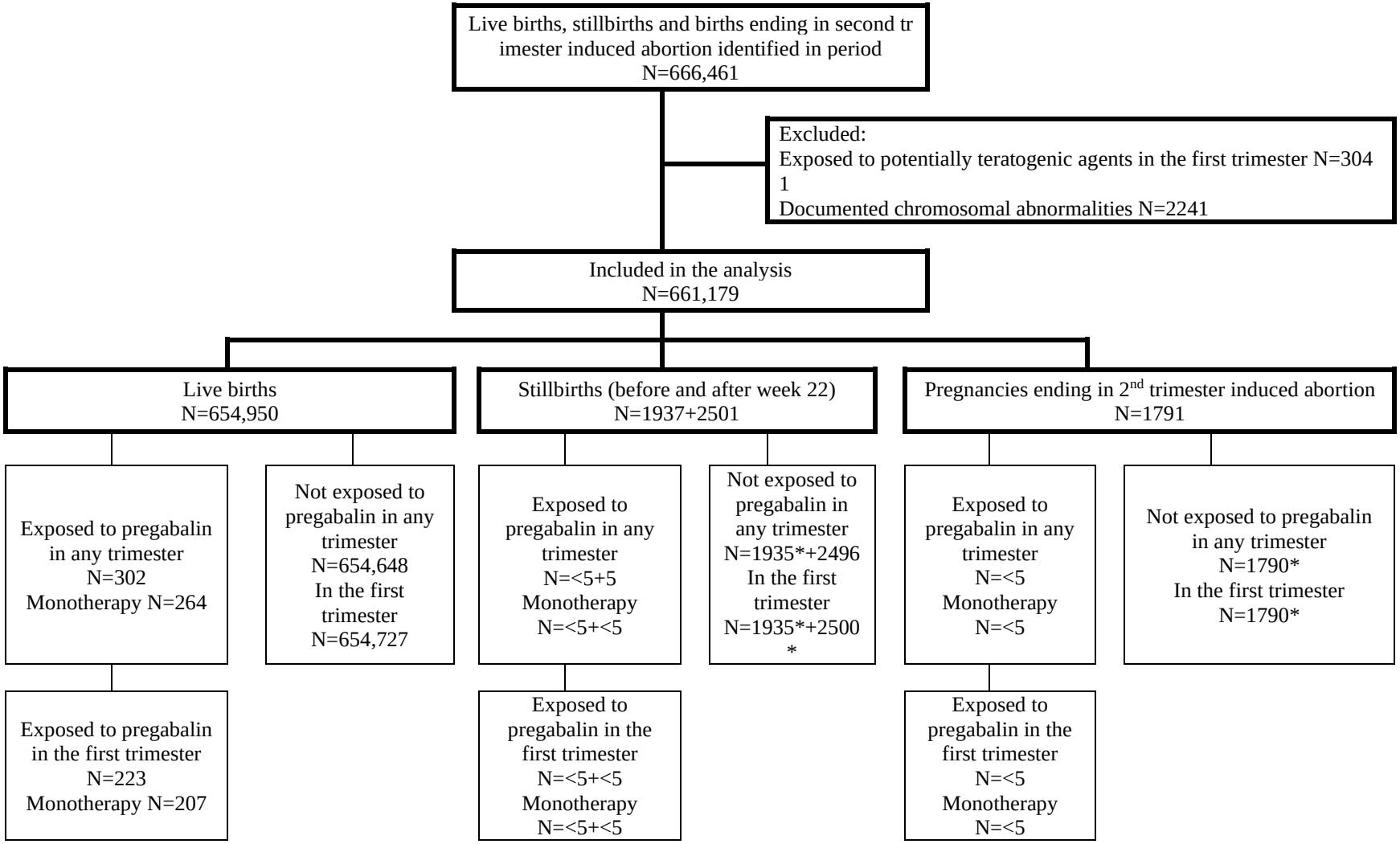


Figure 2. Identification of the study population, Finland



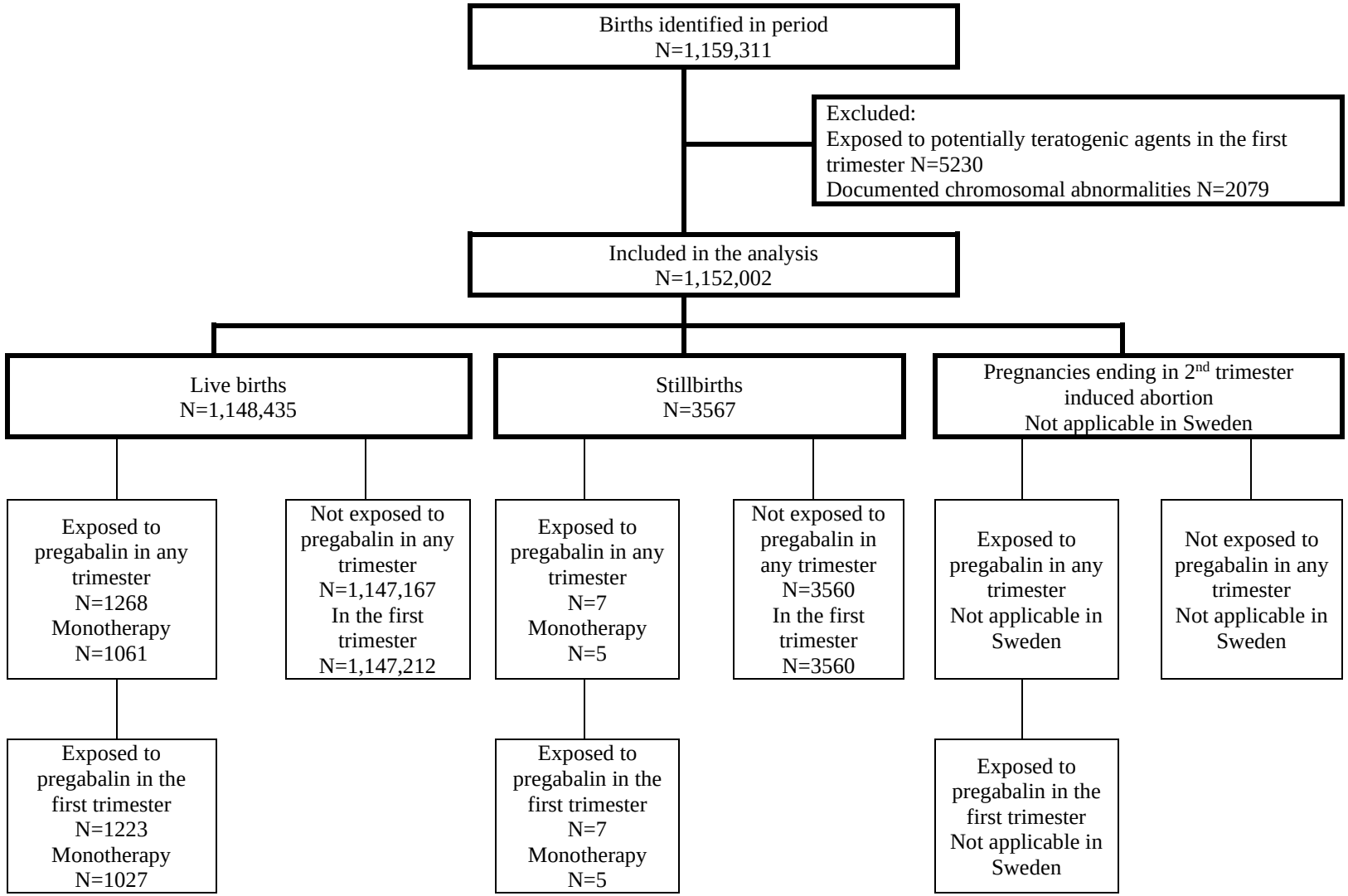
* Rounded to nearest 5 to avoid identification of <5 individuals in the exposed group

Figure 3. Identification of the study population, Norway



*Rounded to nearest 5 to avoid identification of <5 individuals in the exposed group

Figure 4. Identification of the study population, Sweden



10.2. Descriptive data

10.2.1. Baseline characteristics

The utilization of pregabalin, lamotrigine, and duloxetine in each country is described in Supplementary descriptive tables, Table 1. The total number of pregabalin users in a pregnancy ending in a live birth or stillbirth in the study period (2005-2015 for Denmark, Finland, and Norway, and 2006-2016 for Sweden) was 325 out of 666,146 = 0.048% in Denmark, 965 out of 643,088 = 0.16% in Finland, 307 out of 657,451 =0.046% in Norway, and 1275 out of 1,152,002 = 0.11% in Sweden. In all four countries, lamotrigine was used more frequently than pregabalin with an overall use in 0.32% of pregnancies in Denmark, 0.15% in Finland, 0.29% in Norway, and 0.26% in Sweden. Duloxetine was used more frequently than pregabalin in Denmark (0.12% vs. 0.048%) and Sweden (0.14% vs. 0.11%) but less frequently in Finland (0.11% vs. 0.16%) and Norway (0.02% vs. 0.046%).

The distribution of pregabalin users with a potential indication inferred by recorded disease diagnosis, differed between countries. Results of recorded diagnosis of potential indication were: Denmark (n=325; epilepsy, n≤ 5, GAD 3.4%, neuropathic pain 11.7%); Finland (n=965; epilepsy 1.5%, GAD 21.7%, neuropathic pain 16.4%), Norway (n=307; epilepsy 3.6%, GAD 8.5%, neuropathic pain 7.5%), and Sweden (n=1275; epilepsy 1.1%, GAD 43.6%, neuropathic pain 15.8%). Similar results for lamotrigine users were: Denmark (n=2,101; epilepsy 26.6%, GAD 1.4%, neuropathic pain 1.8%); Finland (n=1,012; epilepsy 46.2%, GAD 31.3%, neuropathic pain 4.2%), Norway (n=1934; epilepsy 42.5%, GAD 21.1%, neuropathic pain 1.4%), and Sweden (n=2,991; epilepsy 22.5%, GAD 38.8%, neuropathic pain 3.1%). Results for duloxetine users were: Denmark (n=780; epilepsy, n≤ 5, GAD 2.7%, neuropathic pain 3.1%); Finland (n=718; epilepsy 1.0%, GAD 31.2%, neuropathic pain 8.9%), Norway (n=102; epilepsy 1.0%%, GAD 18.6%, neuropathic pain 3.9%), and Sweden (n=1,660; epilepsy 0.1%, GAD 39.9%, neuropathic pain 10.3%).

The median number of defined daily doses (DDDs) throughout pregnancy ranged from 21 in Finland to 56 in Sweden. In all countries, exposure in the first trimester was markedly more frequent than exposure in the 2nd and 3rd trimester. Pregabalin was predominantly used in monotherapy in pregnancy (84-88%).

The baseline characteristics according to pregabalin use for the four countries are presented in Supplementary descriptive tables, Tables 2.1-2.4. The maternal age distribution was similar in the four countries. Prevalence of smoking was 28-40% of the pregabalin-exposed births and 6-15% of the AED-unexposed births. Most of the comorbidities and medication use were markedly more prevalent in the pregabalin-exposed than in the unexposed births. Births exposed to the active comparators had covariate profiles more similar to those of the pregabalin-exposed than to the unexposed births (Supplementary descriptive tables, Tables 3.1-3.4).

10.2.2. Exposure data

The proportion of users of pregabalin in pregnancy was similar among the Nordic countries, in the range of 0.06-0.15 % pregnancies exposed in the final year of the study, and in general,

use has increased over the decade of the study (Supplementary descriptive figures, Figures 2.1-5.1 for Denmark, 2.2-5.2 for Finland, 2.3-5.3 for Norway, and 2.4-5.4 for Sweden).

Lamotrigine use in pregnancy has also increased during the study period up to approximately 0.4% of pregnancies exposed in 2015 in Denmark, Norway, and Sweden, and 0.1% exposed in Finland (Supplementary descriptive figures, Figures 6.1-9.4). Duloxetine exposure was more stable at approximately 0.15% during the study period in Denmark and Sweden, 0.02% in Norway, and 0.8% in Finland (Supplementary descriptive figures, Figures 10.1-13.4).

10.3. Outcome data

See section 10.4.

10.4. Main results

The pregabalin, comparators (unexposed to AEDs, lamotrigine, duloxetine, duloxetine or lamotrigine) country-specific and meta-analyses results of prevalence, crude prevalence ratio, PS-adjusted prevalence ratio, combined MH adjusted prevalence ratio estimates of major congenital malformations and other birth outcomes, are presented below (Table 4 - Table 10). Similar incidence rate and hazard ratio results for neurodevelopmental outcomes are presented in Table 11 - Table 13. The covariates included in the PS-adjusted models were: calendar year of delivery; maternal age in years at conception; marital/cohabiting status; smoking during pregnancy; obesity (BMI =>30 kg/m2) or a hospital diagnosis of obesity; single or multiple gestation; hospital-recorded morbidity; indicators of maternal healthcare utilization in the 12 months pre-last menstrual period (LMP) (number of inpatient and specialized outpatient encounters); for congenital malformations outcome: maternal medication use, each as a dichotomous variable. In addition, the meta-analyses results are presented as forest plots in the appendices (see Supplementary forest plots Mantel-Haenszel meta-analyses malformations and Supplementary forest plots Mantel-Haenszel meta-analyses birth outcomes and postnatal outcomes).

Major congenital malformations

The main results regarding major congenital malformations are presented below (Table 4). Meta-analysis of prevalence of major congenital malformations occuring in first-trimester pregabalin-exposed pregnancies varied slightly depending on the comparison group, ranging between 5.91% vs. unexposed, and 6.01% vs. duloxetine or lamotrigine. Meta-analysis of prevalence of major congenital malformations occuring in unexposed, lamotrigine, duloxetine, duloxetine or lamotrigine first-trimester exposed pregnancies were 4.05%, 4.85%, not reportable (not reportable due to the possibility of estimating a low number of individuals (<5) in other cells), and not reportable, respectively. The aPRs in the standard meta-analysis for any major congenital malformation were 1.13 (95% CI 0.97–1.33) for first-trimester pregabalin-exposed vs. unexposed, 1.36 (1.07–1.72) for pregabalin vs. lamotrigine-exposed, 1.37 (1.06–1.77) for pregabalin vs. duloxetine, and 1.24 (1.00–1.54) for pregabalin vs. lamotrigine or duloxetine. Restricting to pregabalin, lamotrigine, and duloxetine monotherapy only marginally changed the results. The aPRs of Pregabalin monotherapy

versus: unexposed, 1.14 (0.96–1.35); lamotrigine monotherapy, 1.29 (1.01–1.65); duloxetine monotherapy, 1.39 (1.07–1.82); lamotrigine or duloxetine monotherapy, 1.24 (1.00–1.54).

Table 4. Country-specific and combined crude and propensity score adjusted prevalence ratios of any major congenital malformations in first trimester pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Any major congenital malformation	**Cases, n**	**Total, n**	**Prevalence (%)**	**Cases, n**	**Total, n**	**Prevalence (%)**	**Crude Prevalence Ratio**	**PS-Adjusted Prevalence Ratio**	**MH Adjusted Prevalence Ratio**
Unexposed									
Denmark	20	299	6.69	22,512	621,939	3.62	1.91 (1.21–3.01)	1.56 (0.98-2.47)	-
Finland	64	935	6.84	34,071	639,589	5.33	1.31 (1.01-1.68)	1.11 (0.86-1.44)	-
Norway	7	227	3.08	15,097	655,298	2.30	1.35 (0.64-2.87)	1.22 (0.57-2.61)	-
Sweden	68	1230	5.53	52,512	1,146,425	4.58	1.21 (0.96-1.52)	1.06 (0.84-1.33)	-
Meta-analysis	159	2691	5.91	124,192	3,063,251	4.05	1.32 (1.13–1.55)	1.13 (0.97-1.33)	1.13 (0.97-1.31)
Lamotrigine									
Denmark	20	282	7.09	90	1836	4.90	1.48 (0.90–2.45)	1.83 (1.03–3.26)	-
Finland	64	935	6.84	61	942	6.48	1.06 (0.74-1.53)	1.15 (0.60-2.21)	-
Norway	7	220	3.18	48	1681	2.86	1.12 (0.50-2.51)	1.36 (0.56-3.29)	-
Sweden	64	1149	5.57	151	2757	5.48	1.02 (0.77 - 1.35)	1.30 (0.97 - 1.76)	-
Meta-analysis	155	2586	5.99	350	7216	4.85	1.10 (0.90-1.34)	1.36 (1.07-1.72)	1.30 (1.07-1.59)
Duloxetine									
Denmark	18	281	6.41	22	685	3.21	2.06 (1.09–3.91)	4.44 (2.13–9.23)	-
Finland	64	935	6.84	45	676	6.66	1.03 (0.69-1.53)	1.68 (1.00-2.85)	-
Norway	7	224	3.13	<5	87	NR	NR	NR	-
Sweden	62	1117	5.55	93	1524	6.10	0.91 (0.67 - 1.24)	1.00 (0.72 - 1.37)	-
Meta-analysis	151	2557	5.91	NR	2972	NR	1.06 (0.85-1.33)	1.37 (1.06-1.77)	1.39 (1.09-1.76)
Duloxetine or lamotrigine									
Denmark	18	266	6.77	111	2476	4.48	1.55 (0.92–2.59)	1.89 (1.07–3.33)	-
Finland	64	935	6.84	106	1603	6.61	1.04 (0.75-1.43)	1.26 (0.81-1.97)	-
Norway	7	217	3.23	NR	1768	NR	NR	1.25 (0.52-3.03)	-
Sweden	59	1045	5.65	239	4214	5.67	1.00 (0.75 - 1.31)	1.17 (0.89 - 1.56)	-
Meta-analysis	148	2463	6.01	NR	10,061	NR	1.08 (0.90-1.31)	1.24 (1.00-1.54)	1.27 (1.05-1.54)

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 pregnancies).
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 = Not reportable 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.

For the specific malformations, a few noticeable associations were observed, though it must be noted that no correction for multiple comparisons was conducted. (Supplementary malformation tables Tables 5 and 6, and Supplementary forest plots Mantel-Haenszel meta-analyses malformations Tables 50.1-60.1). In the meta-analyses of the nervous system, we observed pregabalin vs. unexposed aPR (95% CI) 2.03 (0.88–4.64), pregabalin vs. lamotrigine 4.41 (1.37–14.22), pregabalin vs. duloxetine 2.80 (0.57–13.70), and pregabalin vs. lamotrigine or duloxetine 3.83 (1.20–12.22). Similarly, we observed for eye malformations: pregabalin vs. unexposed aPR (95% CI) 2.09 (1.12–3.90), pregabalin vs. lamotrigine 1.88 (0.63–5.65), pregabalin vs. duloxetine 0.82 (0.34–2.00) and pregabalin vs. lamotrigine or duloxetine 2.26 (0.92–5.53). For orofacial clefts we observed: pregabalin vs. unexposed aPR (95% CI) 2.89 (1.19–7.03), pregabalin vs. lamotrigine 4.19 (1.22–14.36), pregabalin vs. duloxetine 3.35 (0.54–20.61), and pregabalin vs. lamotrigine or duloxetine 5.08 (1.59–16.24). In addition, for urinary malformations we observed: pregabalin vs unexposed 1.41 (0.85–2.35), pregabalin vs. lamotrigine 3.03 (1.34–6.84), pregabalin vs. duloxetine 2.14 (0.89–5.13) and pregabalin vs. lamotrigine or duloxetine 1.66 (0.80–3.47). Finally, for genital malformations we observed: pregabalin vs. unexposed 1.46 (0.89–2.39), pregabalin vs. lamotrigine 2.13 (1.05–4.32), pregabalin vs. duloxetine 2.64 (1.13–6.17), and pregabalin vs. lamotrigine or duloxetine 2.26 (1.17–4.38). For the other congenital malformations, no marked increase in the PRs among the pregabalin-exposed were observed compared to the comparators.

The estimates were imprecise due to low number of exposed outcomes, and zero exposed outcomes were frequent in one or more countries.

Birth outcomes

The country-specific and meta-analyses results of prevalence, crude prevalence ratio, PS-adjusted prevalence ratio, and combined MH adjusted prevalence ratio estimates of birth outcomes are presented below (Table 5 - Table 10).

Meta-analysis of prevalence of stillbirths resulting from pregabalin-exposed pregnancies were not reportable due to the low number of cases from the individual countries. Country specific results were generally low, varied slightly depending on the comparison group, and ranged between 0.00% and 1.71%. Meta-analysis of prevalence of stillbirths resulting from unexposed pregnancies was 0.33%, and not reportable for the remaining comparators. Results of stillbirths showed an aPR and (95% CI) 1.72 (1.02–2.91) for pregabalin-exposed compared to unexposed, and 1.87 (0.81–4.32) for comparison with lamotrigine, 1.46 (0.57–3.72) compared to duloxetine, and 2.71 (1.25–5.90) compared with the combined lamotrigine and duloxetine group (Table 5).

Prevalences of low birth weight, preterm birth, SGA, low Apgar score at 5 minutes, and microcephaly are provided in Table 6 - Table 10. In the meta-analyses results of the birth outcomes, we observed aPRs and (95% CI) for low birth weight, preterm birth, SGA, low Apgar score at 5 minutes, and microcephaly for pregabalin-exposed compared to unexposed of 1.05 (0.91–1.21), 1.13 (0.99–1.29), 1.21 (1.01–1.44), 1.18 (0.95–1.48), and 1.09 (0.88–1.36) respectively, but with estimates closer to null effect for comparison to the active comparators. Pregabalin monotherapy compared to unexposed showed similar aPRs (95%

CI) for low birth weight 1.06 (0.90–1.24), preterm birth 1.14 (0.99–1.32), SGA 1.19 (0.98–1.45), 1.05 (0.82–1.36) for low Apgar score at 5 minutes, and microcephaly 1.00 (0.78–1.27) (see Supplementary birth outcomes and postnatal outcomes tables, Figure 31.2).

Table 5. Country-specific and combined crude and propensity score adjusted prevalence ratios of stillbirth in pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Stillbirth	**Cases, n**	**Total, n**	**Prevalence (%)**	**Cases, n**	**Total, n**	**Prevalence (%)**	**Crude Prevalence Ratio**	**PS-Adjusted Prevalence Ratio**	**MH Adjusted Prevalence Ratio**
Unexposed									
Denmark	0	304	0.00	2126	621,719	0.34	NE	NE	-
Finland	<5	965	NR	1928	639,247	0.30	NR	NR	-
Norway	5	307	1.63	2485	654,641	0.38	4.29 (1.8-10.22)	3.23 (1.33-7.85)	-
Sweden	7	1275	0.55	3546	1,145,957	0.31	1.77 (0.85 - 3.72)	1.56 (0.74 - 3.26)	-
Meta-analysis	NR	2851	NR	10,085	3,061,564	0.33	2.14 (1.27-3.60)	1.72 (1.02-2.91)	1.25 (0.74-2.11)
Lamotrigine									
Denmark	0	287	0.00	7	1920	0.36	NE	NE	-
Finland	<5	965	NR	<5	992	NR	NR	NR	-
Norway	5	298	1.68	7	1925	0.36	4.61 (1.48-14.42)	2.71 (0.58-12.63)	-
Sweden	6	1190	0.50	8	2906	0.28	1.83 (0.64 - 5.27)	2.20 (0.73 - 6.64)	-
Meta-analysis	NR	2740	NR	NR	7743	NR	2.24 (1.10-4.57)	1.87(0.81-4.32)	1.30 (0.69-2.47)
Duloxetine									
Denmark	0	284	0.00	<5	697	NR	NE	NE	-
Finland	<5	965	NR	<5	683	NR	NE	NE	-
Norway	5	302	1.66	<5	97	NR	NR	NR	-
Sweden	6	1158	0.52	5	1543	0.32	1.60 (0.49 - 5.23)	1.30 (0.42 - 3.96)	-
Meta-analysis	NR	2709	NR	NR	3020	NR	1.57 (0.61-4.07)	1.46 (0.57-3.73)	1.00 (0.39-2.54)
Duloxetine or lamotrigine									
Denmark	0	269	0.00	9	2571	0.35	NE	NE	-
Finland	<5	965	NR	<5	1660	NR	NR	NR	-
Norway	5	293	1.71	8	2021	0.40	4.31 (1.42-13.07)	5.73 (1.49-22.06)	-
Sweden	5	1082	0.46	13	4380	0.30	1.56 (0.56 - 4.36)	2.44 (0.81 - 7.40)	-
Meta-analysis	NR	2609	NR	NR	10,632	NR	2.09 (1.05-4.17)	2.71 (1.25-5.90)	1.92 (0.98-3.78)

Cases represent the crude number of any stillbirth included in the analysis. Total represents the total number of newborns at risk (first trimester exposed pregnancies).
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 = Not reportable due to the possibility of estimating a low number of individuals (<5) in other cells. 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 6. Country-specific and combined crude and propensity score adjusted prevalence ratios of low birth weight in pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Low birth weight	**Cases, n**	**Total, n**	**Prevalence (%)**	**Cases, n**	**Total, n**	**Prevalence (%)**	**Crude Prevalence Ratio**	**PS-Adjusted Prevalence Ratio**	**MH Adjusted Prevalence Ratio**
Unexposed									
Denmark	26	296	8.78	30,339	613,993	4.94	1.85 (1.24–2.77)	1.38 (0.92–2.08)	-
Finland	54	962	5.61	26,359	636,967	4.14	1.38 (1.04-1.82)	1.03 (0.78-1.37)	-
Norway	22	302	7.28	31,385	652,128	4.81	1.55 (1.01-2.4)	1.03 (0.66-1.59)	-
Sweden	84	1268	6.62	46,939	1,142,411	4.11	1.61 (1.31 - 1.98)	0.99 (0.81 - 1.22)	-
Meta-analysis	186	2828	6.58	135,022	3,045,499	4.43	1.57 (1.36-1.81)	1.05 (0.91-1.21)	1.05 (0.91-1.20)
Lamotrigine									
Denmark	25	279	8.96	137	1889	7.25	1.26 (0.80–1.98)	1.32 (0.78–2.23)	-
Finland	54	962	5.61	52	987	5.27	1.07 (0.70-1.63)	1.09 (0.64-1.85)	-
Norway	22	293	7.51	114	1918	5.94	1.28 (0.79-2.10)	1.22 (0.69-2.15)	-
Sweden	79	1184	6.67	141	2898	4.87	1.37 (1.05 - 1.79)	0.78 (0.61 - 1.00)	-
Meta-analysis	180	2718	6.62	444	7692	5.77	1.27 (1.06-1.54)	0.92 (0.76-1.12)	0.96 (0.81-1.13)
Duloxetine									
Denmark	23	276	8.33	58	692	8.38	0.99 (0.59–1.66)	1.05 (0.57–1.94)	-
Finland	54	962	5.61	40	681	5.87	0.95 (0.61-1.49)	0.62 (0.36-1.07)	-
Norway	22	297	7.41	11	96	11.46	0.62 (0.29-1.32)	0.63 (0.25-1.58)	-
Sweden	73	1152	6.34	97	1538	6.31	1.00 (0.75 - 1.35)	0.84 (0.63 - 1.12)	-
Meta-analysis	172	2687	6.40	206	3007	6.85	0.95 (0.77-1.18)	0.81 (0.65-1.02)	0.79 (0.65-0.96)
Duloxetine or lamotrigine									
Denmark	23	261	8.81	192	2535	7.57	1.18 (0.75–1.86)	1.10 (0.66–1.82)	-
Finland	54	962	5.61	92	1653	5.57	1.01 (0.70-1.45)	0.76 (0.49-1.19)	-
Norway	22	288	7.64	124	2013	6.16	1.26 (0.78-2.05)	1.19 (0.69-2.04)	-
Sweden	69	1077	6.41	235	4367	5.38	1.19 (0.92 - 1.54)	0.83 (0.65 - 1.07)	-
Meta-analysis	168	2588	6.49	643	10,632	6.05	1.15 (0.96-1.38)	0.89 (0.73-1.07)	0.88 (0.75-1.04)

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 pregnancies).
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 7. Country-specific and combined crude and propensity score adjusted prevalence ratios of preterm birth in pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Preterm birth	**Cases, n**	**Total, n**	**Prevalence (%)**	**Cases, n**	**Total, n**	**Prevalence (%)**	**Crude Prevalence Ratio**	**PS-Adjusted Prevalence Ratio**	**MH Adjusted Prevalence Ratio**
Unexposed									
Denmark	26	296	8.78	30,339	613,993	4.94	1.85 (1.24–2.77)	1.38 (0.92–2.08)	-
Finland	27	963	2.80	17,597	637,319	2.76	1.02 (0.69-1.49)	0.85 (0.58-1.26)	-
Norway	33	302	10.93	41,516	652,062	6.37	1.80 (1.26-2.59)	1.23 (0.85-1.78)	-
Sweden	137	1268	10.80	64,904	1,142,411	5.68	1.90 (1.62-2.23)	1.13 (0.96-1.32)	-
Meta-analysis	186	2829	6.57	162,359	3,045,785	5.33	1.75 (1.54-2.00)	1.13 (0.99-1.29)	1.12 (0.91-1.20)
Lamotrigine									
Denmark	32	279	11.47	202	1889	10.69	1.08 (0.70–1.66)	0.91 (0.57–1.47)	-
Finland	27	963	2.80	36	989	3.64	0.76 (0.44-1.31)	1.00 (0.51-1.95)	-
Norway	33	293	11.26	152	1918	7.92	1.47 (0.98-2.22)	1.40 (0.85-2.30)	-
Sweden	130	1184	10.98	230	2989	7.69	1.38 (1.13 - 1.70)	0.93 (0.77 - 1.13)	-
Meta-analysis	222	2719	8.16	620	7692	8.06	1.28 (1.09-1.50)	0.97 (0.83-1.15)	0.99 (0.85-1.14)
Duloxetine									
Denmark	29	276	10.51	81	692	11.71	0.89 (0.55–1.43)	1.14 (0.65–2.00)	-
Finland	27	963	2.80	15	682	2.20	1.28 (0.66-2.50)	1.09 (0.46-2.60)	-
Norway	32	297	10.77	15	96	15.63	0.65 (0.32-1.34)	0.69 (0.31-1.55)	-
Sweden	122	1152	10.59	156	1538	10.14	1.04 (0.83 - 1.31)	1.07 (0.86 - 1.34)	-
Meta-analysis	210	2688	7.81	267	3008	8.88	1.00 (0.83-1.21)	1.05 (0.87-1.28)	1.05 (0.88-1.26)
Duloxetine or lamotrigine									
Denmark	29	261	11.11	275	2535	10.85	1.03 (0.67–1.58)	0.98 (0.62–1.55)	-
Finland	27	963	2.80	51	1656	3.08	0.91 (0.55-1.49)	1.13 (0.62-2.08)	-
Norway	32	288	11.11	166	2013	8.25	1.39 (0.92-2.10)	1.38 (0.87-2.21)	-
Sweden	116	1077	10.77	378	4367	8.66	1.24 (1.02 - 1.52)	1.01 (0.84 - 1.23)	-
Meta-analysis	204	2589	7.88	870	10,571	8.23	1.20 (1.02-1.40)	1.06 (0.90-1.24)	1.06 (0.92-1.23)

Cases represent the crude number of any stillbirth included in the analysis. Total represents the total number of newborns at risk (first trimester exposed pregnancies).
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 8. Country-specific and combined crude and propensity score adjusted prevalence ratios of small for gestational age in pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Small for gestational age	**Cases, n**	**Total, n**	**Prevalence (%)**	**Cases, n**	**Total, n**	**Prevalence (%)**	**Crude Prevalence Ratio**	**PS-Adjusted Prevalence Ratio**	**MH Adjusted Prevalence Ratio**
Unexposed									
Denmark	48	296	16.22	64,500	613,993	10.51	1.65 (1.21–2.25)	1.32 (0.97–1.81)	-
Finland	36	942	3.82	13,727	624,723	2.20	1.76 (1.26-2.46)	1.32 (0.94-1.86)	-
Norway	6	287	2.09	9427	614,294	1.53	1.37 (0.61-3.08)	1.16 (0.51-2.63)	-
Sweden	41	1227	3.34	24,755	1,108,694	2.23	1.50 (1.11 - 2.02)	1.04 (0.77 - 1.40)	-
Meta-analysis	131	2793	4.69	112,409	2,995,421	3.75	1.61 (1.35-1.92)	1.21 (1.01-1.44)	1.19 (1.01-1.40)
Lamotrigine									
Denmark	45	279	16.13	210	1889	11.12	1.54 (1.08–2.20)	1.46 (0.97–2.20)	-
Finland	36	942	3.82	25	974	2.57	1.50 (0.89-2.51)	1.42 (0.72-2.81)	-
Norway	6	279	2.15	20	1814	1.10	1.97 (0.78-4.96)	2.68 (0.99-7.30)	-
Sweden	39	1149	3.39	58	2805	2.07	1.64 (1.10 - 2.45)	0.89 (0.62 - 1.27)	-
Meta-analysis	126	2684	4.69	313	7575	4.13	1.59 (1.26-2.00)	1.20 (0.94-1.54)	1.22 (0.99-1.50)
Duloxetine									
Denmark	43	276	15.58	90	692	13.01	1.23 (0.83–1.83)	1.29 (0.79–2.10)	-
Finland	36	942	3.82	25	669	3.74	1.02 (0.60-1.74)	0.54 (0.28-1.04)	-
Norway	6	283	2.12	<5	89	NR	NR	NR	-
Sweden	37	1120	3.30	36	1485	2.42	1.36 (0.87 - 2.14)	1.06 (0.69 - 1.61)	-
Meta-analysis	122	2653	4.60	NR	2988	NR	1.21 (0.94-1.56)	0.99 (0.75-1.32)	0.94 (0.75-1.17)
Duloxetine or lamotrigine									
Denmark	41	261	15.71	295	2535	11.64	1.42 (0.99–2.03)	1.28 (0.86–1.88)	-
Finland	36	942	3.82	50	1628	3.07	1.25 (0.80-1.94)	0.78 (0.45-1.37)	-
Norway	6	275	2.18	22	1903	1.16	1.91 (0.77-4.75)	2.82 (1.06-7.52)	-
Sweden	35	1049	3.34	93	4223	2.20	1.52 (1.03 - 2.22)	0.97 (0.67 - 1.39)	-
Meta-analysis	118	2555	4.62	460	10433	4.41	1.43 (1.15-1.78)	1.09 (0.87-1.38)	1.04 (0.86-1.26)

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 = Not reportable 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 9. Country-specific and combined crude and propensity score adjusted prevalence ratios of low Apgar score in pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Low Apgar score at 5 minutes	**Cases, n**	**Total, n**	**Prevalence (%)**	**Cases, n**	**Total, n**	**Prevalence (%)**	**Crude Prevalence Ratio**	**PS-Adjusted Prevalence Ratio**	**MH Adjusted Prevalence Ratio**
Unexposed									
Denmark	7	296	2.36	4624	613,993	0.75	3.19 (1.51–6.75)	1.70 (0.79–3.65)	-
Finland	32	963	3.32	12,844	637,319	2.02	1.67 (1.17-2.38)	1.07 (0.75-1.53)	-
Norway	5	302	1.66	8881	652,156	1.36	1.22 (0.5-2.95)	0.87 (0.36-2.11)	-
Sweden	38	1259	3.02	14,245	1,136,650	1.25	2.41 (1.76 - 3.30)	1.25 (0.92 - 1.72)	-
Meta-analysis	82	2779	2.95	40,594	3,045,879	1.33	2.06 (1.08-1.66)	1.18 (0.95-1.48)	1.17 (0.88-1.34)
Lamotrigine									
Denmark	6	279	2.15	27	1889	1.43	1.52 (0.61–3.74)	1.05 (0.39–2.86)	-
Finland	32	963	3.32	43	989	4.35	0.76 (0.47-1.21)	0.59 (0.32-1.09)	-
Norway	5	293	1.71	35	1918	1.82	0.93 (0.36-2.41)	0.81 (0.28-2.32)	-
Sweden	34	1176	2.89	65	2886	2.25	1.28 (0.85 - 1.93)	1.14 (0.76 - 1.71)	-
Meta-analysis	77	2719	2.83	170	7694	2.21	1.06 (0.80-1.40)	0.93 (0.69-1.26)	0.86 (0.66-1.13)
Duloxetine									
Denmark	6	276	2.17	10	692	1.45	1.52 (0.55–4.21)	1.44 (0.40–5.14)	-
Finland	32	963	3.32	26	682	3.81	0.87 (0.51-1.47)	0.66 (0.34-1.31)	-
Norway	5	297	1.68	NR	96	NR	NR	NR	-
Sweden	32	1146	2.79	32	1528	2.09	1.33 (0.82 - 2.16)	0.93 (0.60 - 1.45)	-
Meta-analysis	75	2688	2.79	NR	3008	NR	1.12 (0.81-1.56)	0.87 (0.61-1.23)	0.84 (0.62-1.14)
Duloxetine or lamotrigine									
Denmark	NR	261	NR	37	2535	1.46	NR	NR	-
Finland	32	963	3.32	69	1656	4.17	0.79 (0.52-1.21)	0.70 (0.42-1.18)	-
Norway	5	288	1.74	37	2013	1.84	0.94 (0.37-2.42)	0.67 (0.23-1.94)	-
Sweden	28	1072	2.61	95	4345	2.19	1.19 (0.79 - 1.81)	0.98 (0.65 - 1.48)	-
Meta-analysis	70	2589	2.70	238	10,571	2.25	1.00 (0.76-1.31)	0.86 (0.64-1.15)	0.83 (0.64-1.08)

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 = Not reportable 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.MH = Mantel-Haenszel

Table 10. Country-specific and combined crude and propensity score adjusted prevalence ratios of microcephaly in pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Microcephaly	**Cases, n**	**Total, n**	**Prevalence (%)**	**Cases, n**	**Total, n**	**Prevalence (%)**	**Crude Prevalence Ratio**	**PS-Adjusted Prevalence Ratio**	**MH Adjusted Prevalence Ratio**
Unexposed									
Denmark	23	296	7.77	34,756	613,993	5.66	1.40 (0.92–2.15)	1.11 (0.72–1.70)	-
Finland	33	922	3.58	15,207	608,367	2.50	1.45 (1.03-2.06)	1.12 (0.79-1.60)	-
Norway	7	293	2.39	14,924	611,637	2.44	0.98 (0.46-2.07)	0.91 (0.43-1.93)	-
Sweden	21	1200	1.75	15,121	1,083,505	1.40	1.25 (0.82 - 1.92)	1.10 (0.72 - 1.68)	-
Meta-analysis	84	2779	3.02	80,011	2,976,408	2.69	1.34 (1.08-1.66)	1.09 (0.88-1.36)	1.09 (0.88-1.34)
Lamotrigine									
Denmark	22	279	7.89	109	1889	5.77	1.40 (0.87–2.25)	1.05 (0.61–1.80)	-
Finland	33	922	3.58	34	941	3.61	1.00 (0.61-1.62)	1.31 (0.69-2.49)	-
Norway	6	284	2.11	44	1805	2.44	0.86 (0.36-2.05)	1.26 (0.49-3.25)	-
Sweden	18	1123	1.60	37	2734	1.35	1.18 (0.68 - 2.07)	0.79 (0.47 - 1.35)	-
Meta-analysis	79	2669	2.96	224	7533	2.97	1.15 (0.87-1.51)	1.02 (0.75-1.39)	1.05 (0.80-1.38)
Duloxetine									
Denmark	19	276	6.88	43	692	6.21	1.12 (0.64–1.96)	1.20 (0.61–2.38)	-
Finland	33	922	3.58	15	658	2.28	1.58 (0.85-2.93)	1.18 (0.54-2.56)	-
Norway	7	289	2.42	5	89	5.62	0.42 (0.13-1.35)	0.38 (0.10-1.46)	-
Sweden	19	1094	1.74	18	1454	1.24	1.40 (0.74 - 2.66)	1.04 (0.58 - 1.89)	-
Meta-analysis	78	2639	2.96	81	2977	2.72	1.21 (0.87-1.70)	1.04 (0.71-1.50)	1.05 (0.77-1.44)
Duloxetine or lamotrigine									
Denmark	19	261	7.28	148	2535	5.84	1.27 (0.77–2.08)	1.01 (0.59–1.72)	-
Finland	33	922	3.58	49	1584	3.09	1.16 (0.74-1.82)	1.12 (0.65-1.94)	-
Norway	6	280	2.14	49	1894	2.59	0.82 (0.35-1.94)	1.19 (0.48-2.96)	-
Sweden	16	1024	1.56	55	4125	1.33	1.17 (0.67 - 2.04)	0.87 (0.51 - 1.49)	-
Meta-analysis	74	2540	2.91	301	10,380	2.90	1.15 (0.88-1.51)	1.01 (0.76-1.36)	1.02 (0.79-1.33)

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.

Postnatal neurodevelopmental outcomes

The country-specific and meta-analyses results of crude incidence rate, PS-adjusted hazard ratios, meta-analysis, and combined MH adjusted hazard ratio estimates of postnatal neurodevelopmental outcomes (ADHD, ASD, and ID) results are presented below (Table 11 - Table 13).

Meta-analysis incidence rate per 10,000 person-years of postnatal neurodevelopmental outcomes occuring in pregabalin-exposed pregnancies varied depending on the comparison group. Meta-analysis incidence rate per 10,000 person-years in the unexposed to AEDs offspring were 48.19 for ADHD, and NE (non-estimable due to 0 cases in one or more cells) for ASD and ID. In the meta-analyses of the neurodevelopmental outcomes we observed for ADHD among the pregabalin-exposed, an adjusted hazard ratio and (95% CI) of 1.32 (1.04–1.67) compared with unexposed, 1.09 (0.79–1.52) compared with lamotrigine, 1.11 (0.76–1.61) compared with duloxetine, and 1.20 (0.89–1.63) compared with lamotrigine or duloxetine. Crude estimates suggested markedly stronger associations indicating that confounder adjustment at least partly explained this association. For ASD and ID, the point estimates were close to unity (Table 12, Table 13).

Table 11. Country-specific and combined crude and propensity score adjusted hazard ratios of hyperkinetic disorders incl. ADHD in pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Hyperkinetic disorders incl. ADHD	**Cases, n**	**Total person-years**	**Incidence Rate per 10,000 person-years**	**Cases, n**	**Total person-years**	**Incidence Rate per 10,000 person-years**	**Crude Hazard Ratio**	**PS-Adjusted Hazard Ratio**	**MH Adjusted Hazard Ratio**
Unexposed									
Denmark	6	1287	46.62	5861	3,989,650	14.69	8.84 (4.12–18.98)	4.04 (1.86–8.78)	-
Finland	17	4698	36.19	10,764	4,112,313	26.18	2.41 (1.50-3.87)	1.04 (0.64-1.68)	-
Norway	8	1512	52.91	4029	2,875,145	14.01	3.25 (1.61-6.56)	1.53 (0.75-3.12)	-
Sweden	38	6821	55.71	14,424	6,902,800	20.90	3.77 (2.74 - 5.18)	1.17 (0.85-1.61)	-
Meta-analysis	69	14,318	48.19	35,078	17,879,908	19.62	3.60 (2.85-4.55)	1.32 (1.04-1.67)	1.22 (0.96-1.54)
Lamotrigine									
Denmark	<5	1157	NR	11	7657	14.37	NR	NR	-
Finland	17	4698	36.19	24	5547	43.27	1.20 (0.64-2.25)	0.97 (0.39-2.42)	-
Norway	8	1451	55.13	17	9043	18.80	2.32 (0.97-5.53)	1.17 (0.44-3.17)	-
Sweden	37	6398	57.83	60	14,555	41.22	1.42 (0.94 - 2.15)	0.99 (0.67-1.45)	-
Meta-analysis	NR	13,721	NR	120	39,841	30.12	1.53 (1.12-2.09)	1.09 (0.79-1.52)	1.10 (0.81-1.48)
Duloxetine									
Denmark	6	1184	50.68	14	3996	35.04	3.07 (1.23–7.69)	1.71 (0.56–5.16)	-
Finland	17	4698	36.19	12	3580	33.52	1.15 (0.55-2.44)	0.74 (0.31-1.79)	-
Norway	8	1472	54.35	<5	530	NR	NR	NR	-
Sweden	35	6215	56.32	45	8334	54.00	1.17 (0.75 - 1.82)	1.16 (0.73-1.85)	-
Meta-analysis	66	13,569	48.64	NR	16,441	NR	1.32 (0.93-1.85)	1.11 (0.76-1.61)	1.03 (0.73-1.46)
Duloxetine or lamotrigine									
Denmark	<5	1117	NR	33	14,526	22.72	NR	NR	-
Finland	17	4698	36.19	36	9055	39.76	1.20 (0.67-2.14)	0.80 (0.38-1.68)	-
Norway	8	1411	56.70	20	9573	20.89	2.19 (0.93-5.16)	1.20 (0.45-3.16)	-
Sweden	34	5834	58.28	104	22,538	46.14	1.34 (0.91 - 1.97)	1.16 (0.79-1.70)	-
Meta-analysis	NR	13,060	NR	193	55,691	34.66	1.56 (1.17-2.07)	1.20 (0.89-1.63)	1.12 (0.85-1.48)

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 = Not reportable due to the possibility of estimating a low number of individuals (<5) in other cells. NE = non-estimable due to 0 cases in one or more cells.

Table 12. Country-specific and combined crude and propensity score adjusted hazard ratios of pervasive development disorders incl. ASD in pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Pervasive development disorders incl. ASD	**Cases, n**	**Total person-years**	**Incidence Rate per 10,000 person-years**	**Cases, n**	**Total person-years**	**Incidence Rate per 10,000 person-years**	**Crude Hazard Ratio**	**PS-Adjusted Hazard Ratio**	**MH Adjusted Hazard Ratio**
Unexposed									
Denmark	0	1287	0.00	1072	3,995,490	2.68	NE	NE	-
Finland	6	4724	12.70	3192	4,125,576	7.74	1.96 (0.88-4.36)	1.21 (0.54-2.72)	-
Norway	<5	1523	NE	2510	2,875,364	8.73	NR	NR	-
Sweden	19	6846	27.75	9808	6,905,677	14.20	2.16 (1.38 - 3.39)	0.97 (0.62 - 1.53)	-
Meta-analysis	NR	14,380	NR	16,582	17,902,108	9.26	2.03 (1.38-2.98)	1.00 (0.68-1.47)	0.96 (0.66-1.41)
Lamotrigine									
Denmark	0	1157	0.00	6	7657	7.84	NE	NE	-
Finland	6	4724	12.70	9	5565	16.17	0.95 (0.32-2.78)	0.72 (0.18-2.86)	-
Norway	<5	1462	NE	13	9050	14.36	NR	NR	-
Sweden	19	6418	29.60	30	14622	20.52	1.44 (0.81 - 2.56)	0.70 (0.42 - 1.16)	-
Meta-analysis	NR	13,677	NE	59	39,938	14.77	1.23 (0.75-2.02)	0.67 (0.43-1.10)	0.68 (0.43-1.06)
Duloxetine									
Denmark	0	1184	0.00	<5	4003	NR	NE	NE	-
Finland	6	4724	12.70	7	3583	19.54	0.70 (0.22-2.28)	0.48 (0.13-1.78)	-
Norway	0	1487	0.00	0	536	0.00	NE	NE	-
Sweden	17	6243	27.23	25	8351	29.94	0.97 (0.52 - 1.80)	0.71 (0.39 - 1.27)	-
Meta-analysis	23	13,638	16.86	NR	16,473	NR	0.91 (0.52-1.57)	0.66 (0.39-1.13)	0.62 (0.38-1.03)
Duloxetine or lamotrigine									
Denmark	0	1117	0.00	8	14,537	5.50	NE	NE	-
Finland	6	4724	12.70	16	9076	17.63	0.80 (0.30-2.14)	0.57 (0.17-1.93)	-
Norway	0	1426	0.00	13	9586	13.56	NE	NE	-
Sweden	17	5857	29.03	54	22,621	23.87	1.23 (0.71 - 2.12)	0.83 (0.49 - 1.40)	-
Meta-analysis	23	13,124	17.53	91	55,820	16.30	1.11 (0.69-1.79)	0.78 (0.48-1.27)	0.68 (0.44-1.08)

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 = Not reportable due to the possibility of estimating a low number of individuals (<5) in other cells. NE = non-estimable due to 0 cases in one or more cells.

Table 13. Country-specific and combined crude and propensity score adjusted hazard ratios of intellectual disability (mental retardation) in pregabalin-exposed pregnancies vs. comparators

	Pregabalin			Comparator					
Intellectual disability (mental retardation)	**Cases, n**	**Total person-years**	**Incidence Rate per 10,000 person-years**	**Cases, n**	**Total person-years**	**Incidence Rate per 10,000 person-years**	**Crude Hazard Ratio**	**PS-Adjusted Hazard Ratio**	**MH Adjusted Hazard Ratio**
Unexposed									
Denmark	<5	1280	NR	1601	3,992,697	4.01	NR	NR	-
Finland	35	4653	75.22	25,500	4,049,007	62.98	1.33 (0.95-1.87)	0.95 (0.67-1.34)	-
Norway	7	1507	46.45	4498	2,869,246	15.68	2.90 (1.39-6.08)	1.82 (0.86-3.86)	-
Sweden	20	6840	29.24	12,389	6,890,480	17.98	1.65 (1.06 - 2.55)	0.88 (0.57 - 1.36)	-
Meta-analysis	NR	14,280	NR	43,988	17,801,431	24.71	1.61 (1.26-2.06)	1.03 (0.80-1.32)	1.00 (0.78-1.28)
Lamotrigine									
Denmark	<5	1157	NR	<5	7657	NR	NR	NR	-
Finland	35	4653	75.22	50	5474	91.34	0.87 (0.56-1.36)	0.68 (0.38-1.20)	-
Norway	7	1445	48.44	32	8992	35.59	1.27 (0.56-2.87)	1.28 (0.43-3.86)	-
Sweden	20	6411	31.20	39	14,550	26.80	1.11 (0.65 - 1.90)	1.12 (0.66 - 1.90)	-
Meta-analysis	NR	13,677	NR	NR	39,729	NR	1.05 (0.77-1.43)	0.97 (0.67-1.39)	0.94 (0.70-1.27)
Duloxetine									
Denmark	<5	1176	NR	<5	3993	NR	NR	NR	-
Finland	35	4653	75.22	37	3510	105.41	0.75 (0.47-1.21)	0.86 (0.46-1.61)	-
Norway	6	1471	40.79	<5	523	NR	NR	NR	-
Sweden	18	6232	28.88	26	8343	31.16	0.94 (0.52 - 1.73)	0.72 (0.41 - 1.28)	-
Meta-analysis	NR	13,532	NR	70	16,369	42.76	0.82 (0.58-1.17)	0.84 (0.57-1.25)	0.82 (0.58-1.17)
Duloxetine or lamotrigine									
Denmark	<5	1109	NR	7	14,539	4.81	NR	NR	-
Finland	35	4653	75.22	86	8913	96.49	0.82 (0.55-1.23)	0.88 (0.55-1.41)	-
Norway	6	1409	42.58	36	9515	37.83	1.06 (0.45-2.49)	1.05 (0.36-3.07)	-
Sweden	18	5846	30.79	62	22,551	27.49	1.09 (0.65 - 1.85)	1.14 (0.67 - 1.91)	-
Meta-analysis	NR	13,017	NR	191	55,518	34.40	0.97 (0.72-1.30)	1.04 (0.75-1.44)	1.02 (0.76-1.38)

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 = Not reportable due to the possibility of estimating a low number of individuals (<5) in other cells.

10.5. Other analyses

10.5.1. Sensitivity analyses

In the sensitivity analyses defining pregabalin monotherapy as excluding SSRIs and benzodiazepines in addition to AEDs, we observed relative risk estimates in all countries with a meta-analysis crude and aPR of all major malformations compared to unexposed of 1.44 95% CI (1.17–1.78) and 1.13 95% CI (0.97–1.33) respectively. For the analysis of monotherapy not excluding SSRIs and benzodiazepine, the crude PR of the meta-analysis was 1.31 (1.10–1.55); the aPR was not estimated due to low (<5) cell counts (Supplementary malformation tables, Tables 5 and 6).

An additional sensitivity analysis including the 2nd trimester induced abortions in the analyses of pregnancies (available in Denmark, Finland, and Norway) produced similar or slightly higher estimates as in the tables not including the 2nd trimester induced abortions. However, the inclusion of the 2nd trimester induced abortions added only 1-3% extra pregabalin-exposed pregnancies (data not shown due to restrictions on displaying tables with low (<5) cell counts).

Post-hoc meta-analyses results based on the MH method for meta-analysis, which allowed cells with 0 counts to be included, is presented in Table 4 - Table 13 (and also in Supplementary forest plots Mantel-Haenszel meta-analyses malformations, Figures 50.1- Supplementary forest plots Mantel-Haenszel meta-analyses birth outcomes and postnatal outcomes Figure 81.2). Regarding specific malformations, the only noticeable elevated PR in the comparison of pregabalin with unexposed was eye malformations with aPR (95% CI) of 1.88 (1.01–3.49) (Supplementary forest plots Mantel-Haenszel meta-analyses malformations, Figure 50.2). For pregabalin vs. lamotrigine-exposed, the MH estimates showed for malformations of the nervous system an aPR (95% CI) of 3.22 (0.86–12.1), urinary 2.53 (1.09–5.88) and genital organs 1.94 (0.97–3.89) (Supplementary forest plots Mantel-Haenszel meta-analyses malformations, Figure 53.2). For pregabalin vs. duloxetine, aPRs for urinary and genital malformations was 2.05 (0.86–4.88) and 2.69 (1.09–6.64), respectively (Supplementary forest plots Mantel-Haenszel meta-analyses malformations, Figure 56.2) and for pregabalin vs. lamotrigine or duloxetine genital malformations showed aPR of 2.03 (1.06–3.88) (Supplementary forest plots Mantel-Haenszel meta-analyses malformations, Figure 60.2).

The PR of stillbirths for pregabalin-exposed compared to unexposed was 1.72 (1.02–2.91) in the traditional meta-analysis and 1.25 (0.74–2.11) in the MH meta-analysis. The stillbirth aPR in relation to the active comparator was for lamotrigine 1.87 (0.81–4.32) in the traditional meta-analysis and 1.30 (0.69–2.47) in the MH meta-analysis. Similarly, for the duloxetine comparator: 1.46 (0.57–3.72) in the traditional analysis and 1.00 (0.39–2.54) in the MH meta-analysis and for lamotrigine or duloxetine 2.71 (1.25–5.90) in the traditional meta-analysis and 1.92 (0.98–3.78) in the MH meta-analysis.

Post-hoc analysis of eye malformations in Sweden

To investigate further the observed increased risk of eye malformations in Sweden, the analysis was repeated with different follow-up times. The aPR (95% CI) of eye malformations up to 1 year of follow-up was 2.71 (1.22–6.02). Up to 2 years of follow-up the estimate was 1.12 (0.53–2.34), up to 3 years 1.13 (0.56–2.25), up to 4 years 1.09 (0.55–2.18), and up to 5 years 1.19 (0.62–2.28).

10.6. 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 total proportion of pregabalin users in a pregnancy ending in a live birth or stillbirth in the study period (2005-2015 for Denmark, Finland, and Norway, and 2006-2016 for Sweden) was 0.048% in Denmark, 0.16% in Finland, 0.046% in Norway, and 0.11% in Sweden. The main results of the present study suggested no elevated risk [1.13 (0.97–1.33)] of major congenital malformations among live or stillborn offspring of women exposed to pregabalin in pregnancy compared to offspring unexposed to any AED. Elevated aPRs were observed when pregabalin exposed offspring were compared to lamotrigine [1.36 (1.07–1.72)], duloxetine [1.37 (1.06–1.77)], or the two combined [1.24 (1.00–1.54)]. Estimates on specific malformations were imprecise due to the low number of events, but suggested that eye malformations may be more prevalent in pregabalin-exposed offspring compared with unexposed [aPR 2.09 (1.12–3.90)], and urinary and genital malformations may be more prevalent in pregabalin-exposed births compared with active comparators [pregabalin vs.: lamotrigine, aPR 2.13 (1.05–4.32); duloxetine, aPR 2.64 (1.13–6.17); lamotrigine or duloxetine aPR 2.26 (1.17–4.38)]. In post-hoc analyses to further investigate the observed increased risk of eye malformations in Sweden, the analysis was repeated with different follow-up times. The aPR (95% CI) of eye malformations up to 1 year of follow-up was 2.71 (1.22–6.02), up to 2 years of follow-up the estimate was 1.12 (0.53–2.34), up to 3 years 1.13 (0.56–2.25), up to 4 years 1.09 (0.55–2.18), and up to 5 years 1.19 (0.62–2.28). The estimates for all outcomes were similar for any first-trimester exposure and when restricted to monotherapy in comparison with the polytherapy estimates.

In the meta-analyses results of the other birth outcomes, we observed aPRs and (95% CI) for low birth weight, preterm birth, SGA, low Apgar score at 5 minutes, and microcephaly for pregabalin-exposed compared to unexposed of 1.05 (0.91–1.21), 1.13 (0.99–1.29), 1.21 (1.01–1.44), 1.18 (0.95–1.48), and 1.09 (0.88–1.36) respectively, but with estimates closer to null effect for comparison to the active comparators. Although the prevalence of SGA was slightly elevated in the pregabalin-exposed compared to offspring unexposed to AEDs, it was not elevated in comparison with the active comparators. Higher aPRs of stillbirth were

observed in pregabalin-exposed compared to two comparator groups: compared to unexposed to AEDs, 1.72 (1.02–2.91); compared to lamotrigine and duloxetine group, 2.71 (1.25–5.90). In the post-hoc meta-analysis including countries with zero events, stillbirth was no longer associated with pregabalin exposure.

For the postnatal neurodevelopmental outcomes, the risk of ADHD was marginally elevated in pregabalin-exposed offspring compared to unexposed to AEDs [1.32 (1.04–1.67)], but no association was observed when compared with active comparators [1.09 (0.79–1.52) compared with lamotrigine, 1.11 (0.76–1.61) compared with duloxetine, and 1.20 (0.89–1.63) compared with lamotrigine or duloxetine]. No difference in the risk of ASD and ID was observed in pregabalin-exposed offspring compared to unexposed to AEDs, lamotrigine, and duloxetine.

Our results on major congenital malformations are in line with the previous largest and best designed study related to this topic from Patorno et al [6] who found a relative risk (95% CI) of 1.33 (0.83–2.15) of major congenital malformations for first-trimester exposure to pregabalin compared to unexposed to AEDs and 1.02 (0.69–1.51) for pregabalin monotherapy compared with unexposed to AEDs, which is similar to our aPR (95% CI) of 1.13 (0.97–1.33) for any first-trimester pregabalin exposure and 1.14 (0.96–1.35) for pregabalin monotherapy compared with unexposed. However, our study showed a marginally elevated risk of any major malformations in pregabalin exposed offspring, when compared to lamotrigine or duloxetine of 1.24 95% CI (1.00–1.54). The study by Patorno et al [6] did not compare pregabalin-exposed offspring with active comparators. A study by Cohen et al found that pregabalin monotherapy compared with lamotrigine monotherapy conferred a RR (95% CI) of 1.2 (0.9–1.7) for major malformations,[8] which is similar to the aPR of 1.29 (1.01–1.65) for pregabalin monotherapy vs. lamotrigine monotherapy in first trimester in the present report.

Results from birth outcomes (preterm birth and SGA) in pregabalin-exposed compared to lamotrigine-exposed pregnancies have recently been reported in a Swedish study.[10] Pregabalin-exposed infants were born, on average, 1.1 days before [-1.1 (-3.0 to 0.8)]; were 0.1 SDs lighter [-0.1 (-0.3 to 0.0)]; and had the same head circumference as lamotrigine-exposed infants. In our MH meta-analysis, we observed adjusted prevalence ratios of preterm birth [0.99 (0.85–1.140], SGA [1.22 (0.99–1.50)], and microcephaly [1.05 (0.80–1.38)] for pregabalin-exposed pregnancies compared to lamotrigine. Microcephaly was 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 study population as the reference standard.

Neurologic morbidity after prenatal pregabalin exposure has not been studied previously, but among other AEDs tested previously, valproate, most notably, has been associated with increased risk of ADHD and decreased learning and memory function.[61 62]

Animal studies on developmental toxicity after fetal exposure to pregabalin are not consistent, with one study reporting no teratogenic effect in rats or rabbits even at high doses,[63] whereas another study found teratogenic events in rats even at therapeutic doses.[64]

11.2. Limitations

Population-based healthcare registries in Nordic countries are an optimal setting for examining the safety of medicines in pregnancy. Their most important strengths are capture of all births and, in some cases, clinically relevant birth and postnatal outcomes; routine capture of dispensings of prescription medications to pregnant women; extensive information about maternal and offspring health outcomes; and exact linkage between the maternal and the offspring record. Thus, unlike studies based on data from TIS, for example, there is no bias by self-referral, recall, or access to health care. Dispensings of medicines, represent a better proxy of actual drug intake than issued prescriptions, thus reducing misclassification of the actual drug intake.

The meta-analyses of several of the specific congenital malformations, stillbirth, and some of the postnatal outcomes were limited by zero or small number of cases for several of the outcomes in the pregabalin and active comparator groups. Especially the duloxetine comparator was limited by low number of exposed. Traditional meta-analysis methods cannot include an estimate from a study with zero events and therefore the estimates would be inflated by excluding these. Due to the low number of events, low precision of the estimates was observed, and the results should be interpreted with caution as unstable or even inflated when countries with zero events are excluded from the meta-analyses. The post-hoc MH meta-analysis allowing countries with zero events in the exposed groups confirmed these concerns producing attenuated results of outcomes with zero cases in one or more country, and conclusions should be based on the post-hoc MH meta-analysis.

The post-hoc analysis on eye malformations in Sweden indicated that surveillance bias may be occurring, where children exposed to pregabalin in utero may have more medical checkups than unexposed children, which will manifest itself by an earlier diagnosis of eye malformations and possibly also other outcomes.

Selection bias due to lack of data on all pregnancy outcomes in all countries cannot be ruled out.

Residual confounding, especially confounding by indication may not be fully accounted for by the applied methods as indication is not available from the data sources. Also, the pregabalin-exposed women may differ considerably from not only the unexposed but also the active comparators and residual confounding due to uneven underreporting of confounders in pregabalin or comparator groups may have influenced the results.

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 spectrum as they have resulted in a hospital contact.

11.3. Interpretation

The results of this study do not provide strong evidence of human teratogenicity, or effects on birth outcomes and postnatal neurodevelopmental outcomes after pregabalin exposure. However, in line with previous studies, a small increased risk of adverse birth outcomes in the pregabalin exposed group compared with unexposed or active comparator groups cannot be completely ruled out, and the associated estimates remain imprecise despite inclusion of data from four countries. Of note, prevalence of smoking during pregnancy, a known risk factor associated with adverse birth outcomes,[65] and included in the PS-adjusted models, was 28–40% of the pregabalin-exposed births and 6–15% in AED-unexposed births. Regarding the criteria for proof of teratogenicity mentioned by Shepard,[66] the present available information on pregabalin exposure lacks sufficient number of exposed cases and even though detailed PS-adjusted estimates have been provided, residual confounding cannot be excluded since this was an observational study. Also, we observed no maximum upper CI in the MH meta-analyses greater than 1.76 (excluding specific malformations and stillbirths with imprecise estimates due to low number of cases).

11.4. Generalisability

The study was a nationwide study in Denmark, Finland, Norway, and Sweden covering a 10-year period after introduction of pregabalin to the market. In the Nordic countries, >90 % of the population is Caucasian, and thus the available data on other racial 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

The present study is consistent with the earlier evidence from published population-based studies of an absence of substantially increased risks of congenital malformations, adverse birth outcomes, or postnatal neurodevelopment in pregabalin-exposed fetuses in identifiable pregnancies. Several estimates in this study were imprecise due to the low number of events and the results should be interpreted with caution.

14. REFERENCES

1. European Medicines Agency. Lyrica (pregabalin) product information. 2017 [Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/medicines/000546/human_med_000894.jsp&mid=WC0b01ac058001d124 accessed 5 January 2018.
2. Hurault-Delarue C, Morris JK, Charlton R, et al. Prescription of antiepileptic medicines including valproate in pregnant women: A study in three European countries. *Pharmacoepidemiology and drug safety* 2019;28(11):1510-18. doi: 10.1002/pds.4897 [published Online First: 2019/09/14]
3. Daugaard CA, Sun Y, Dreier JW, et al. Use of antiepileptic drugs in women of fertile age. *Danish medical journal* 2019;66(8) [published Online First: 2019/07/19]
4. Asomaning K, Abramsky S, Liu Q, et al. Pregabalin prescriptions in the United Kingdom: a drug utilisation study of The Health Improvement Network (THIN) primary care database. *Int J Clin Pract* 2016;70(5):380-8. doi: 10.1111/ijcp.12791 [published Online First: 2016/03/31]
5. Wettermark B, Brandt L, Kieler H, et al. Pregabalin is increasingly prescribed for neuropathic pain, generalised anxiety disorder and epilepsy but many patients discontinue treatment. *Int J Clin Pract* 2014;68(1):104-10. doi: 10.1111/ijcp.12182 [published Online First: 2013/07/03]
6. 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]
7. Winterfeld U, Merlob P, Baud D, et al. Pregnancy outcome following maternal exposure to pregabalin may call for concern. *Neurology* 2016;86(24):2251-7. doi: 10.1212/WNL.0000000000002767 [published Online First: 2016/05/20]
8. Cohen JML, M.K.; Alvestad, S ;, Bjørk MHC, C.E. ; Einarsdóttir, K.;, Engeland AG, M; Hálfdánarson, O;, et al. Comparative Safety of Antiepileptic Drugs and Risk of Major Congenital Malformations. ICPE 2019. Philedelphia: Wiley, 2019.
9. Blotiere PO, Raguideau F, Weill A, et al. Risks of 23 specific malformations associated with prenatal exposure to 10 antiepileptic drugs. *Neurology* 2019;93(2):e167-e80. doi: 10.1212/wnl.0000000000007696 [published Online First: 2019/06/14]
10. 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]
11. 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. *Journal of neurology, neurosurgery, and psychiatry* 2018;89(2):223-24. doi: 10.1136/jnnp-2017-316143 [published Online First: 2017/07/19]
12. Charlton R, Garne E, Wang H, et al. Antiepileptic drug prescribing before, during and after pregnancy: a study in seven European regions. *Pharmacoepidemiology and drug safety* 2015;24(11):1144-54. doi: 10.1002/pds.3847 [published Online First: 2015/08/15]
13. (EMA) EMA. Lamictal [Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/human/referrals/Lamictal/human_referral_000037.jsp accessed 12 November 2017.

14. Dolk H, Wang H, Loane M, et al. Lamotrigine use in pregnancy and risk of orofacial cleft and other congenital anomalies. *Neurology* 2016;86(18):1716-25. doi: 10.1212/WNL.0000000000002540 [published Online First: 2016/04/08]
15. (EMA) EMA. Duloxetine [Available from: http://www.ema.europa.eu/ema/index.jsp?curl=pages/medicines/landing/epar_search.jsp&mid=WC0b01ac058001d124&source=homeMedSearch&keyword=duloxetine&category=human&isNewQuery=true accessed 12 December 2018.
16. Lassen D, Ennis ZN, Damkier P. First-Trimester Pregnancy Exposure to Venlafaxine or Duloxetine and Risk of Major Congenital Malformations: A Systematic Review. *Basic Clin Pharmacol Toxicol* 2016;118(1):32-6. doi: 10.1111/bcpt.12497 [published Online First: 2015/10/06]
17. Andrade C. The safety of duloxetine during pregnancy and lactation. *J Clin Psychiatry* 2014;75(12):e1423-7. doi: 10.4088/JCP.14f09631 [published Online First: 2015/01/01]
18. Hoog SL, Cheng Y, Elpers J, et al. Duloxetine and pregnancy outcomes: safety surveillance findings. *Int J Med Sci* 2013;10(4):413-9. doi: 10.7150/ijms.5213 [published Online First: 2013/03/09]
19. 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
20. Wilcox AJ. Fertility and pregnancy: an epidemiologic perspective. New York, NY: Oxford University Press 2010.
21. Savitz DA, Hertz-Picciotto I, Poole C, et al. Epidemiologic measures of the course and outcome of pregnancy. *Epidemiol Rev* 2002;24(2):91-101.
22. Svensson E, Ehrenstein V, Norgaard M, et al. Estimating the proportion of all observed birth defects occurring in pregnancies terminated by a second-trimester abortion. *Epidemiology* 2014;25(6):866-71. doi: 10.1097/EDE.0000000000000163 [published Online First: 2014/08/29]
23. European Surveillance of Congenital Anomalies EUROCAT Guide 1.4, Section 3.3 EUROCAT Subgroups of Congenital Anomalies (Version 2014) 2014 [Available from: http://www.eurocat-network.eu/content/EUROCAT-Guide-1.4-Section-3.3.pdf accessed 16 July 2017.
24. 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]
25. 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
26. 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.
27. 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.

28. Johansson LA, Westerling R. Comparing Swedish hospital discharge records with death certificates: implications for mortality statistics. *Int J Epidemiol* 2000;29(3):495-502.
29. 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.
30. 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.
31. 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
32. 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
33. 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
34. 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
35. 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]
36. Artama M, Gissler M, Malm H, et al. Nationwide register-based surveillance system on drugs and pregnancy in Finland 1996-2006. *Pharmacoepidemiology and drug safety* 2011;20(7):729-38. doi: 10.1002/pds.2159 [published Online First: 2011/06/01]
37. 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]
38. Gissler M, Ulander VM, Hemminki E, et al. Declining induced abortion rate in Finland: data quality of the Finnish abortion register. *International journal of epidemiology* 1996;25(2):376-80. [published Online First: 1996/04/01]
39. Gissler M, Shelley J. Quality of data on subsequent events in a routine Medical Birth Register. *Medical informatics and the Internet in medicine* 2002;27(1):33-8. doi: 10.1080/14639230110119234 [published Online First: 2003/01/02]
40. Langhoff-Roos J, Krebs L, Klungsoyr K, et al. The Nordic medical birth registers--a potential goldmine for clinical research. *Acta obstetricia et gynecologica Scandinavica* 2014;93(2):132-7. doi: 10.1111/aogs.12302 [published Online First: 2013/11/19]
41. Teperi J. Multi method approach to the assessment of data quality in the Finnish Medical Birth Registry. *Journal of epidemiology and community health* 1993;47(3):242-7. [published Online First: 1993/06/01]
42. 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.

43. 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
44. 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
45. Schmidt M, Pedersen L, Sorensen HT. The Danish Civil Registration System as a tool in epidemiology. *European journal of epidemiology* 2014;29(8):541-9. doi: 10.1007/s10654-014-9930-3 [published Online First: 2014/06/27]
46. 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]
47. 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]
48. Schmidt M, Schmidt SA, Sandegaard JL, et al. The Danish National Patient Registry: a review of content, data quality, and research potential. *Clinical epidemiology* 2015;7:449-90. doi: 10.2147/clep.S91125 [published Online First: 2015/11/26]
49. 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
50. 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]
51. Socialstyrelsenregister. The National Patient Register of Sweden. [Available from: https://www.socialstyrelsen.se/en/statistics-and-data/registers/register-information/the-national-patient-register/
52. 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]
53. https://helsedirektoratet.no/english/norwegian-patient-register.
54. Cnattingius S, Ericson A, Gunnarskog J, et al. A quality study of a medical birth registry. *Scandinavian journal of social medicine* 1990;18(2):143-8. doi: 10.1177/140349489001800209 [published Online First: 1990/06/01]
55. Brooke HL, Talback M, Hornblad J, et al. The Swedish cause of death register. *European journal of epidemiology* 2017;32(9):765-73. doi: 10.1007/s10654-017-0316-1 [published Online First: 2017/10/07]
56. Viale L, Allotey J, Cheong-See F, et al. Epilepsy in pregnancy and reproductive outcomes: a systematic review and meta-analysis. *Lancet (London, England)* 2015;386(10006):1845-52. doi: 10.1016/s0140-6736(15)00045-8 [published Online First: 2015/09/01]
57. 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

58. 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]
59. Williamson E, Morley R, Lucas A, et al. Propensity scores: from naive enthusiasm to intuitive understanding. *Stat Methods Med Res* 2012;21(3):273-93. doi: 10.1177/0962280210394483
60. Ludvigsson JF, Håberg 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
61. Cohen MJ, Meador KJ, May R, et al. Fetal antiepileptic drug exposure and learning and memory functioning at 6years of age: The NEAD prospective observational study. *Epilepsy & behavior : E&B* 2019;92:154-64. doi: 10.1016/j.yebeh.2018.12.031 [published Online First: 2019/01/21]
62. Christensen J, Pedersen L, Sun Y, et al. Association of Prenatal Exposure to Valproate and Other Antiepileptic Drugs With Risk for Attention-Deficit/Hyperactivity Disorder in Offspring. *JAMA network open* 2019;2(1):e186606. doi: 10.1001/jamanetworkopen.2018.6606 [published Online First: 2019/01/16]
63. Morse DC. Embryo-Fetal Developmental Toxicity Studies with Pregabalin in Mice and Rabbits. *Birth defects research Part B, Developmental and reproductive toxicology* 2016;107(2):85-93. doi: 10.1002/bdrb.21174 [published Online First: 2016/04/05]
64. Singh KP, Gupta K. Teratogenic Effects of Third-Generation Antiepileptic Drug, Pregabalin: An In vivo Study. *Current drug safety* 2018;13(2):113-21. doi: 10.2174/1574886313666180402145645 [published Online First: 2018/04/03]
65. https://www.cdc.gov/tobacco/basic_information/health_effects/pregnancy/index.htm. Accessed on 09 May 2020.
66. Shepard TH. "Proof" of human teratogenicity. *Teratology* 1994;50(2):97-8. doi: 10.1002/tera.1420500202 [published Online First: 1994/08/01]

15. LIST OF SOURCE TABLES AND FIGURES

TABLES

Table 1. Outcome-specific study population and follow-up for the primary analyses, secondary analyses, and sensitivity analyses

Table 2. National registries in Denmark, Finland, Norway, and Sweden and type of data available from each registry

Table 3. Estimated study population size before study start and actual numbers of pregnancies ending in live birth or stillbirth according to exposure categorization

Table 4. Country-specific and combined crude and propensity score adjusted prevalence ratios of any major malformations in first-trimester pregabalin-exposed pregnancies vs. comparators

Table 5. Country-specific and combined crude and propensity score adjusted prevalence ratios of stillbirth in pregabalin-exposed pregnancies vs. comparators

Table 6. Country-specific and combined crude and propensity score adjusted prevalence ratios of low birth weight in pregabalin-exposed pregnancies vs. comparators

Table 7. Country-specific and combined crude and propensity score adjusted prevalence ratios of preterm birth in pregabalin-exposed pregnancies vs. comparators

Table 8. Country-specific and combined crude and propensity score adjusted prevalence ratios of small for gestational age in pregabalin-exposed pregnancies vs. comparators

Table 9. Country-specific and combined crude and propensity score adjusted prevalence ratios of low Apgar score in pregabalin-exposed pregnancies vs. comparators

Table 10. Country-specific and combined crude and propensity score adjusted prevalence ratios of microcephaly in pregabalin-exposed pregnancies vs. comparators

Table 11. Country-specific and combined crude and propensity score adjusted hazard ratios of hyperkinetic disorders incl. ADHD in pregabalin-exposed pregnancies vs. comparators

Table 12. Country-specific and combined crude and propensity score adjusted hazard ratios of pervasive development disorders incl. ASD in pregabalin-exposed pregnancies vs. comparators

Table 13. Country-specific and combined crude and propensity score adjusted hazard ratios of intellectual disability (mental retardation) in pregabalin-exposed pregnancies vs. comparators

FIGURES

Figure 1. Identification of the study population, Denmark

Figure 2. Identification of the study population, Finland

Figure 3. Identification of the study population, Norway

Figure 4. Identification of the study population, Sweden

16. APPENDICES

16.1. Appendix 1. Supplementary tables

16.1.1. Supplementary descriptive tables

16.1.2. Supplementary malformation tables

16.1.3. Supplementary birth outcomes and postnatal outcomes tables

16.2. Appendix 2. Supplementary figures

16.2.1. Supplementary descriptive figures

16.2.2. Supplementary forest plots Mantel-Haenszel meta-analyses malformations

16.2.3. Supplementary forest plots Mantel-Haenszel meta-analyses birth outcomes and postnatal outcomes

16.3. Appendix 3. Protocol

Protocol

16.4. Appendix 4. Codes used to identify study variables

Codes used to identify study variables