Valproate EU consortium

A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring – a population-based retrospective study

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Prepared For:
Valproate marketing authorisation holders being part of study consortium

Report Approval and Sign-off

I confirm that I have read the contents of this Report and its attachments. I approve the Report in its current form.

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PASS information

Title	A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring – a population-based retrospective study
Version identifier of the final study protocol	Version 6.0
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EU PAS register number	EUPAS34201
Active substance	Antiepileptic drugs (AEDs) including valproate ATC WHO code: N03A
Medicinal product	Antiepileptic drugs (AEDs) including valproate
Product reference	EMEA/H/A-31/1454
Marketing authorisation holder(s)	The joint initiative involves several companies via a consortium: *APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; BIOGARAN; BIOMO PHARMA GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA LIMITED; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZIHEXAL AG; LUPIN HEALTHCARE LIMITED;MYLAN BVBA/SPRL: BE; VIATRIS SANTE (LYON): FR; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; PHARMASWISS ČESKÁ REPUBLIKA S.R.O.; SANOFI AVENTIS GROUP; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE and; WOCKHARDT UK LIMITED*
Joint PASS	YES
Research question and objectives	**Overall aim** The aim of this retrospective cohort study is to assess the risk of neurodevelopmental disorders (NDD), including autism spectrum disorder (ASD), as well as congenital malformation (CM) in offspring from fathers exposed to valproate monotherapy at the time of conception, compared to offspring from fathers exposed to lamotrigine or levetiracetam monotherapy, at the time of conception. The comparative group of fathers exposed to lamotrigine or levetiracetam has been chosen because those treatments are considered associated with the lowest risk of teratogenicity for their offspring in women but it is unknown whether the effect is the same in men. **Primary objective** 1. To investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment (composite monotherapy) at the time of conception. **Secondary objectives**

	2. To investigate the risk of CM in live and non-live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment (composite monotherapy) at the time of conception, in Norway and Denmark. 3. To describe AED exposure (posology and duration) data and health characteristics of male patients prescribed AEDs (including valproate and lamotrigine/levetiracetam) in treatment of epilepsy and other indications at the time of conception of their offspring, both for NDD and CM cohort. 4. To identify potentially important risk factors for outcomes of interest, in offspring paternally exposed to valproate (monotherapy) or lamotrigine/levetiracetam (composite monotherapy) at the time of conception, by examining AED exposure and health characteristics of the offspring and their mothers. **Exploratory objectives** 5. To describe the putative risk factors and frequency of NDD, including ASD, as well as CM in offspring paternally exposed to valproate (in combination with other AEDs, excluding lamotrigine/levetoracetam) and those exposed to lamotrigine/levetiracetam (in combination with other AEDs, excluding valproate) at the time of conception. 6. To describe the risk factors and frequency of NDD, including ASD, as well as CM in paternally and maternally matched exposure-discordant (valproate vs. lamotrigine/levetiracetam monotherapy) siblings at conception. 7. To investigate the risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment (composite monotherapy) at the time of conception in Sweden. 8. To describe the frequency of CM by target body system organ class in live and non-live offspring paternally exposed to valproate (monotherapy), and to lamotrigine/levetiracetam treatment (composite monotherapy) at the time of conception.
Country(-ies) of study	The study is conducted in Denmark, Sweden, and Norway.
Authors	[redacted] On behalf of IQVIA and the Consortium

Marketing authorisation holder(s)

Marketing authorisation holder(s)	APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; BIOGARAN; BIOMO PHARMA GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA LIMITED; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG; LUPIN HEALTHCARE LIMITED; *MYLAN BVBA/SPRL : BE; VIATRIS SANTE (LYON) : FR* ; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; PHARMASWISS CESKA REPUBLIKA S.R.O.; SANOFI AVENTIS GROUP; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROP and; WOCKHARDT UK LIMITED
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1. List of Abbreviations

Table 1 List of abbreviations

Abbreviation	Definition
ADHD	Attention Deficit Hyperactivity Disorder
AED	Antiepileptic Drug
ASD	Autism Spectrum Disorders
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CM	Congenital Malformations
CMV	Cytomegalovirus
CRS	Danish Civil Registration System
CSR	Clinical Study Report
DDD	Defined Daily Dose
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EU	European Union
HR	Hazard Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IQR	Interquartile Range
IVF	In vitro fertilisation
LMP2	Last Menstrual Period Date Plus 2 weeks
MAH	Marketing Authorisation Holders
Max	Maximum
Min	Minimum
NDD	Neurodevelopmental Disorders
OR	Odds ratio
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity Score
PY	Person-Years
RR	Risk ratio
SD	Standard Deviation
SSRI	Selective Serotonin Reuptake Inhibitors
WHO	World Health Organisation

2. Abstract

This abstract in the clinical study report (CSR) provides a comprehensive overview of the full study, covering both the content of the present CSR v1.1 AND the addendum. This same abstract is also available as standalone document.

Title

A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring – a population-based retrospective study

Version 1.1, 20 March 2023

Keywords

Valproate; paternal exposure; neurodevelopmental disorders; congenital malformations; post-authorisation safety study

Rationale and Background

Valproate-containing medicines are approved and marketed in more than 120 countries worldwide, and in the European Union for epilepsy and for bipolar disorders in case of contraindication or intolerance to lithium. In recent years, due to an increased risk of neurodevelopmental disorders (NDD), including autism spectrum disorders (ASD), and congenital malformations (CM) in offspring after valproate exposure in utero, the use of valproate has been restricted to cases in which no other effective or tolerated treatment is available in women of childbearing potential suffering from epilepsy or bipolar disorder or in pregnant women suffering from epilepsy; it has been contraindicated in pregnant women suffering from bipolar disorder. There is currently scarce real-world evidence of an increased risk of NDD including ASD, or CM in offspring following paternal exposure to antiepileptic drugs (AEDs) at the time of conception. Following the Pharmacovigilance Risk Assessment Committee request dated 8 February 2018, a post-authorisation safety study was conducted aiming to evaluate the association between paternal exposure to valproate at the time of conception and risk of NDD, including ASD, and CM in offspring, in comparison to paternal exposure to lamotrigine or levetiracetam at the time of conception.

Research Questions and Objectives

The aim of this retrospective cohort study was to examine the association between paternal exposure to valproate at conception and the risk of NDD, including ASD, and CM in offspring, from data in Denmark, Sweden, and Norway. Paternal exposure to valproate was compared to paternal exposure to lamotrigine/levetiracetam at the time of conception.

The primary objective was:

1. To investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam (composite monotherapy) treatment at the time of conception.

The secondary objectives were:

2. To investigate the risk of CM in live and non-live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam (composite monotherapy) treatment at the time of conception, in Denmark and Norway.
3. To describe AED exposure (posology and duration) data and health characteristics of male patients prescribed AEDs (including valproate and lamotrigine/levetiracetam) in treatment of epilepsy and other indications at the time of conception of their offspring, for NDD and CM cohort.
4. To identify potentially important risk factors for outcomes of interest, in offspring paternally exposed to valproate (monotherapy) or lamotrigine/levetiracetam (composite monotherapy) at the time of conception, by examining AED exposure and health characteristics of the offspring and their mothers.

The exploratory objectives were:

5. To describe the putative risk factors and frequency of NDD, including ASD, as well as CM in offspring paternally exposed to valproate in combination with other AEDs, excluding lamotrigine/levetiracetam, and to lamotrigine/levetiracetam in combination with other AEDs, excluding valproate, at the time of conception.
6. To describe the risk factors and frequency of NDD, including ASD, as well as CM in paternally and maternally matched exposure-discordant (valproate vs. lamotrigine/levetiracetam monotherapy) siblings at conception.
7. To investigate the risk of CM live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam (composite monotherapy) treatment at the time of conception in Sweden.
8. To describe the frequency of CM by target body system organ class in live and non-live offspring paternally exposed to valproate (monotherapy), and to lamotrigine/levetiracetam treatment (composite monotherapy) at the time of conception.

Besides the main and exploratory analyses listed above, several sensitivity analyses were performed, to assess the robustness of the methodology considered and allow a better understanding of the results. Among those, only three are presented in this abstract, which consisted in repeating the statistical analysis for the primary objective and secondary objective 2: sensitivity analysis 2 restricted outcome of interest to ASD specifically, ignoring all other NDD diagnoses; sensitivity analysis 10 investigated the risk of outcome associated with exposure using a continuous measure of cumulative exposure to treatment; and sensitivity analysis 11 used a narrower definition of NDD as outcome of interest.

Study Design

This was a multi-country, population-based, retrospective cohort study using data from national registries in Denmark, Sweden, and Norway. A cohort of offspring paternally exposed to valproate was compared to a cohort of offspring paternally exposed to lamotrigine/levetiracetam, at the time of conception, to investigate the risk of NDD, including ASD, as the primary outcome of interest and the risk of CM (as a composite of major and/or minor CM) as a secondary outcome.

Setting

The study period began on 1st January 1997 (1st April 2004 or the secondary outcome) in Denmark, 1st January 2007 in Sweden and 1st January 2006 in Norway, and, based on the availability of information from national registries. The study time period ended on 31st December 2018 for Denmark and 31st December 2019 for both Sweden and Norway.

Subjects and Study Size

Pregnancies were included if they met all the following inclusion criteria:

- Singleton pregnancies, with known pregnancy-length of at least 12 weeks within the study time period
- Pregnancies linked to both mother and father within the study time period
- Father with a continuous enrolment in the database for ≥12 months prior to linked mother at the date of the last menstrual period plus 2 weeks (LMP2)
- Father with at least one AED in the data available

Pregnancies were excluded if they met any of the following exclusion criteria:

- Adopted children
- Pregnancy associated with in vitro fertilisation
- Pregnancies with missing gestational age and/or missing maternal LMP2 (for these pregnancies it will not be possible to identify the exposure window for the study)
- Different cohorts were constructed for analysis with further inclusion/exclusion criteria to address the research questions related to the primary (NDD including ASD), and secondary (CM) outcomes

For the primary outcome, NDD including ASD, to observe a hazard ratio (HR) of 2.00 with 5% significance and 80% power, a sample size of 1178 offspring within the family linked unit was needed across all 3 countries. This required a minimum of 589 offspring within a family linked unit with paternal exposure to valproate (monotherapy) and a minimum of 589 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (composite monotherapy).

For the secondary outcome, CM, assuming to observe an odds ratio (OR) of 2.5 with 5% significance and 80% power, sample size of 826 offspring within the family linked unit was needed across all 3 countries. This required a minimum of 413 offspring within a family linked unit with paternal exposure to valproate (monotherapy) and a minimum of 413 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (composite monotherapy).

Variables and Data Sources

The primary outcome of interest was NDD, including ASD, and the secondary outcome of interest was a composite of CM (major and/or minor), in offspring up to 12 years of age for both outcomes, based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnostic codes.

The primary exposure of interest was paternal use of valproate during the spermatogenic risk window prior to conception of the offspring (defined by the first day of the LMP2 date of the mother within the linked family unit). Exposure information was derived from prescription data, as recorded in the National Prescription Registries for each country (from 1995 in Denmark, 2005 in Sweden and 2004 in Norway). Country-specific cohorts of eligible linked family units were then identified.

The data sources used to retrieve this information were national registries in Denmark, Sweden and Norway:

- Denmark: Danish civil registration system, Register of medicinal product statistics, National patient registry, Cause of death register, Medical birth registry, The in vitro fertilisation register
- Sweden: Multigenerational register, Cause of death register, National prescription registry, National patient registry, Medical birth registry
- Norway: Central person register, Norwegian prescription database, Norwegian patient registry, Medical birth registry, Cause of death register

Results

Primary outcome, NDD including ASD.

Primary outcome, descriptive results

The Primary outcome cohort for descriptive analyses included 2031 offspring (respectively, 832 and 1199 paternally exposed to valproate and to lamotrigine/levetiracetam) in Denmark, 2451 (respectively, 968 and 1483) in Sweden, and 2019 (respectively, 640 and 1379) in Norway.

Offspring characteristics were similar in Denmark, Sweden, and Norway: mostly male (52.2%, 51.2%, and 52.2%, respectively), born at term between 37-41 weeks of gestational age (89.6%, 88.5% and 89.5%, respectively), and weighted ≥2500 grams at birth (96.5%, 96.3%, and 96.6%, respectively); similar in both exposure group. Year of birth was unbalanced between the two paternal exposure groups. Consistently in the three countries, more offspring in the valproate exposed group were conceived in the earliest years of the study period compared to those in the lamotrigine/levetiracetam group. As a results, the mean follow-up period in years per offspring was longer in offspring paternally exposed to valproate than those to lamotrigine/levetiracetam (respectively, 9.2 and 6.6 years in Denmark, 6.7 and 5.1 years in Sweden, and 7.0 and 6.2 years in Norway).

Mothers' age at childbirth was similar in Denmark, Sweden, and Norway (median of 30 years, 31 years, and 30 years, respectively); similar in both exposure groups. Consistently across the three countries, mothers of offspring paternally exposed to valproate were less frequently affected by comorbidities prior to childbirth compared to those to lamotrigine/levetiracetam: neurotic disorder

(respectively, 5.8% and 7.5% in Denmark, 9.8% and 13.1% in Sweden, 10.0% and 11.3% in Norway), gestational diabetes (respectively, 3.6% and 3.8% in Denmark, 2.7% and 3.2% in Sweden, 4.5% and 5.7% in Norway) and affective disorder (respectively, 2.6% and 5.0% in Denmark, 9.0% and 10.5% in Sweden, 4.2% and 9.0% in Norway). Maternal smoking during pregnancy was slightly more frequently recorded in the valproate exposure group compared to the lamotrigine/levetiracetam exposure group (respectively, 16.6% and 15.8% in Denmark, 7.9% and 5.5% in Sweden, 9.2% and 6.7% in Norway).

The maternal use of medications during pregnancy was similar across the three countries. Lower proportions of mothers were observed with a polypharmacy index between 1 and 4 during pregnancy in the valproate group than in the lamotrigine/levetiracetam group (respectively, 44.0% and 51.6% in Denmark, 45.4% and 48.2% in Sweden, 44.5% and 47.1% in Norway); likewise for the concomitant use of medications associated with valproate-indicated psychiatric conditions during pregnancy (respectively 3.4% and 6.3% in Denmark, 6.4% and 8.4% in Sweden, 4.4% and 6.7% in Norway). The use of AEDs was very low (<1% for individual AEDs) both before LMP2 and during pregnancy irrespective of the exposure groups and the country.

Fathers' age at childbirth was also similar in Denmark, Sweden, and Norway (median of 33 years in all countries); similar in both exposure groups. Consistently across the three countries, fathers of offspring paternally exposed to valproate were less frequently affected by comorbidities prior to childbirth compared to those to lamotrigine/levetiracetam: neurotic disorders (respectively, 6.3% and 11.3% in Denmark, 13.5% and 27.4% in Sweden, 5.0% and 12.7% in Norway), affective disorder excluding bipolar and mania (respectively, 3.7% and 13.0% in Denmark, 11.1% and 30.3% in Sweden, 5.5% and 17.9% in Norway) and bipolar affective disorder (respectively, 2.6% and 7.5 in Denmark, 12.9% and 29.5% in Sweden, 10.5% and 22.2% in Norway).

The paternal use of medication in the 3-months lookback from LMP2 was similar across the three countries. Lower proportions of fathers were observed with a polypharmacy index between 1 and 4 in the valproate group than in the lamotrigine/levetiracetam group (respectively, 29.1% and 41.5% in Denmark, 30.5% and 47.7% in Sweden, 37.7% and 46.3% in Norway); likewise for the use of medications associated with neuropsychiatric adverse events (respectively, 49.3% and 56.0% in Denmark, 48.5% and 64.1% in Sweden, 59.4% and 65.8% in Norway). In Denmark and Sweden, the most common indication for AED use was epilepsy, both among fathers exposed to valproate and lamotrigine/levetiracetam (respectively, 70.0% and 59.0% in Denmark, 70.7% and 46.1% in Sweden). In Norway, the most common indication of AED use was for conditions other than epilepsy or bipolar disorder (50.6% for valproate and 44.5% for lamotrigine/levetiracetam group) followed by epilepsy (39.1% for valproate group and 33.6% for lamotrigine/levetiracetam group).

The overall cumulative incidence proportions of NDD including ASD over the study follow-up period were higher in offspring paternally exposed to valproate than in those to lamotrigine/levetiracetam in the three countries: respectively, 6.6% (95% confidence interval [CI]: 4.9%, 8.3%) and 3.7% (95% CI: 2.6%, 4.7%) in Denmark, 5.4% (95% CI: 4.0%, 6.8%) and 3.5% (95% CI: 2.6%, 4.4%) in Sweden, and 6.7% (95% CI: 4.8%, 8.7%) and 4.0% (95% CI: 3.0%, 5.2%) in Norway. The pooled ratio of these cumulative incidence proportions (valproate over lamotrigine/levetiracetam paternal exposure groups) across the three countries was 1.67 (95% CI: 1.34, 2.08); no heterogeneity observed between country-specific estimates (I^2 = 0.0%, 95% CI: 0.0, 89.6).

The overall cumulative incidence rates of NDD including ASD over the study follow-up period were also higher in offspring paternally exposed to valproate than in those to lamotrigine/levetiracetam in

the three countries: respectively, 7.2 (95% CI: 5.4, 9.3) per 1000 person-year and 5.6 (95% CI: 4.0, 7.5) per 1000 person-year in Denmark, 8.0 (95% CI: 6.0, 10.5) per 1000 person-year and 6.9 (95% CI: 5.2, 9.1) per 1000 person-year in Sweden, and 9.6 (95% CI: 6.9, 12.9) per 1000 person-year and 6.4 (95% CI: 4.8, 8.3) per 1000 person-year in Norway. The pooled ratio of these cumulative incidence rates (valproate over lamotrigine/levetiracetam paternal exposure groups) across the three countries was 1.32 (95% CI: 1.05, 1.66); no heterogeneity observed between country-specific estimates (I^2=0.0%, 95% CI: 0.0%, 89.6%).

Primary outcome, comparative results

From the Primary outcome cohort for descriptive analyses described above, 253 offspring in total across the three countries, who had a diagnosis of epilepsy and/or having received AEDs and/or from epileptic mother and/or being maternally exposed to AEDs (including valproate, lamotrigine or levetiracetam) in utero, or in the 3-months lookback from LMP2, were excluded from the Primary outcome cohort for the comparative analyses. This comparative cohort consisted of 1950 offspring (respectively, 793 and 1157 paternally exposed to valproate and to lamotrigine/levetiracetam) in Denmark, 2355 offspring (respectively, 930 and 1425) in Sweden, and 1943 offspring (respectively, 617 and 1326) in Norway.

The risk of NDD including ASD associated with the paternal exposure to valproate compared to the paternal exposure to lamotrigine/levetiracetam was assessed using crude Cox regression models: occurrence of NDD was observed in 43 out of 793 (5.4%) and 41 out of 1157 (3.5%) offspring in the valproate and in the lamotrigine/levetiracetam groups respectively in Denmark, in 49 out of 930 (5.3%) and 41 out of 1425 (2.9%) offspring respectively in Sweden, and in 38 out of 617 (6.2%) and 49 out of 1326 (3.7%) offspring respectively in Norway. The resulting HRs indicated no significant higher risk of NDD including ASD with the paternal exposure to valproate compared to lamotrigine/levetiracetam in the three countries: 0.94 (95% CI: 0.60, 1.46) in Denmark, 1.16 (95% CI: 0.76, 1.76) in Sweden, and 1.40 (95% CI: 0.90, 2.18) in Norway. The pooled crude HR across the three countries was consistent with the country-specific estimates in terms of strength and non-significance of the risk: 1.15 (95% CI: 0.90, 1.48); no heterogeneity observed between country-specific estimates (I^2=0.0%, 95% CI: 0.0%, 89.6%).

The risk of NDD including ASD associated with paternal exposure to valproate compared to that to lamotrigine/levetiracetam was further assessed using propensity score (PS)-weighted Cox regression models after the further exclusion of offspring with outlier weights: occurrence of NDD was observed in 35 out of 678 (5.6%) and 36 out of 1118 (3.2%) offspring in the valproate and in the lamotrigine/levetiracetam groups respectively in Denmark, in 47 out of 841 (5.6%) and 34 out of 1334 (2.5%) offspring respectively in Sweden, and in 32 out of 505 (6.3%) and 34 out of 1165 (3.6%) offspring respectively in Norway. The HRs adjusted for PS-weights (PSW) were higher than crude HRs in all countries but remained non-significant: 1.34 (95% CI: 0.79, 2.25; also adjusted for unbalanced risk factors: maternal affective disorders and maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy) in Denmark, 1.54 (95% CI: 0.95, 2.51) in Sweden, and 1.52 (95% CI: 0.93, 2.49) in Norway. However, the pooled PSW adjusted HR across the three countries showed a significant higher risk with the paternal exposure to valproate due to a more precise estimation as the population size increased: 1.47 (95% CI: 1.10, 1.96); no heterogeneity observed between country-specific estimates (I^2=0.0%, 95% CI: 0.0%, 89.6%).

Sensitivity analysis 11 (i.e., considering a narrow case definition of NDD) indicated a stronger and significant association compared to that of the main analysis in Sweden (PSW adjusted HR of NDD: 1.70, 95% CI: 1.02, 2.81); in Denmark and Norway, results were similar to those of the main analyses.

Sensitivity analysis 2 (i.e., considering ASD alone as primary outcome) indicated a non-significant association in the opposite direction compared to that of the main analysis in Denmark (PSW adjusted HR of ASD: 0.76, 95% CI: 0.30, 1.89) and a stronger and significant association in Sweden (PSW adjusted HR of ASD: 2.70, 95% CI: 1.19, 6.17). In Norway, results were similar to those of the main analyses.

Sensitivity analysis 10 (i.e., considering continuous measure of cumulative exposure) indicated a non-significant association in the opposite direction compared to that of the main analysis in Denmark (PSW adjusted HR: 0.58, 95% CI: 0.31, 1.08) and stronger and significant association in Norway (PSW adjusted HR: 2.75, 95% CI: 1.03, 7.33).

All other sensitivity analyses provided similar adjusted HRs as those of the main analysis, for the three countries.

Primary outcome, exploratory results

Exploratory analysis to address objective 5 indicated, consistently across the paternal exposure groups, similar distributions of risks factors and confounders (in all countries) and higher proportions of offspring presenting a NDD including ASD (in Sweden and Norway) (numbers were masked in Denmark) in offspring paternally exposed to polytherapy with AEDs compared to in offspring paternally exposed to valproate or to lamotrigine/levetiracetam in monotherapy (i.e., from the main analysis).

Exploratory analysis to address objective 6 was conducted in very few numbers of offspring in all countries, preventing the run of the analysis for associations of risk factors and confounders with the occurrence of NDD including ASD (0 out 21 offspring presented the outcome in Denmark; 3 out 29 offspring presented the outcome in Sweden, and 1 out 8 offspring presented the outcome in Norway).

Secondary outcome, CM

Secondary outcome, descriptive results

The Secondary outcome cohort for descriptive analyses included 1655 offspring (respectively, 549 and 1106 paternally exposed to valproate and to lamotrigine/levetiracetam) in Denmark, and 2027 offspring (respectively, 644 and 1383) in Norway.

Offspring, maternal and paternal demographic characteristics in the two exposure groups of the Secondary outcome cohorts were similar as those from the Primary outcome cohorts for descriptive analyses in all countries.

Consistently across Denmark and Norway, mothers of offspring paternally exposed to valproate were similarly affected by comorbidities prior to childbirth as those to lamotrigine/levetiracetam: gestational diabetes (respectively, 3.6% and 3.4% in Denmark, 1.7% and 1.9% in Norway), diabetes (respectively, 0.9% and 1.2% in Denmark, 1.9% and 2.1% in Norway), obesity (respectively, 1.5% and 1.8% in Denmark, 0.9% and 0.8% in Norway) and epilepsy (respectively, 2.7% and 1.6% in Denmark, 1.1% and 1.2% in Norway). They were less likely to use medications associated with

teratogenic activity/foetal toxicity than mothers of offspring paternally exposed to lamotrigine/levetiracetam prior to LMP2 (respectively, 25.9% and 30.8% in Denmark, 27.0% and 29.2% in Norway) and/or during the pregnancy (respectively, 27.0% and 33.5% in Denmark, 24.8% and 31.2% in Norway).

Fathers of offspring paternally exposed to valproate were more likely to receive their AED to treat epilepsy than those of offspring paternally exposed to lamotrigine/levetiracetam in the two countries (respectively, 75.4% and 58.3% in Denmark, 39.0% and 33.6% in Norway).

The overall cumulative incidence proportion of reported CM diagnoses (major and minor as composite) over the study follow-up period was lower in offspring paternally exposed to valproate compared to those to lamotrigine/levetiracetam in Denmark, while they were similar between the two paternal exposure groups in Norway: respectively, 9.3% (95% CI: 6.9%,11.7%) and 14.1% (95% CI: 12.1%,16.2%) in Denmark, and 16.6% (95% CI: 13.7, 19.5) and 15.1% (95% CI: 13.2, 17.0) in Norway.

Secondary outcome, comparative results

From the cohort described above, 2329 offspring in total across the three countries, who had a diagnosis of epilepsy and/or having received AEDs and/or from epileptic mother and/or being maternally exposed to AEDs (including valproate, lamotrigine or levetiracetam) in utero, or in the 3-months lookback from LMP2, were excluded from the Secondary outcome cohort for the comparative analyses. This comparative cohort consisted of 648 offspring (respectively, 259 and 389 paternally exposed to valproate and to lamotrigine/levetiracetam) in Denmark, and 705 offspring (respectively, 262 and 443) in Norway.

The risk of CM associated with paternal exposure to valproate compared to paternal exposure to lamotrigine/levetiracetam was assessed using crude logistic regression models.CM was found in 23 out of 259 (8.9%) and 53 out of 389 (13.6%) offspring in the valproate and the lamotrigine/levetiracetam groups respectively in Denmark, and in 41 out of 262 (15.6%) and 64 out of 443 (14.4%) offspring respectively in Norway. The resulting ORs indicated no significant association with paternal exposure to valproate in the two countries: 0.62 (95% CI: 0.37, 1.04) in Denmark, and 1.10 (95% CI: 0.72, 1.68) in Norway. The crude pooled OR across the two countries was estimated: 0.84, 95% CI: 0.48, 1.48); but substantial heterogeneity was observed between country-specific estimates (I^2=64.6%, 95% CI: 0.0%, 91.9%).

The risk of CM associated with the paternal exposure to valproate compared to that to lamotrigine/levetiracetam was further assessed using propensity score PS-weighted logistic regression models in smaller populations due exclusion of offspring with outlier weights: respectively, 21 out of 238 (8.8%) and 52 out of 381 (13.6%) offspring with the outcome in Denmark, and 32 out of 222 (14.4%) and 54 out of 383 (14.1%) offspring with the outcome in Norway. The ORs adjusted for PS-weights were similar as the crude ORs in the two countries: 0.61 (95% CI: 0.36, 1.06) in Denmark and 1.00 (95% CI: 0.62, 1.61) in Norway. The pooled PSW adjusted OR across the two countries was 0.79 (95% CI: 0.49, 1.29); heterogeneity was observed between country-specific estimates (I^2=44.7%, 95% CI: not available).

All the sensitivity analyses generated similar PSW adjusted ORs as that of the main analysis in Denmark and Norway.

Secondary outcome, exploratory results

Exploratory analyses to address exploratory objectives 5 and 6 were conducted on very low number of offspring, either preventing the run of the analysis or limiting the interpretation of the results. Exploratory analysis to address exploratory objective 7 (risk of CM live offspring in Sweden) was conducted on 2451 offspring (968 paternally exposed to valproate and 1483 paternally exposed to lamotrigine/levetiracetam) for descriptive analyses and on 888 offspring (418 paternally exposed to valproate and 470 paternally exposed to lamotrigine/levetiracetam) for comparative analyses. Offspring, maternal and paternal characteristics were similar as those observed in Denmark and Norway with regards to the paternal exposure group. The overall cumulative incidence proportions of CM over the study follow-up in offspring paternally exposed to valproate was similar to that in offspring paternally exposed to lamotrigine/levetiracetam: respectively, 10.4% (95% CI: 8.5%, 12.4%) and 10.5% (95% CI: 9.0%, 12.1%). The crude and the PS-weights adjusted ORs of CM in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam were in favour of an absence of an increased risk, being respectively 1.01 (95% CI: 0.66, 1.55) and 0.92 (95% CI: 0.59, 1.44).

Exploratory analysis to address objective 8 was conducted on 76 offspring that reported 111 CM diagnoses in Denmark and 105 offspring that reported 139 CM diagnoses in Norway. Proportion of major CM was higher in the reported CM, in both countries and both exposure groups: 24 out 34 (70.6%) in the valproate group and 61 out of 77 (79.2%) in the lamotrigine/levetiracetam group were major CM diagnoses in Denmark, 38 out of 63 (60.3%) and 39 out of 76 (51.3%) respectively in Norway. Distribution of the most frequently reported target body organ classes according to the exposure group was not consistent between the two countries. In Norway, the most reported was the limbs in both groups (30.2% in valproate group, 31.6% in lamotrigine/levetiracetam group); the second was the digestive system (25.4% and 25.0% respectively), the third one was congenital heart defects (14.3% and 11.8% respectively). In Denmark, all numbers were masked in the valproate group except for limbs (17.7%) whereas in lamotrigine/levetiracetam group, the limbs were the second most reported (20.8%), the first one being congenital heart defects (26%).

Discussion

This comprehensive real-world retrospective study provides the first results on NDD including ASD and CM outcomes in offspring paternally exposed to valproate at the time of conception, compared to those exposed to lamotrigine/levetiracetam, in Denmark, Sweden and Norway.

A significant increased risk of NDD including ASD associated with paternal exposure to valproate compared to paternal exposure to lamotrigine/levetiracetam at the time of conception was observed when pooling the country-specific adjusted risk estimates into a meta-analysis (PSW adjusted HR: 1.47, 95% CI: 1.10, 1.96; I^2=0.0%). However, due to the observational nature of this study, no causal relationship can be established, and neither the biological nor the pharmacological mechanisms to explain the relationship.

The nature of the NDD and specific subtypes (ASD, intellectual disabilities, attention deficit hyperactivity disorder) was not assessed because the study was powered to investigate NDD as a composite outcome. However, sensitivity analyses focusing on a narrow definition of NDD showed that the risk estimates varied in strength, direction, and significance compared to those from the main analysis, and these variations were not consistent across the three countries. For example, with sensitivity analysis 2 focused on ASD as primary outcome, the association reversed toward a non-

significant reduced risk with the paternal exposure to valproate in Denmark, while the risk almost doubled and became significant with this exposure in Sweden. It is noteworthy that among the three countries, follow-up was the shortest in Sweden, with 23.3% of the offspring in the lamotrigine/levetiracetam group were followed-up more than eight years (vs 41.8% in the valproate group); follow-up was the longest in Denmark with 40.2% lamotrigine/levetiracetam group followed-up more than 8 years (vs 74.3 in the VPA group). This may explain the lower rate of ASD captured in the lamotrigine/levetiracetam in Sweden compared to other countries, and may highlight the impact of the follow-up duration on the results. While these sensitivity analyses relied on lower number of events and estimates may be more prone to instability and lower reliability, they call for caution in the interpretation of the study results. It is worthwhile to note that offspring paternally exposed to valproate were systematically more frequently conceived in the earlier years of inclusion than those exposed to lamotrigine/levetiracetam. As a result, offspring paternally exposed to valproate had in average a longer follow-up time and a higher probability of presenting NDD, including ASD diagnoses. Considering that the risk of being diagnosed with NDD including ASD is not constant across ages but rather detected at later ages when children start school (i.e., from 5 or 6 years old), this may have biased the risk estimates generated from Cox regression models.

In line with previous published studies, this study found no increased risk of CM associated with the paternal exposure to valproate compared to the paternal exposure to lamotrigine/levetiracetam in the three months preconception period, consistent across Denmark and Norway (pooled OR: 0.79, 95% CI: 0.49, 1.29; I^2=44.7%). The presence of such heterogeneity may be due to that only two estimates were pooled in the meta-analysis.

Additionally, some methodological limitations may be acknowledged. This study used secondary data that was not collected primarily for research purposes and therefore information on certain parameters, such as some known risk factors and/or causal factors (e.g., genetic abnormalities, congenital infectious diseases, paternal condition severity that required AED use, lifestyle factors) which were not identified nor controlled for. These factors were assumed to be balanced between the two paternal exposure groups, but this assumption could not be verified, and unmeasured confounding may bias the risk estimates. Especially the type of epilepsy, which may not be balanced between the two paternal exposure groups: indeed, valproate is the treatment of choice (or first-line drug) for male patients with idiopathic generalised epilepsy, a type of epilepsy which could be associated with neurodevelopmental disorder and is known to have a genetic basis and as such can be found in several members of the same family.

This study found an increased risk of NDD, including ASD, with the paternal exposure to valproate, compared to lamotrigine/levetiracetam at the time of conception. Due to methodological limitations, especially the difference in follow-up time between the two paternal exposure groups which may impact the interpretation of the results, these findings regarding risk of NDD should be interpreted with caution. While the study did not find any difference in risks of CM between the two paternal exposure groups, the moderate-to-substantial heterogeneity due to inconsistency in results observed across the countries calls for caution when interpreting these findings too.

Marketing authorisation holders (MAH)

APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; BIOGARAN; BIOMO PHARMA GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA LIMITED; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG; LUPIN HEALTHCARE LIMITED;MYLAN BVBA/SPRL: BE; VIATRIS SANTE (LYON): FR; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; PHARMASWISS ČESKÁ REPUBLIKA S.R.O.; SANOFI AVENTIS GROUP; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE and; WOCKHARDT UK LIMITED

Name and affiliations of principal investigator

Paula Thompson, PhD; IQVIA, Real World Solutions, Global Epidemiology

3. Investigators

Principal Investigator: Paula Thompson

4. Other Responsible Parties

Project Manager: [redacted]

Epidemiological Oversight: [redacted]

Biostatistical Oversight: [redacted]

External Medical and Methods Advisers: [redacted]

5. Milestones

Table 2 Study milestones

Milestone	Planned Date	Actual Date	Comments
Registration in the EU PAS register	Q1 2020	19th March 2020	After endorsement of protocol and before data extraction
Start of data extraction	Q4 2020	21st October 2020	in Denmark
End of data extraction	Q1 2021	8th June 2021 (Norway)	Norway data is not included in the interim report. For this interim, the last data extraction was 26th March 2021 (Sweden)
Progress report	Q1 2021	20th January 2021	12 months after PRAC endorsement
Interim report	Q3 2021	23rd July 2021	Analyses included from Denmark and Sweden for descriptive analyses and univariate analyses for the Primary outcome and Secondary outcome cohorts) No results from Norway are included.
Final report of study results	Q3 2022	28th March 2023	Initial, but incomplete*, study report V1.0 was submitted on January 19th 2023. * because complete results sensitivity analysis 2 and exploratory analysis 8 were not available

6. Rationale and Background

Background

Valproate-containing medicines are approved in the European Union (EU) to treat epilepsy and bipolar disorder. These are also approved in some countries for prevention of migraine, but not supported by all Marketing Authorisation Holders (MAHs). In recent years, due to an increased risk of neurodevelopmental disorders (NDD) including autism spectrum disorders (ASD), as well as of congenital malformations (CM) in offspring after valproate exposure in utero (1), the use of valproate has been restricted to cases in which no other effective or tolerated treatment is available (2) in women of childbearing potential suffering from epilepsy and bipolar disorder, or in pregnant women suffering from epilepsy; it has been contraindicated in pregnant women suffering from bipolar disorder.

While the effects of maternal exposure of drugs prior to and during pregnancy on offspring outcomes are widely studied, the role of paternal exposure to drugs prior to conception on offspring's health has not yet been clearly demonstrated. Evidence from paternal exposure to radiation, antimitotic drugs or environmental toxins suggests that (epi-)genetic modifications may be transmitted through the father to the next generation (3). Engeland *et al*. studied the possible association between drugs dispensed to the father in the 3 months prior to conception and adverse pregnancy outcomes (4), with no strong conclusion.

Previous literature showed that paternal exposure to valproate in mice might lead to behavioural alterations in offspring (5). It is still unclear if these results may be translated to the human population.

The spermatogenic cycle in humans lasts about 74 days (2.5 months) (6), which may be a vulnerable time for acute exposures such as drug intake. Large population-based studies addressing the associations between increased risk of adverse outcomes in the offspring following paternal exposure to drugs prior to conception are rare, as few databases offer the possibility of paternal-offspring linkage, and the effect of the paternal exposure may be very small. Thus far, only one study based on Danish national registers has reported an increased risk of ASD following paternal use of selective serotonin reuptake inhibitors (SSRIs) before conception (7). Other studies which evaluated the paternal exposure to disease-modifying antirheumatic drugs in Norwegian registries (8), or a large number of different prescription drugs in Norwegian registries including antiepileptic drugs (AEDs) (4,9), did not find an increased risk for adverse outcomes in offspring. Specifically, the risk of paternal exposure to valproate has thus far not been found to significantly affect offspring's outcomes (4,10).

Rationale

There is currently scarce real-world evidence of an increased risk of NDD including ASD, or CM in offspring following paternal exposure to AEDs. Therefore, following the Pharmacovigilance Risk Assessment Committee (PRAC) recommendation dated 8 February 2018, this post-authorisation safety study (PASS) is being conducted to evaluate the association between paternal exposure to valproate and the risk of NDD, including ASD, as well as CM in offspring in comparison to lamotrigine/levetiracetam (composite treatment).

7. Research Question and Objectives

The aim of this retrospective cohort study was to examine the association between paternal exposure to valproate at conception and the risk of NDD, including ASD, as well as CM in offspring. Paternal exposure to valproate was compared to paternal exposure to lamotrigine/levetiracetam, which was considered a safer treatment (11–14). In women, these drugs were generally associated with lower risk of teratogenicity for their offspring compared to valproate, but it is unknown whether the effect is the same in fathers.

7.1 Primary Objective

1. To investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment (composite monotherapy) at the time of conception.

7.2 Secondary Objectives

2. To investigate the risk of CM in live and non-live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment (composite monotherapy) at the time of conception, in Norway and Denmark.

3. To describe AED exposure (posology and duration) data and health characteristics of male patients prescribed AEDs (including valproate and lamotrigine/levetiracetam) in treatment of epilepsy and other indications at the time of conception of their offspring, both for NDD and CM cohort.

4. To identify potentially important risk factors for outcomes of interest, in offspring paternally exposed to valproate (monotherapy) or lamotrigine/levetiracetam (composite monotherapy) at the time of conception, by examining AED exposure and health characteristics of the offspring and their mothers.

7.3 Exploratory Objectives

5. To describe the putative risk factors and frequency of NDD, including ASD, as well as CM in offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine and levetiracetam) and those paternally exposed to lamotrigine / levetiracetam (in combination with other AEDs, excluding valproate) at the time of conception.

6. To describe the risk factors and frequency of NDD, including ASD, as well as CM in paternally and maternally matched exposure-discordant (valproate vs. lamotrigine/levetiracetam monotherapy) siblings at conception.

7. To investigate the risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment (composite monotherapy) at the time of conception in Sweden.

8. To describe the frequency of CM by target body system organ class in live and non-live offspring paternally exposed to valproate (monotherapy), and to lamotrigine/levetiracetam treatment (composite monotherapy) at the time of conception.

8. Amendments and Updates

Table 3 Summary of major and minor amendments to the Protocol after approval of version 5.0

Section	Description of change made	Justification	Minor or Major Change
Protocol V5.0	The Protocol V5.0 was amended to Protocol V6.0, and all changes and updates are better described in the referred document.	Inclusion of an additional sensitivity analysis	Major
PASS Information	MAH participating in consortium	Update of MAH list	Minor

9. Research Methods

9.1 Study Design

The study was carried out using a retrospective non-interventional longitudinal population-based cohort design conducted using secondary data derived from multiple registry databases recording longitudinal medical data in Denmark, Sweden, and Norway. Design and methods were approved by the Consortium of MAHs and the PRAC.

The overall aim was to study the risk of NDD including ASD, as well as CM in offspring following paternal exposure to valproate.

For the evaluation of NDD, including ASD, the population for analysis was comprised of live births for whom medical record linkage to mother and father was available within such registries. For the evaluation of CM for Denmark and Norway, the population for analysis was comprised of live births, stillbirths, and spontaneous abortions[1] during gestation (2nd and 3rd trimester) for whom medical record linkage to mother and father was available. For Sweden, the corresponding population for analysis was comprised of live births only. The primary outcome of interest was NDD, including ASD, and the secondary outcome of interest was a composite of CM (minors and/or majors), in offspring up to 12 years of age for both outcomes, based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) diagnostic codes. The primary exposure of interest was paternal use of valproate during the spermatogenic risk window prior to conception of the offspring (defined by the first day of the last menstrual period date plus 2 weeks [LMP2] of the mother within the linked family unit). Exposure information was derived from prescription data, as recorded in the National Prescription Registry for each country (from 2005 in Sweden, 2004 in Norway and 1995 in Denmark) to 31st December 2018 for Denmark and 31st December 2019 for Sweden and Norway. Country-specific cohorts of eligible linked family units were then identified.

An overview of the study design conducted in Denmark, Norway, and Sweden for the primary and secondary outcomes are provided in Figure 1 and in Figure 2.

[1] Data about voluntary and medically required abortions, that can have a diagnosis of CM, were not linked to fathers in any of the countries in the study.

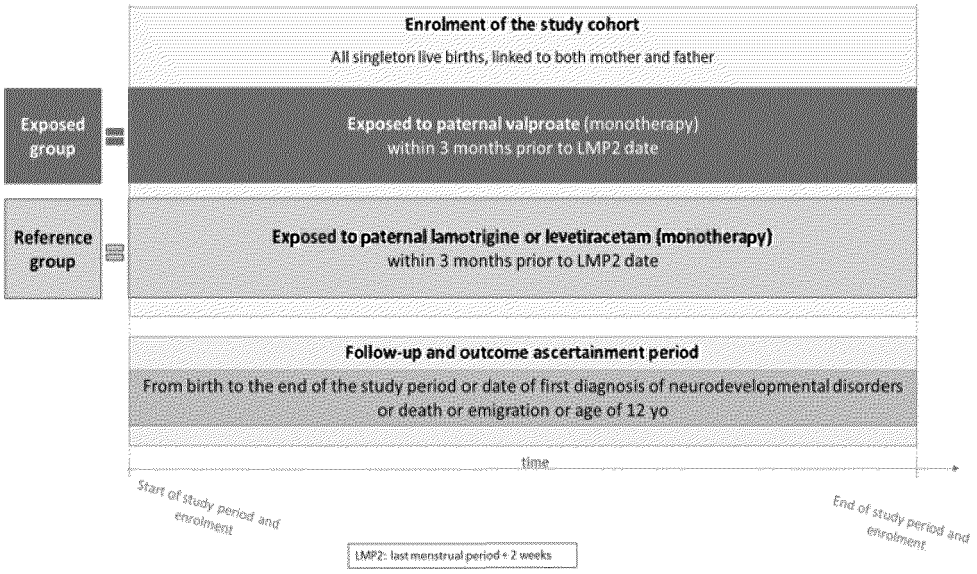

Figure 1 Overview of the study design for evaluating the primary outcome

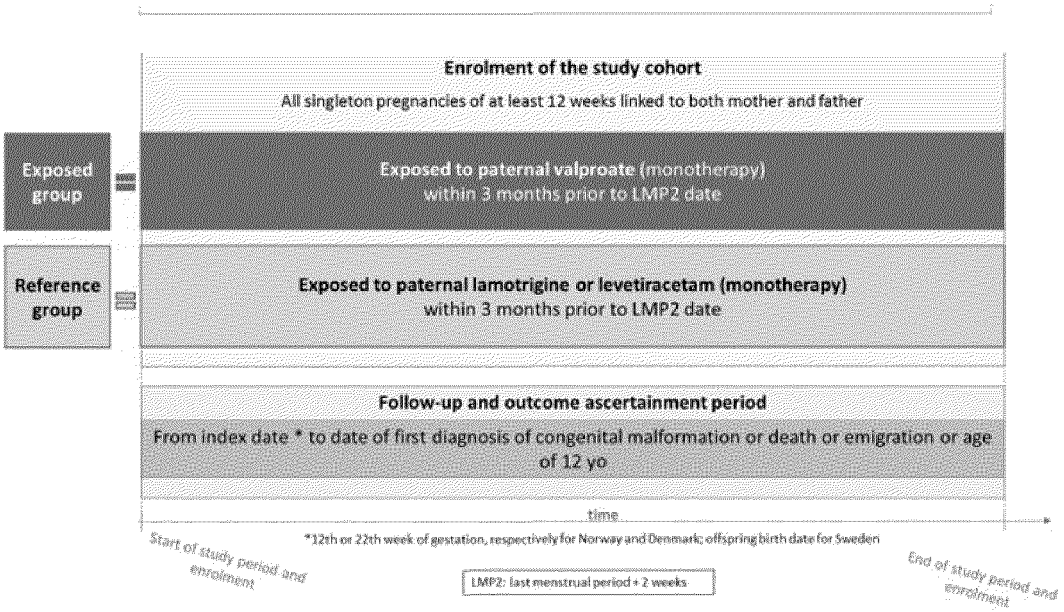

Figure 2 Overview of the study design for evaluating the secondary outcome

9.2 Setting

For real-world evidence generation, secondary longitudinal data sources can offer insights into clinical characteristics and outcomes. However, linkage of fathers to offspring was rare in most European countries, as typically only the mother was linked to the offspring within the data. It was also rarely noted in the record of a man, that they became a father. The exception of this were the Scandinavian

countries, which offer the possibility to link paternal data to offspring using national identification numbers and registers. This study was therefore focused on the 3 Scandinavian countries: Sweden, Denmark, and Norway. The study had a larger population size and a broader geographic scope compared to previous studies on valproate and offspring outcomes.

Study time period

The study time period was based on the availability of information from the National Registries; starting from 1st January 2007 in Sweden, 1st January 2006 in Norway, and 1st January 1997 (1st April 2004[2] for secondary outcome) in Denmark in order to allow for a 24 months average lookback period for live births:

- pregnancy duration (9 months on average for live births)
- maternal and paternal preconceptional exposure (3 months)
- minimum lookback period for confounders (12 months)

The study time period ended on 31st December 2018 for Denmark and 31st December 2019 for Sweden and Norway. The index date was the day of childbirth. The rationale for this choice was to include all data available from the linked registers, to capture a sufficient number of outcomes, exposures and linked family units, and to include the most up-to-date data available.

9.3 Subjects

Since this PASS was an observational study, minimal inclusion and exclusion criteria were used to minimise potential selection bias and represent real clinical practice.

To address the research questions related to the primary outcome (NDD including ASD) and secondary outcome (CM), 2 separate cohorts were created, and additional selection criteria, nested within the criteria for data extraction, were applied. These cohorts are referred to as the Primary and Secondary outcome cohort, respectively.

Neurodevelopmental disorders, including autism

For the purpose of the evaluation of NDD, including ASD, Figure 3, illustrates the family linkage of the study participants, the paternal exposure period (3 months prior to LMP2 date), follow-up period for the offspring (from birth to maximum 12 years of age), and the lookback periods for confounders for each linked family member (mother: at least 12 months prior to delivery, father: at least 12 months prior to LMP2 date).

[2] In Denmark, for the period 1997-1st April 2004, stillborn born between 22nd and 28th weeks of gestation were not included in the Medical Birth Register but in the National Patient Register. However, since in the National Patient Register the linkage with the father was not available, the study period for the secondary outcome in Denmark was limited to 2004-2018

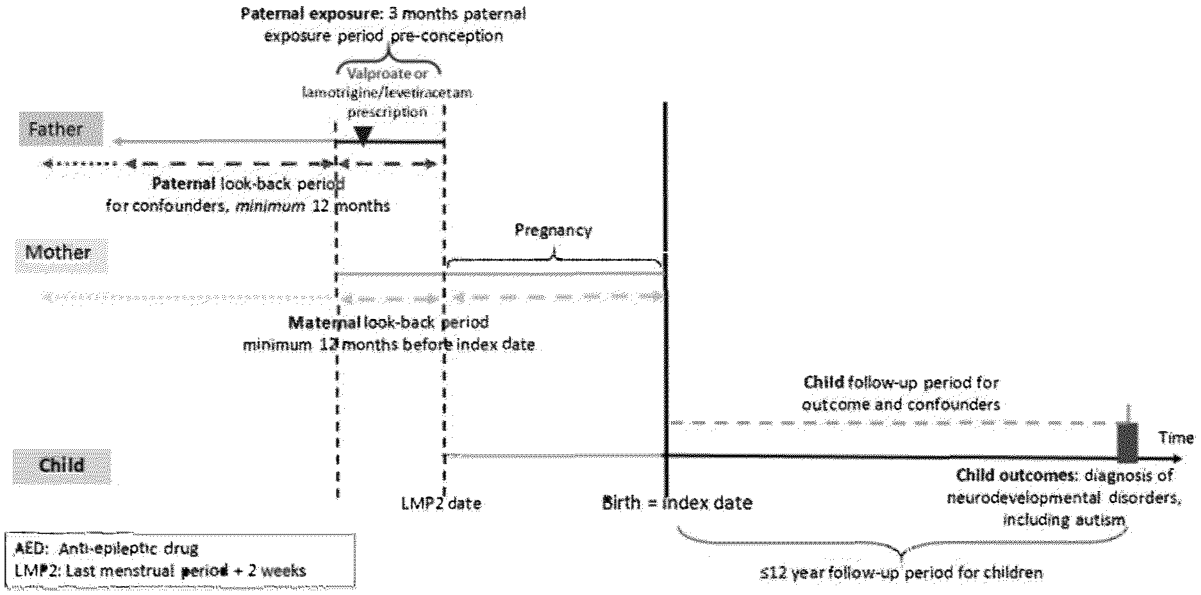

Figure 3 Overview of the family linkage, Neurodevelopmental Disorders (NDD) including Autism Spectrum Disorders (ASD)

Congenital malformations

For the purpose of the evaluation of CM, Figure 4 and Figure 5 illustrate the registry linkage of the study participants, the paternal exposure period (3 months prior to LMP2 date), follow-up period for the offspring (from 12th or 22nd

week of gestation, respectively, for Norway and Denmark and from birthdate of offspring for Sweden to maximum 12 years of age), and the lookback periods for confounders for each linked family member (mother: minimum of 12 months prior to index date, father: minimum of 12 months prior to LMP2 date).

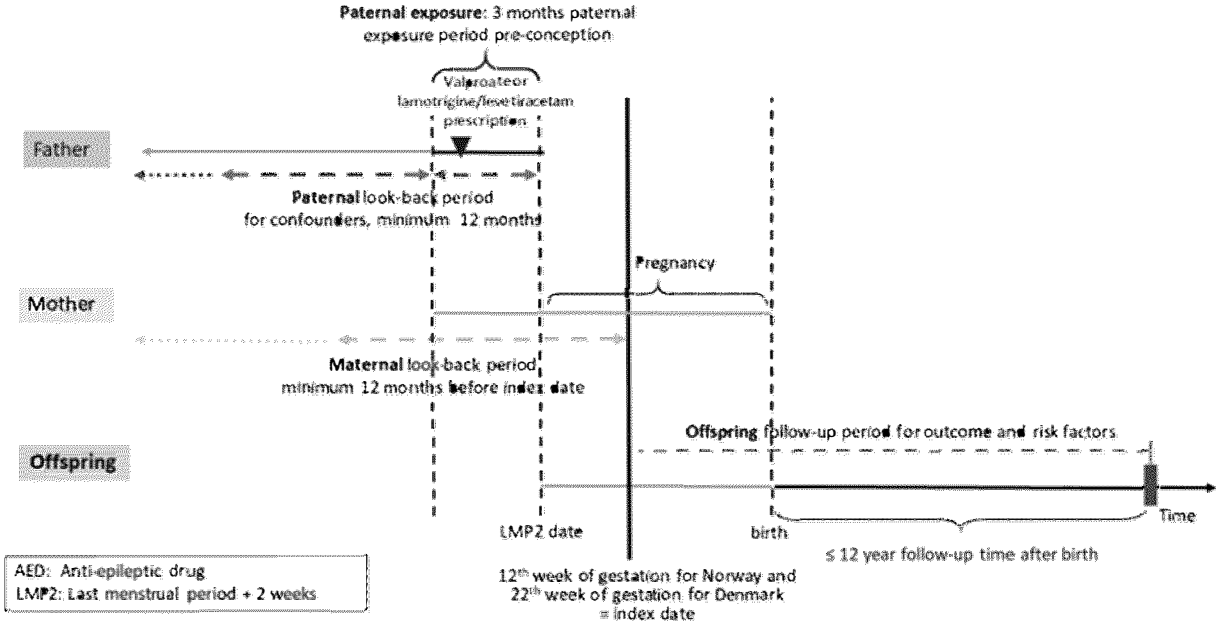

Figure 4 Overview of the family linkage, congenital malformations (CM) for Norway and Denmark

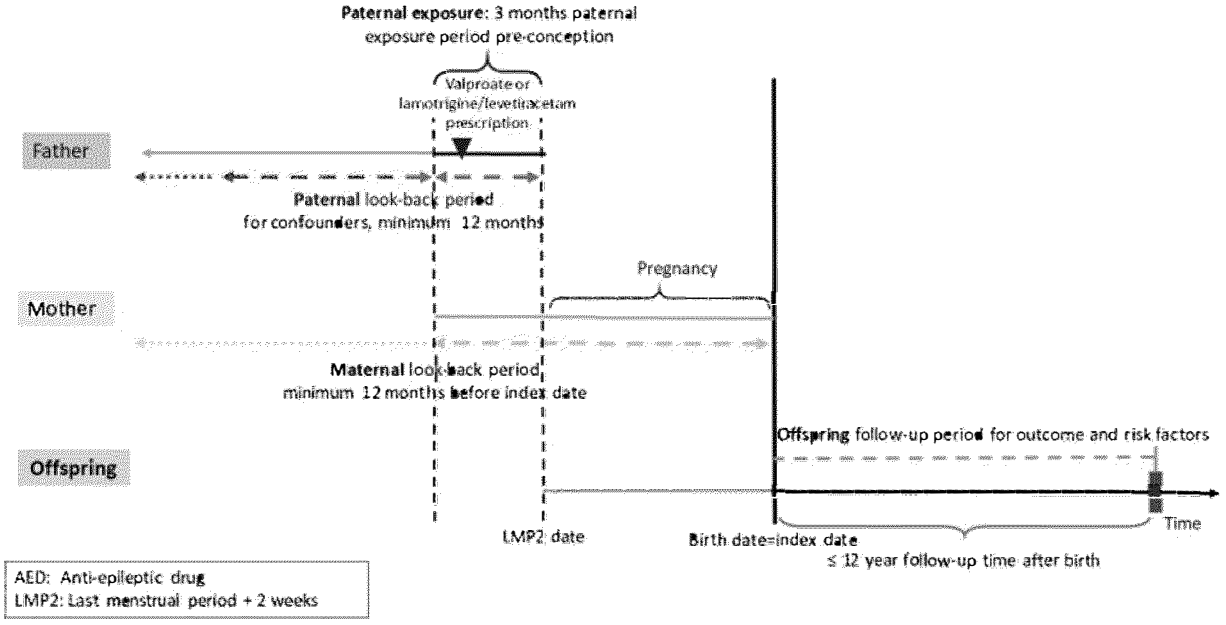

Figure 5 Overview of the family linkage, congenital malformations (CM) for Sweden

9.3.1 Eligibility criteria

The following criteria describe the population of patients extracted for Sweden, Denmark, and Norway.

Inclusion criteria for data extraction

- Singleton[3] pregnancies, with known pregnancy-length of at least 12 weeks[4] within the study time period
- Pregnancies linked to both mother and father within the study time period
- Father with a continuous enrolment[5] in the database for ≥12 months prior to linked mother LMP2 date
- Father with at least one AED in the data available.

For Sweden, the inclusion criteria were different, as only live births were included

- Singleton[4] pregnancies resulting in live births
- Pregnancies linked to both mother and father within the study time period
- Father with a continuous enrolment[6] in the database for ≥12 months prior to linked mother LMP2 date
- Father with at least one exposure to AED during 192 days prior to 28 days after LMP2 date

Exclusion criteria for data extraction

- Adopted children
- Pregnancy associated with in vitro fertilisation (IVF)
- Pregnancies with missing gestational age and/or missing maternal LMP2 (for these pregnancies it was not possible to identify the exposure window for the study)

To address the research questions related to the primary outcome (NDD including ASD) and secondary outcome (CM), separate cohorts were created, and additional selection criteria, nested within the criteria for data extraction were applied. Within each of these cohorts, 2 nested sub-cohorts were created for descriptive and comparative analyses, respectively.

9.3.1.1 Primary outcome cohort

Additional exclusion criteria applied to the eligible extracted cohort:

- Non-live births[6]
- Mother without a continuous enrolment[7] of 12 months prior to index date (date of childbirth)

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[3] Twins were excluded because they share the same paternal exposure and it was not known how medication was absorbed, distributed and metabolised by each of them. Moreover, preterm birth and low birth weight (associated with NDD and CM) occurred more frequently in twin and triplet pregnancies than in singleton pregnancies.
[4] Pregnancy terminations (e.g. spontaneous abortions) before 12 weeks gestation were not recorded in the data sources.
[5] A patient was considered continuously enrolled in a specific time period if that patient had a contact with healthcare services (such as drug prescription or hospitalisation) prior to that period and if emigration or death were not notified after this contact.
[6] Non-live births were not included because a diagnosis of NDD could not be made.

- Offspring whose parent(s) had a history of CM or NDD (according to all available records up to and including LMP2)
- Father unexposed to AED in the 3 months prior to linked mother LMP2 date

9.3.1.1.1 Primary outcome cohort for descriptive analysis

Additional exclusion criteria applied to the Primary outcome cohort:

- Offspring paternally exposed to AED polytherapy in the 3 months lookback from LMP2
- Offspring paternally exposed to any AEDs (in mono or polytherapy) other than valproate lamotrigine or levetiracetam in the 3 months lookback from LMP2

9.3.1.1.2 Primary outcome cohort for comparative analysis

Additional exclusion criteria applied to the Primary outcome cohort for descriptive analyses:

- Offspring maternally exposed to AEDs in utero or in the 3 months lookback from LMP2
- Offspring with a mother with history of epilepsy
- Offspring exposed to AEDs and/or diagnosed with epilepsy after birth

9.3.1.2 Secondary outcome cohort

Additional exclusion criteria applied to the eligible extracted cohort:

- Mother without a continuous enrolment[8] of 12 months prior to index date (12th week of gestation in Norway, 22nd week of gestation in Denmark and birthdate of live offspring in Sweden)
- Offspring whose parent(s) had a history of CM or NDD (according to all available records up to and including LMP2)
- Offspring from father unexposed to at least one AED in the 3 months prior to linked mother LMP2 date

9.3.1.2.1 Secondary outcome cohort for descriptive analyses

Additional exclusion criteria applied to the Secondary outcome cohort:

- Offspring paternally exposed to AED polytherapy in the 3 months lookback from LMP2
- Offspring paternally exposed to any AEDs (in mono or polytherapy) other than valproate, lamotrigine or levetiracetam in the 3 months lookback from LMP2

[8] A patient was considered continuously enrolled in a specific time period if that patient had have a contact with healthcare services (such as drug prescription or hospitalisation) prior to that period and if emigration or death were not notified after this contact.

9.3.1.2.2 Secondary outcome cohort for comparative analyses

Additional exclusion criteria applied to the Secondary outcome cohort for descriptive analyses:

- Offspring maternally exposed to AEDs (including valproate, lamotrigine and levetiracetam in utero or in the 3 months lookback from LMP2
- Offspring from a mother with a history of epilepsy
- Offspring maternally exposed (3 months lookback from LMP2 or during pregnancy) to drugs with known teratogenic activity/foetal toxicity (please see SAP v2.0)
- Offspring paternally exposed (3 months lookback from LMP2) to drugs with known teratogenic activity (please see SAP v2.0)

9.4 Variables

In order to meet the study objectives, the following parameters were obtained from the selected data sources, analysed, and presented in this final report:

- Demographic characteristics for descriptive cohort
- Exposure of interest
- Outcome of interest for descriptive and comparative cohorts
- Potential confounding variables and risk factors for comparative cohort

9.4.1 Exposure definition and measures

Within the AEDs, the primary exposure of interest is the dispensation of valproate. Brand names and generics of all forms of valproate salts were considered (sodium valproate, valproic acid, valproate semisodium and valpromide) and summarised under the term “valproate”. Valproate was identified using Anatomical Therapeutic Chemical (ATC) code N03AG01.

Drug exposure of the offspring was based on the use of AEDs by the father during a risk window prior to conception. Since the spermatogenic cycle is approximately 2.5 months, the risk window considered was 3 months prior to conception.

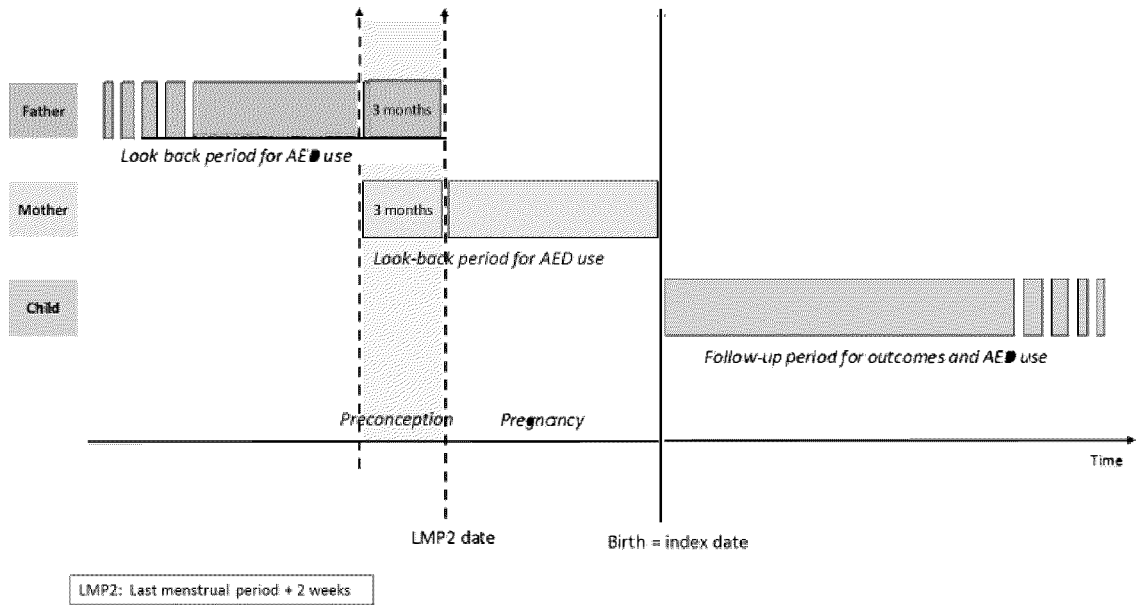
In the primary analysis, paternal exposure to valproate (monotherapy) was compared to paternal exposure to lamotrigine/levetiracetam which was considered a safer treatment (11–14). Lamotrigine and levetiracetam were identified using ATC codes N03AX09 and N03AX14, respectively. Since polytherapy was indicated for medically refractory epilepsy (15), in order to avoid the risk of disease severity bias associated to polytherapy, evaluation of AED exposure according to monotherapy was preferred for comparative analyses. In this section, definitions of monotherapy and polytherapy are only discussed for AEDs. Co-medications (other than AEDs) were defined in section 9.4.4. Monotherapy was defined as the exposure to a single AED, while polytherapy was defined as any combination of AEDs (including valproate among the exposed and excluding valproate among the unexposed), simultaneously or in sequence, within the 3 months risk window. For example, switching to or switching from an AED other than valproate, lamotrigine or levetiracetam, was considered as polytherapy, and the offspring of these fathers were excluded from the comparative analyses. This is because a washout period is not possible in clinical practice since subjects may not be unexposed for seizure control. Including subjects who were exposed to more drugs of the same class in the period of interest could lead to uncertainty in defining which drug was associated with the outcome.

Paternal exposure to AEDs other than valproate during the 3 months risk window and also maternal and offspring exposure (section 9.4.4*)* to AEDs were also described.
Other AEDs identified using (ATC) codes include:

- N03AA - Barbiturates and derivatives
- N03AB - Hydantoin derivatives
- N03AC - Oxazolidine derivatives
- N03AD - Succinimide derivatives
- N03AE - Benzodiazepine derivatives
- N03AF - Carboxamide derivatives
- N03AG (excluding N03AG01) - Fatty acid derivatives
- N03AX (excluding N03AX09 and N03AX14) - Other antiepileptics

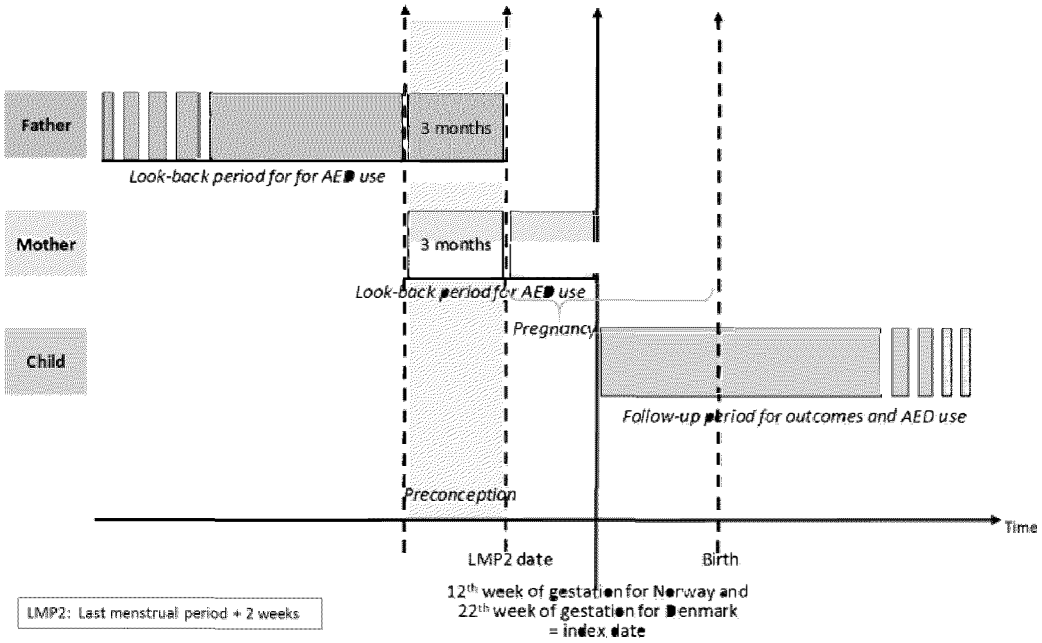
Different AED exposure periods were applied for the father, mother and offspring, and also for NDD (including ASD) and CM for Denmark and Norway, as shown in Figure 6 and Figure 7, respectively. For the CM analysis for Sweden, the exposure periods correspond to those specified for NDD (Figure 6).

The paternal exposure to AEDs was the exposure of interest in this study, whereas maternal and offspring exposure to AEDs were considered as potential risk factors and exclusion criteria for the comparative cohort. Methodologies related to the maternal and offspring exposure are further explained in section 9.4.4.



LMP2: Last Menstrual Period Date Plus 2 weeks, AED: antiepileptic drugs

Figure 6 Treatment exposure windows, Neurodevelopmental Disorders (NDD) including Autism Spectrum Disorders (ASD)



LMP2: Last Menstrual Period Date Plus 2 weeks, AED: antiepileptic drugs

Figure 7 Treatment exposure windows, congenital malformations for Norway and Denmark

Neurodevelopmental disorders, including autism

Two of the exposure periods were considered fixed and one not fixed.

Fixed exposure periods:

- 3 months[9] preconception for father (due to spermatogenic cycle)
- 3 months preconception for mother (section 9.4.4)

Not fixed exposure periods:

- pregnancy duration for mother (section 9.4.4)

Congenital malformations

Fixed exposure periods:

[9] In order to account for potential dispensations that can have led to an intake during the 3 months look-back period under investigation, all dispensations that were recorded in the 6 months before conception that gave rise to an AED intake during the 3 months prior to conception were considered. Because information on the exact number of days supplied were not available, patients' drug use periods were calculated using the defined daily doses (DDD) metric as defined by the World Health Organization. For each prescription the total number of DDDs was translated into the number of days in which the patient was treated, counting 1 DDD per day and distributing all available DDDs to the days of follow-up and allowing for the use of accumulated DDDs over time.

- 3 months [10] preconception for father (due to spermatogenic cycle)
- 3 months preconception for mother (section 9.4.4)
- 12 or 22 weeks prior to index date for mother, respectively, in Norway and Denmark (section 9.3.1)

Not fixed exposure periods:

- Pregnancy duration for mother, in Sweden (section 9.3.1)

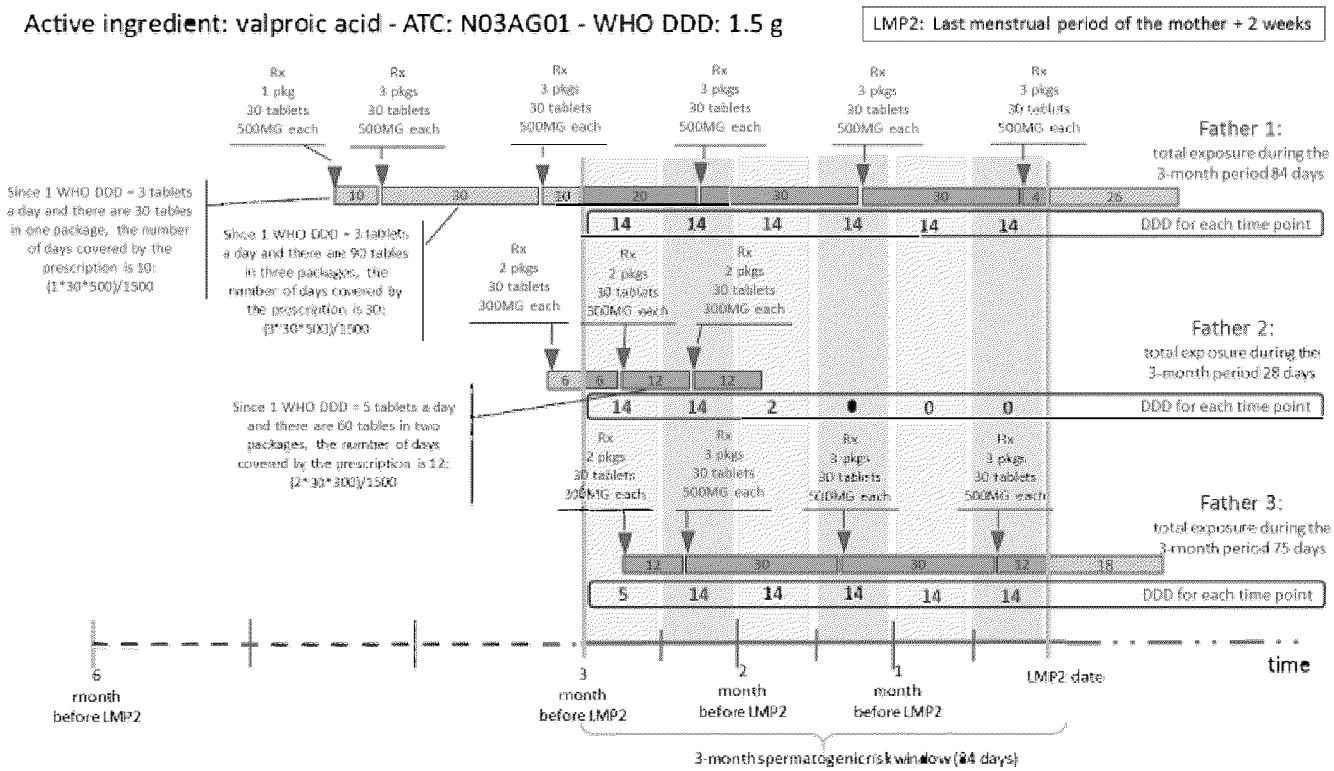
Classification of exposure

Particular care was taken in the definition and classification of paternal exposure. Person-time exposed was classified to take into account intensity of drug exposure during the 3 months preconception risk window using the longitudinal K-means clustering (R package kml) algorithm (16). This method allowed for a more precise description of exposure of fathers to drugs and allowed profiles to be distinguished improving evaluation of effects of drugs on outcomes. In summary the following steps were applied:

- To quantify drug exposure, for each individual, prescription data were transformed into the standard units of measurement of the World Health Organisation (WHO): the Defined Daily Dose (DDD) (Figure 8). The duration of treatment and dates of exposure were estimated assuming individuals were exposed to one DDD per day and used information on number of units and dates of prescriptions, where available. For the father, drug prescribed and dispensed 3 months before the LMP2 date (including the LMP2 date) were considered. A validation of the assumption that individuals were exposed to one DDD per day was provided as a sensitivity analysis in this final report.
- After superimposing length of exposure onto the spermatogenic risk window, exposure data were individually transformed into number of DDDs (Figure 8) dispensed during every 14 day interval within the 3 months exposure period. This way, the cumulative drug exposure of each father was evaluated at several time points, and the exposure data became longitudinal, which allowed drawing individual trajectories of exposure through the preconception period. Data were censored at the LMP2 date.
- For the analysis, clusters of fathers with homogenous trajectories of drug exposure were identified. The longitudinal K-means clustering algorithm was applied to create K clusters with homogenous trajectories, as empirically driven by the data. No assumption about the number of clusters was made prior to running the algorithm. Mean DDD trajectories were plotted for each cluster and shape described. Several clusters of exposed fathers may then be identified with homogenous trajectories of exposure during the 3 months risk window.
- The empirically defined clusters were described as part of the analyses for secondary objective 3. In the comparative analyses, for this report, the exposure was expressed as a dichotomous variable: exposure to valproate in monotherapy vs. exposure to lamotrigine/levetiracetam in monotherapy. The classification in cluster identified with the longitudinal K-means algorithm was used to stratify the comparative analysis in cluster homogeneous for duration and intensity of exposure.

The K-means algorithm was also applied to maternal exposure within the 3 months period prior to LMP2 and during the reported period of gestation. However, since mothers exposed to AEDs were excluded from the comparative analyses, these data were only provided for descriptive purposes.

[10] See footnote 15



DP: during pregnancy, NDD: neurodevelopmental disorders. LMP2: Last Menstrual Period Date Plus 2 weeks, CMV: Cytomegalovirus, MG: Milligram, ATC: Anatomical Therapeutic Chemical, WHO: World Health Organisation, DDD: Defined daily dose

Figure 8 Calculation of paternal exposure in each 14-day interval during the 3 months risk window prior to conception

9.4.2 Outcome definition and measures

During the observation period, which spaned from the index date to the exit date for each offspring, outcome events were identified based on ICD-10 codes recorded in patient registries.

Neurodevelopmental disorders, including autism

The **index date** was defined as the birth date of the offspring from which offspring were observed for occurrence of the outcome of interest[11].

The **exit date/end of follow-up** was defined as the end of the study period (31st December 2018 in Denmark and 31st December 2019 in Sweden and Norway), death, emigration (where available), reaching the age of 12 years or date of first diagnosis of the outcome at study, whichever was the soonest.

[11] Period between LMP2 (date of conception) and date of birth is immortal - child must survive to be eligible and diagnosis of NDD, including ASD cannot occur in utero

The primary outcome, NDD including ASD, was defined as a diagnosis of at least one ICD-10 code reported in the categories below:

ICD 10	Clinical Code Description	Category
F70	Intellectual Disability - Mild	Intellectual disabilities
F71	Intellectual Disability - Moderate	
F72	Intellectual Disability - Severe	
F73	Intellectual Disability - Profound	
F78	Other Intellectual Disability	
F79	Unspecified Intellectual Disability	
F80	Specific developmental disorders of speech and language	Communication disorders
F81	Specific developmental disorders of scholastic skills	Disorders of psychological development
F83	Mixed specific developmental delays	
F84	Pervasive developmental disorders	
F88	Other disorders of psychological development	
F89	Unspecified disorder of psychological development	
F99	Mental disorder, not otherwise specified	
R48	Dyslexia and other symbolic dysfunctions, not elsewhere classified	
F90	Hyperkinetic disorders	Hyperkinetic disorders
F988	Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	
F95	Tic disorders	Tic Disorders
F82	Specific developmental disorder of motor function	Movement Disorders
F984	Stereotyped movement disorders	
G250	Essential tremor	
G252	Other specified forms of tremor	
G253	Myoclonus	
G255	Other chorea	
G258	Other specified extrapyramidal and movement disorders	
G259	Extrapyramidal and movement disorder, unspecified	
G242	Idiopathic nonfamilial dystonia	
G243	Spasmodic torticollis	
G244	Idiopathic orofacial dystonia	
G245	Blepharospasm	
G248	Other dystonia	
G249	Dystonia, unspecified	
G26	Extrapyramidal and movement disorders in diseases classified elsewhere	

Congenital malformations

With the objective of investigating the risk of CM in offspring paternally exposed to valproate, all CM were included, with the caveat that minor CM were usually under-reported, therefore estimates could be underestimated (17). However, a sensitivity analysis (sensitivity analysis 4) was performed to address this concern for Norway and Denmark.

The **index date (start of follow-up)** was defined as the start of the 2nd and 3rd trimester (12th or 22nd week of gestation), respectively for Norway and Denmark, and from offspring birth date for Sweden from which pregnancies were followed-up for the outcome of interest.

The **exit date/end of follow-up** was defined as the end of the study period (31st December 2018 for Denmark and 31st December 2019 for Sweden and Norway) death, emigration (where available), reaching the age of 12 years or date of first diagnosis of the outcome at study, whichever was the soonest.

The analysis of the secondary outcome of CM was defined according to the presence of at least one of the following criteria:

- An ICD-10 code of CM among live births
- An ICD-10 code of CM in diagnosis/reason for spontaneous abortion/stillbirth (Norway and Denmark only)

9.4.3 Case assessment

Where cases of interest were reported, in order to minimise misclassification, further assessments of offspring identified as cases with the primary outcome of interest (NDD including ASD) (details as recorded in the registries) was undertaken.

Due to data access restrictions, it was not possible to undertake manual assessment of computerised profiles of NDD including ASD cases identified through diagnostic codes. Therefore, the assessment was undertaken on all NDD including ASD cases, based only on available coded data for the live-birth offspring.

All offspring from the Primary outcome cohort for descriptive analyses who were identified as having the outcome of interest (NDD including ASD) were included in this assessment. Each offspring identified as a case of NDD including ASD was assessed, and categorised into one of the following categories:

- Probable case: The offspring aged ≤12 years were considered a probable case if they satisfied the criterion that multiple diagnoses for NDD including ASD were recorded during follow-up, regardless of whether the same code was recorded multiple times or different codes were recorded
- Possible case: The offspring aged ≤12 years were considered a possible case if they satisfied the criterion that only one diagnosis record for NDD including ASD was recorded during follow-up

"Non-cases" were not captured since the analysis focuses on offspring with at least one record indicating NDD including ASD.

Frequency and percentages of probable and possible cases were presented calculated over the total number of cases identified as NDD including ASD.

9.4.4 Potential confounders/risk factors

A broad range of risk factors and potential confounders, related to the offspring, father and mother, were considered in the adjusted analysis for this final report. These included, but were not limited to, demographic and clinical characteristics and concomitant medications. The final selection of confounders depended on the availability of data, clinical relevance and model fit.

The list of potential risk factors and potential confounders for NDD and CM are summarised below in Table 4, Table 5, and Table 6. Additional information can be found in the study protocol (please see Section 9.3.3). Factors listed as exclusion criteria for the descriptive, comparative, sensitivity and exploratory objective analyses presented in this final report and the potential confounder list (Table 6) were omitted from the potential risk factors tables (Table 4 and Table 5).

Table 4 Potential risk factors for NDD

Mother	Father	Offspring
• Age • Obesity (12 months look back from LMP2) • Smoking (12 months look back from LMP2 and DP)[12] • Substance abuse (12 months look back from LMP2 and DP) • Alcohol abuse (12 months look back from LMP2 and DP) • Schizophrenia, schizotypal and delusional disorders (ever) • Affective Disorder (ever) • Neurotic Disorder (ever) • Rubella (DP) • CMV (DP) • Diabetes (ever) & Gestational Diabetes (DP) • Any concomitant medications associated with valproate-indicated psychiatric conditions (12 months look back from LMP2 and DP) [1] • Any concomitant medications associated with neuropsychiatric adverse effects (12 months look back from LMP2 and DP) [1,2]	• Substance Abuse (12 months look back from LMP2) • Affective Disorders (excluding bipolar and mania) (ever) • Schizophrenia, schizotypal and delusional disorders (ever) • Neurotic Disorder (ever) • Any concomitant medications associated with valproate-indicated psychiatric conditions (12 months look back from LMP2) [1] • Any concomitant medications associated with neuropsychiatric adverse effects (12 months look back from LMP2) [1]	• Sex • Foetal Alcohol syndrome • Fragile X Syndrome • Congenital CMV • Congenital Rubella • Lejeune/cri du chat syndrome • Tuberous sclerosis

[1] In addition to recognised risk factors, any co-medications received (including other psychoactive treatments received) during the exposure periods described in section "Exposure definition and measures", were investigated and adjusted for in the analysis using a polypharmacy index.

[12] In Denmark smoking during pregnancy is collected during sessions with midwife when all pregnant women are asked if they smoke. Smoking before pregnancy is only recorded if the woman is in contact with secondary healthcare before pregnancy and if the doctor asks.
In Sweden, smoking habit 3 months before current pregnancy is based on self-reported information where the mother was asked upon admission to the maternity healthcare unit. During pregnancy, there were two time points checks - one is smoking habits at admission to the maternity healthcare unit, the other was current status around week 30-32 (regular check during this period in Sweden).
In Norway, maternal smoking status was registered in the Medical Birth Registry. During an antenatal visit, an obstetric nurse midwife or physician fills checkboxes of mothers as non-smoker, occasional smoker (less frequent than daily), or daily smoker, in an antenatal chart that follows the woman throughout her pregnancy.

[2] Medications associated with neuropsychiatric adverse effects were medications with the potential to cause these side effects, not mothers actually experiencing the side effects.
DP: during pregnancy, NDD: neurodevelopmental disorders. LMP2: Last Menstrual Period Date Plus 2 weeks, CMV: Cytomegalovirus.

Omitted from this list were

- risk factors that were considered as exclusion criteria:
  - Mother: history of epilepsy and NDD,
  - Father: history of NDD,
  - Child: exposure to AEDs and diagnosis of epilepsy after birth
- Paternal factors listed in Table 6

Table 5 Potential risk factors for CM

Mother	Father	Offspring
• Age • Obesity (12 months look back from LMP2) • Smoking (12 months look back from LMP2 and DP) • Alcohol abuse (12 months look back from LMP2 and DP) • Substance abuse (12 months look back from LMP2 and DP) • Diabetes (ever) • Gestational diabetes (DP) • Rubella (DP) • Varicella (DP) • Toxoplasmosis (DP) • Herpes Simplex virus (DP) • CMV (DP) • Folate deficiency (DP)		• Congenital Rubella • Congenital Varicella • Congenital CMV • Congenital Herpes Syndrome • Congenital toxoplasmosis • Foetal Alcohol Syndrome

DP: during pregnancy; CM: congenital malformations; LMP2: Last Menstrual Period Date Plus 2 weeks; CMV: Cytomegalovirus

Omitted from this list were:
- Risk factors that were considered as exclusion criteria:
  - Mother and father: congenital malformations including chromosomal disorders
  - Mother: teratogenic drugs
- paternal factors listed in Table 6.

Table 6 Potential confounding variables by outcome

Outcome	Father
NDD, including ASD	• Age • Bipolar affective disorder and mania (ever) • Calendar year of conception of offspring
CM	• Age • Calendar year of conception of offspring

NDD: neurodevelopment disorders; ASD: autism spectrum disorder; CM: congenital malformation

9.5 Data Sources and Measurement

Database selection was based on availability of mandatory variables, good quality of data and the possibility to link mothers, fathers, and offspring records to create the family linked units of analysis.

Databases used in the study are listed in Table 7 from Sweden, Denmark, and Norway. Sweden, where the linkage with fathers is not possible for non-live births, was not included in the secondary outcome analysis. However, for completeness an exploratory analysis was proposed to explore risk of CM in live births.

Table 7 Rationale and data source description by country

Country	Data source	Type of data and brief description
Sweden	Multigenerational Register	Source of data for personal identifier for mothers, fathers and offspring, biologic vs. adoptive parents, siblings, migration status and marital status. Source of linkage to father (available only for live births).
	Cause of Death Register	Source of data for vital status and further details on diagnosis or cause leading to spontaneous abortions or stillbirths.
	National Prescription registry	Source of data for all outpatient dispensations of prescription medications. Recorded information includes data of dispensations, active substance using ATC code, amount sold, pack size and route of administration. Data available since 2005.
	National Patient Registry	Source of data for all diagnosis outcomes of interest in live births. The registry tracks discharge diagnoses with dates and information about procedures. The ICD-10 coding system was used for the duration of our study period.
	Medical Birth Registry	Source of data for information on gestational age, birth weight, 5-minute Apgar score, live births, stillbirths, smoking during pregnancy, body mass index (BMI), date of conception (estimated from gestational age and date of birth), procedures connected to assisted fertilisation.
Norway	Central Person Register	Source of data for personal identifier for mothers, fathers and children, vital status, migration status and marital status.
	Norwegian Prescription Database	Source of data for all outpatient dispensations of prescription medications. Recorded information includes data of dispensations, active substance using ATC code, amount sold, pack size and route of administration. Data available since 2004.
	Norwegian Patient Registry	Source of data for all diagnosis outcomes of interest in live births. The registry tracks discharge diagnoses with dates and information about procedures. The ICD-10 coding system was used for the duration of our study period.
	Medical Birth Registry	Source of data for information on gestational age, birth weight, 5-minute Apgar score, live births, stillbirths, spontaneous abortions, smoking during pregnancy, BMI, date of conception (estimated from gestational age and date of birth), assisted reproductive technology (ART). Source of linkage to father.

Country	Data source	Type of data and brief description
	Cause of Death Register	Source of data for vital status and further details on diagnosis or cause leading to spontaneous abortions or stillbirths.
Denmark	The Danish Civil Registration System	Source of data for personal identifier for mothers, fathers and children, vital status, migration status and marital status.
	Register of Medicinal Product Statistics (RMPS)	Source of data for all dispensations of prescription medications at community pharmacies at individual patient-level. Recorded information includes data of dispensations, active substance using ATC code, amount sold, pack size and route of administration. Data available since 1995.
	National Patient Registry	Source of data for all diagnosis outcomes of interest at public and private hospitals (somatic and psychiatric wards). The registry tracks primary and secondary diagnoses with dates and information about procedures and treatment. The ICD-10 coding system was used for the duration of our study period. Diagnoses at psychiatrists (and other specialists) who have their own private practice are not registered in the National Patient Registry.
	Cause of Death Register	Source of data for further details on diagnosis or cause leading to spontaneous abortions or stillbirths.
	Medical Birth Registry	Source of data for gestational age, birth weight, 5-minute Apgar score, live births, stillbirths, malformations, smoking during pregnancy, BMI, date of conception (estimated from gestational age and date of birth). Source of linkage to father.
	The In Vitro Fertilisation Register	The IVF register contains information on IVF treatment carried out at public as well as private fertility clinics in Denmark. For IVF treatments resulting in pregnancy, information on birth, miscarriage or stillbirth is also available.

IVF: In Vitro Fertilisation; BMI: Body Mass Index; RMPS: Register of Medicinal Product Statistics; ART: Assisted Reproductive Technology; ATC: Anatomical Therapeutic Chemical; ICD-10: International Classification of Diseases 10th Revision.

The data sources considered are routinely used for PASS requested by the European Medicines Agency and the subject of many publications.

Nordic National Registers for Sweden, Norway, and Denmark

The availability of National Registries makes the Scandinavian countries an optimal choice to identify parent-offspring combinations with linked longitudinal records data. Each individual in Sweden, Norway and Denmark is provided with a unique personal identification number at birth or upon immigration. The personal identification number is used for many administrative purposes, such as an identifier in population and health care registers in all 3 countries. The number forms the basis for the precise linkage of individual-level data between different registers within each country, allowing the creation of a dataset with individual-level data for any given study. The number also allows family linkage of data.

Sweden, Norway and Denmark have National Patient Registers, which contain data from in- patient and out-patient care. The key variables of the patient registries include diagnosis, surgery, and other procedures, as well as gender, age, region, hospital, specialty, referrals to/treatment in hospitals or by specialists and hospital admissions/discharges. The National Prescription Registries include all prescribed and dispensed medication to the individual patient covering all pharmacy transactions retrospectively from 1995 (Denmark), 2004 (Norway) and 2005 (Sweden). Country-specific information on the registers is provided below.

Sweden

Individual patient data is collected from both in-patient and out-patient hospital-based specialist care across all of Sweden. The National Patient Register dates back to 1964. From 1987 onward, there is information on all completed in-patient admissions across the country. The collection of outpatient care data began in 2000. The register is updated annually and available from September/October the following year.

All medicines are prescribed electronically in Sweden. The National Prescription Register tracks the full details of all dispensed medications at individual patient-level in Sweden since July 1, 2005. Patients are followed longitudinally through their personal identification number, regardless of which pharmacy they visit. The National Prescription Register is updated monthly and covers all sales of dispensed medication from Swedish pharmacies.

The Medical Birth Register contains information about all pregnancies resulting in delivery in Sweden and is frequently used for quality improvement work and for research. The register contains detailed information about mothers and births. The Swedish Multigeneration Register was established in 1973 and contains information on more than 9 million individuals. Data on mothers are available in 97% and on fathers in 95% of index people (those born from 1932 onwards and those alive on January 1, 1961). Individual-level data on breastfeeding is not available in the Swedish registers.

Norway

In Norway, data about live offspring and their parents are obtained from the Medical Birth Registry, a national registry containing information about all births, maternal health before and during pregnancy, and any complications during pregnancy or birth, as well as for pregnancies ending after week 12. Data are linked to the National Population and Housing Censuses (1960-1990), the Central Person Register, and some other national registers. The database is completely anonymous, in that the 11-digit national identity number has been removed and substituted by another number with no connection to the original number. Thus, it is not possible to connect to micro data from sources outside the database. To further prevent the identification of individuals, information such as

municipality of birth and residence is replaced by the corresponding information at county level. The Medical Birth Registry of Norway holds information on all pregnancies and births since 1967 (notification is compulsory) from 12 completed weeks of gestation onwards. Linkage to fathers is available for 97% of live and non-live births (4). Individual-level data on breastfeeding may not be available in the Norwegian registers.

Denmark

Denmark has the longest-standing civil registration system in the world. From 1968 and onwards, the Danish Civil Registration System (CRS) has held information on all persons with a permanent address in Denmark, and the relations between spouses, parents and offspring. Therefore, there is considerable scope for creating a multigenerational database that can accommodate multiple research purposes. The National Patient Register holds good quality data on diagnoses of childhood NDD and adults with psychiatric disorders in secondary care. The Danish Medical Birth Register has held near complete information on pregnancy (live and non-live births) and birth details for mothers and offspring respectively since 1973, from 22 completed weeks of gestation onwards. Data on fathers are available for 97.5% of live births (7). Information on breastfeeding is available from 2012 in the Danish registers.

9.6 Bias

9.6.1 Selection Bias

To minimize potential selection bias, minimal inclusion and exclusion criteria were used for this study. Considerations to address the possible related biases are presented below.

Primary outcome cohort (NDD)

- Because the potential for reverse causality may apply and since there is likely to be correlation between epilepsy and NDD, offspring having received AED therapy or with a diagnosis of epilepsy were excluded in the comparative analyses. This could have resulted in introducing a selection bias. To assess the potential impact of having excluded children exposed to AEDs and/or diagnosed with epilepsy, a sensitivity analysis was performed (sensitivity analysis 7, section 9.9.4.7).
- Selection of the cohort based on paternal valproate or lamotrigine/levetiracetam monotherapy use could have resulted in selection bias. Conversely, exposure to more than one AED would not allow the identification of which AED was associated with the outcome of interest, making it impossible to draw any association conclusions; hence, justifying the exclusion of paternal AED polytherapy exposure. Therefore, fathers switching their treatments were considered polytherapy in this study and their offspring were excluded from the main analyses. The frequency of switchers was described to evaluate the extent of possible bias and a descriptive analysis of polytherapy users was conducted as an exploratory objective (exploratory objective 3, section 7.3) to understand this population.
- Evaluation of AED exposure according to monotherapy is preferred for comparative analyses, to limit: the risk of disease severity bias, associated with polytherapy.

Secondary outcome cohort (CM)

- Offspring from parents exposed to teratogenic drugs were excluded from the secondary outcome cohort, resulting in possible selection bias.
- Information about spontaneous abortions and stillbirths (linked to the mother and father) were not available for Denmark before the 22nd week of pregnancy and for Norway before the 12th week of pregnancy. Accordingly, diagnoses of CM leading to spontaneous abortion and elective terminations of pregnancies that occurred before these weeks of gestation were not detectable and not included in this study. This may have led to a selection of cases and to a survivor bias as the distribution of type of CM and severity is likely to be different.

9.6.2 Information Bias

Due to the nature of the data sources, some possible information biases have to be anticipated.

- Exposure misclassification: it is assumed that all prescribed drugs are dispensed and then taken by patients in a compliant manner. Non-compliance would result in misclassification of exposure and could cause an underestimation of the association between exposure and outcome. Another source of exposure misclassification is related to the definition of the risk window of 3 months prior to the estimated date of conception; if conception date was incorrectly estimated, exposure risk window was also possibly incorrectly estimated. But such exposure misclassifications were not expected to be differential.
- Outcome misclassification, on the other hand was very unlikely: hospitalizations and outpatient visits within secondary care are comprehensively covered in the National Patient Registers in Denmark, Norway and Sweden.
    - ASD: In a study evaluating the quality of childhood ASD diagnosis in the Danish Psychiatric Central Register, it was found that 94% of the childhood ASD diagnoses met the ICD-10 criteria for a correct diagnosis (18). Therefore, the identification of ASD cases by ICD-10, as proposed in this study seemed valid.
    - NDD: Diagnosis of NDD can be challenging, since NDD is a broad term covering multiple signs/diagnoses; with sometimes lack of specific medical tests or consensus to diagnose disorders: specialists must have a holistic approach to deal with behavior and/or anomalies not necessarily being obvious for several years after birth. The final diagnosis might occur late, with possible differences in the identification of certain disorders over others, as well as delayed recording. Furthermore, it is very likely mild NDD such as “walking late” for instance may have not been as well captured as severe ones were.

  This outcome misclassification, if present, is not expected to be differential between the paternal exposure groups, except in one circumstance: in case of different time periods of diagnosis in the offspring of the two groups, as methods of NDD diagnosis have evolved

overtime (see detection bias below). In this regard, difference in year of conception of the offspring might bias the risk ratio.

- Immortal time bias in risk of NDD assessment: in the case an offspring may have no contact with the health care system for an extended period time, that individual could potentially experience an outcome before it can be recorded. This could cause a delayed diagnosis observation and immortal time bias.
- Informative censoring bias in the Cox model (NDD): an insufficient length of follow-up may lead to a reduced probability to capture events and subsequently produce biased results and reduce the validity of the findings. In this study, differences in the length of follow-up were observed between exposure groups - longer follow-up being in the valproate group, and between countries - longer follow-up being in Denmark. In addition, informative censoring may occur when time to event and time to censoring are dependent, either directly or through covariates. In the latter situation, dependent censoring occurs when one or more covariates are associated to both the lifetime/outcome and censoring mechanism. In these situations, standard survival techniques such as Kaplan-Meier estimators can be biased. Specific statistical methods could have been considered to mitigate this bias, but none had been anticipated and none were performed.
- Detection bias (heterogeneous between countries): the likelihood of being diagnosed with NDD or ASD was not the same across the three countries. In Sweden some specific financial help and healthcare management are offered for children diagnosed with NDD including ASD; this could explain a higher incidence rate in this country.
- Detection bias (overtime)/period bias: in the three countries, detection of NDD improved overtime and occurred at younger age, thanks to progressive implementation of screening campaigns. As examples, an early screening program including children aged 2.5 years was progressively implemented by Swedish Child Health Care Services starting in 2012. A similar implementation has been made in Denmark where the age at diagnosis decreased progressively from 1997 onward. Similarly, in Norway the early diagnosis has been implemented starting in 1999, with good specificity in detecting more severe cases of ASD, but with quite poor sensitivity (19). Along with the detection at a younger age, the definitions of ASD also evolved overtime, such as introduction of ASD including Asperger recently. This timebias might have impacted not only the cumulative risk and incidence rate estimates but also the risk ratios, as the year of conception was an unbalanced parameter between the two groups.
- Time bias: in the case of probability of outcome detection is not constant over time and the length of follow-up very different between the two groups, offspring from one of the exposure groups would have a higher chance of being diagnosed with the outcome. This could lead to a violation of the proportional hazard assumption which is the key assumption of the Cox model, and thus resulting in a biased estimation of the hazard ratio.

9.6.3 Confounding

Given that registries may not contain information on all relevant known and unknown confounding variables, residual confounding may still be present in the study results. Examples are outlined below:

- Small numbers issues: all relevant measured covariates found as risk factors and or confounders were entered into the propensity score model, and the multivariate Cox model (NDD and ASD outcomes) or Logistic regression (CM outcome) were adjusted accordingly. Due to the small number of events, it was not possible to include all the covariates remained unbalanced after PS-weighting in the final PS-weighted Cox model. Only the one with the higher size effect was included. Therefore, the presence of residual confounding in the estimation of the HR cannot be ruled out.
- Unmeasured covariates: certain potential risk factors and / or confounders were not measured in this study:
    - Among the known risk factors for NDD, genetic disorders, perinatal situations or conditions, certain infectious diseases such as measles or meningitis, and brain trauma in early childhood. It was assumed that these characteristics were balanced between the 2 exposure groups, though this assumption was not verified as these characteristics were not derived. There could have been a difference in the distribution of these characteristics between the 2 exposure groups, resulting in bias in the HR estimate.
    - Regarding the parents, information on medicines without prescription purchased from a retailer was not available in the registers. For example, not accounting for folic acid supplementation could lead to a bias in either direction for the risk estimates for both primary and secondary outcomes, in both exposure groups; however, folic acid supplementation is anticipated to be nondifferential, so the OR (CM) and HR (NDD) estimates should not be impacted. A similar situation should be acknowledged regarding some lifestyle factors poorly measured in this study, such as smoking, alcohol consumption, recreational drugs consumption, and regarding some environmental or viral toxic substances.
    - Family history: familial history is not taken into account, which in some cases could explain the developmental disorders, e.g. familial history of intellectual deficiency, this is suggesting a genetic origin. Similarly for ASD, the risk of ASD is higher if siblings of the parents have ASD. Risk of ASD estimates may therefore be biased in this study.
- Indication/Severity bias: valproate and lamotrigine, levetiracetam are not indicated for the exact same conditions: lamotrigine is more used for patients with mood disorders, while levetiracetam and valproate are for epilepsies. Indication bias may therefore exist, which was addressed with the pairwise comparison in some sensitivity analyses. But the severity bias might still be present in the study as the type of epilepsy was not available in this study. Hence, we were not able to identify parents with "genetic" epilepsy, for which valproate is the preferred treatment, and which may be more impactful on the parental educational activities, causing delay in the development of their child. Valproate is the treatment of choice (or first-line drug) for male patients with idiopathic generalised epilepsy, a type of epilepsy which could be associated with neurodevelopmental disorder and is known to have a genetic basis and as such can be found in several members of the same family.
- Regarding estimation of the risk of NDD: offspring with CM are more at risk of NDD. Not having excluded offspring suffering from CM in the primary outcome cohorts might have

biased the estimate of the NDD risk, overestimating it in both groups. But the magnitude of potential bias in each exposure group is unknown. It can be very different between the two exposure groups, depending on the number of offspring with CM actually developing NDD in each group. Hence, these groups of offspring not excluded could also have impacted the estimate of the HR. Similarly with chromosomal anomalies, which seem to be unbalanced between the two groups.

9.7 Study Size

The primary objective of this observational study was to explore the association of risk of NDD, including ASD in offspring paternally exposed to valproate in comparison to lamotrigine / levetiracetam (composite comparator). Given the interest in ASD, the sample size was estimated for this endpoint, with the assumption that this endpoint was nested within the primary endpoint. Accordingly, the sample size would be sufficient to observe the desired effect size for the composite primary endpoint.

The sample size calculations for ASD endpoint are presented in Table 8, more details about methodology can be found in the Study protocol v6.0 (please see Section 9.5).

Table 8 Expected sample sizes to estimate various effect size given different reference risks of ASD in offspring paternally exposed to other AEDs (by power: 90% and 80%)

Reference Risk of ASD	Effect size											
	1.5	2	2.5	3	3.5	4	1.5	2	2.5	3	3.5	4
	Power: 90%						Power: 80%					
0.5%	42948	12970	6718	4302	3082	2364	32482	9888	5154	3316	2384	1836
1.0%	21346	6440	3334	2132	1526	1170	16144	4910	2558	1644	1182	910
1.5%	14144	4264	2204	1410	1008	772	10700	3252	1692	1088	780	600
2.0%	10544	3176	1640	1048	748	574	7976	2422	1260	808	580	446
3.0%	6944	2086	1076	686	490	374	5254	1592	826	530	380	292
4.0%	5144	1542	794	506	360	274	3892	1178	610	390	280	214

ASD: Autism Spectrum Disorders

For the ASD endpoint, it was assumed that the risk of ASD in the reference group (live offspring paternally exposed to lamotrigine/levetiracetam monotherapy) was 1.5%. In order to be able to observe a hazard ratio (HR) of 2.00 (i.e. doubling of risk in offspring paternally exposed to valproate) with 5% significance and 80% power, a sample size of 3252 children within the family linked unit was needed across all 3 countries. This required a minimum of 1627 offspring within a family linked unit with paternal exposure to valproate (monotherapy), and a minimum of 1627 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (monotherapy).

For the primary endpoint, the same assumptions with the exception that the assumed risk of NDD (including ASD) in the reference group is 4%. Therefore, in order to observe a HR of 2.00 (i.e. doubling of risk in offspring paternally exposed to valproate) with 5% significance and 80% power, a sample size of 1178 offspring within the family linked unit was needed across all 3 countries. This

required a minimum of 589 offspring within a family linked unit with paternal exposure to valproate (monotherapy), and a minimum of 589 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (monotherapy).

For the comparative analysis, the total number of offspring selected in the Primary outcome cohort for comparative analyses in Denmark was 1950 (with 793 offspring paternally exposed to valproate and 1157 offspring paternally exposed to lamotrigine/levetiracetam).

For the comparative analysis, the total number of offspring selected in the Primary outcome cohort for Sweden was 2355 (with 930 offspring paternally exposed to valproate and 1425 offspring paternally exposed to lamotrigine/levetiracetam).

For the comparative analysis, the total number of offspring selected in the Primary outcome cohort for comparative analyses in Norway was 1943 (with 617 offspring paternally exposed to valproate and 1326 offspring paternally exposed to lamotrigine/levetiracetam). This demonstrates that the minimum sample size was achieved for the primary outcome in the 3 countries

For the secondary outcome, CM, assuming a minimum effect size of 2.5, where the background incidence was 3%, with 80% power, a study with a total sample size of 826 family linked offspring (n=413) in the valproate monotherapy group and (n=413) in the comparator monotherapy group would be desirable.

For the comparative analysis, the total number of offspring selected in the Secondary outcome cohort for comparative analyses in Denmark was 648 (with 259 offspring paternally exposed to valproate and 389 offspring paternally exposed to lamotrigine/levetiracetam). The corresponding total number of offspring selected in the Secondary outcome cohort for comparative analyses in Norway was 673 (with 251 offspring paternally exposed to valproate and 422 offspring paternally exposed to lamotrigine/levetiracetam). Thus, the sample size attained for the Secondary outcome cohort allowed to achieve power for the descriptive analyses, including incidence risk and rate and time-to-event, but not for the comparative analyses.

9.8 Data Transformation

The raw data were extracted by the data owners of each registry, based on the inclusion criteria presented in the protocol (section 9.2.2) and the SAP (section 6.2.2).

The subsequent processes for data handling differed by country but the processes were implemented to ensure all the analyses were performed the same way in the three countries while complying with the local regulation and policy.

- In Sweden, the extracted raw data were delivered to the vendor in charge of the analyses (vendor also in charge of writing the study programs for the three countries); the vendor then run the programs developed according to the SAP. SAS or R language (version 3.1.1, or above) was utilized for extraction of the raw data, for analytic datasets management and data analysis.
- In Norway and Denmark, the process was different: no vendor is allowed to have any direct access to the raw data per local policy. So the whole analyses process from the raw data to

the results tables was performed by the data holders themselves, using the programs developed by the vendors.

The derived variables were generated as described in section 6.3. of the SAP:

- Exposure information was derived from dispensation data, as recorded in the National Prescription Registries for each country (SAP section 6.3.1):
    - As binary variable (yes/no) (SAP section 6.3.1.1) and as categorical variable (SAP section 6.3.1.2), in the 3-months lookback from [Last Menstrual Period + 2 weeks] (LMP2) for fathers.
    - As categorical variable (SAP section 6.3.1.2), both in the 3-months from LMP2 lookback and during pregnancy for mothers.

For these exposure information derivations, months were defined as periods of 28 days.

- The number of days covered were derived as intermediate variable using the DDD of each AED and the K-means method was used to derive intensity of the exposure.
- Indication for AED for fathers was derived from the medical history (SAP section 6.3.1.3).
- Indication for AED for mothers was derived from the medical history (SAP section 6.3.1.3).
- Outcomes (NDD, ASD, CM) in offspring were identified based on ICD-10 codes recorded in patient registries (SAP section 6.3.2); specific code lists apply for each outcome.
- Continuous variables were derived by calculation, e.g.:
    - "Pregnancy duration" was derived from offspring birth and LMP2 dates, by difference between those dates.
    - "Mother Age" and "Father age" at inclusion were derived from calendar offspring conception date and Mother/Father year of birth.
- Categorical variables were created by the grouping of reported values of discrete or continuous parameters e.g.:
    - Variable "Age group" for mother and father was defined in 6 categories ≤20, [21–25], [26-30], [31–35], [36–40] and >40 years based on continuous parameter "age", and a 'missing' category when the parameter was unknown.
    - "Maternal polypharmacy in the 3-months lookback from LMP2" was first derived as continuous variable, by calculation as the total number of distinct ATC codes for the medications received during the defined periods (in the 3-months lookback from LMP2); and the calculated continuous variable was then defined in 4 categories 0, 1-4, 5-10, >10.
    - "Maternal polypharmacy during pregnancy" was first derived as continuous variable, by calculation as the total number of distinct ATC codes for the medications received during the defined periods (during pregnancy); and the calculated continuous variable was then defined in 4 categories 0, 1-4, 5-10, >10.

- "Paternal polypharmacy in the 3-months lookback from LMP2" was first derived as continuous variable, by calculation as the total number of distinct ATC codes for the medications received during the defined periods (in the 3-months lookback from LMP2); and the calculated continuous variable was then defined in 4 categories 0, 1-4, 5-10, >10.
- "Gestational age" category for offspring was defined in 5 categories <28; 28-31; 32-36;37-41; ≥42 weeks, based on continuous parameter "gestational age" from the registry and a 'missing' category when the parameter was unknown.
- "Birth weight" group for offspring was defined in 4 categories <1000; 1000-1499; 1500-2499; ≥2500gr, based on continuous parameter "birth weight" and a 'missing' category when the parameter was unknown.
- "Year of conception" group for the comparative analyses were defined by using 5-years categories.
- "Age at first diagnosis of NDD" group for offspring was defined in 6 categories 0-1, 2-3, 4-5, 6-7, 8-9, 10-11 from the continuous age of the offspring at the diagnosis of NDD.
- "Age at first diagnosis of ASD" group for offspring was defined in 6 categories 0-1, 2-3, 4-5, 6-7, 8-9, 10-11 from the continuous age of the offspring at the diagnosis of ASD.

- Binary variables ("yes/no") other than those listed above were generated as follows (full list of variables detailed in SAP section 6.3.3):
  - Medical conditions, as comorbidity in fathers and in mothers were identified based on ICD-10 codes recorded in the registries.
  - Medications, in fathers and in mothers were identified based on presence of at least one dispensation during the assessment window (in the 3-months lookback from LMP2 for fathers, in the 3-months lookback from LMP2 and during pregnancy for mothers).

Some derivation definitions specific to exploratory analyses and to sensitivity analyses were also used; they are detailed in the SAP section 7.4 and 7.5 respectively.

9.9 Statistical Methods

9.9.1 Main Summary Measures

Statistical analyses were performed using statistical packages (SAS Enterprise Guide, STATA, and R [version 3.1.1, or above]).

Continuous variables were summarised using mean, standard deviation (SD), median, minimum-maximum (where permitted to describe) and 25^{th}-75^{th} percentile. Some of quantitative variables are categorised into discrete categories.

Categorical variables were summarised using N and % within each category. Percentages were calculated over non-missing cases, unless otherwise specified. For binary variables (including risk factors, confounders, and outcomes), the absence of a relevant code was considered as indicative of no formal diagnosis for that condition, rather than missing information.

All statistical tests used a 0.05 significance level and are double-sided.

All analyses use the offspring (or non-live-birth) as unit; each offspring/non-live-birth. All variables collected for fathers and mothers were described in relation to each individual offspring/non-live-birth.

All analyses for this final report were conducted and presented separately for Denmark, Sweden and Norway.

9.9.2 Main Statistical Methods

9.9.2.1 Descriptive Analyses

These analyses included the creation of a STROBE diagram which visually describes the selection of the population used in each study analysis.

Descriptive analyses that were as per below mentioned criteria:

- Characterisation of Primary outcome cohort and Secondary outcome cohort.
- Characterisation of the Primary outcome cohort for descriptive analysis and Secondary outcome cohort for descriptive analysis (offspring paternally exposed to valproate, lamotrigine/levetiracetam in monotherapy in the 3 months lookback from LMP2).
- Incidence of the primary and secondary outcomes conducted in the Primary outcome cohort for descriptive Analysis and Secondary outcome cohort for descriptive analysis (offspring paternally exposed to valproate, lamotrigine/levetiracetam in monotherapy in the 3 months lookback from LMP2).

The descriptive analyses were described in detail in the sections below.

Characterisation of the study population

This analysis described the Primary outcome cohort and Secondary outcome cohort, which were obtained after applying initial extraction inclusion and exclusion criteria to the extracted cohort (see section 9.3.1).

Characteristics of offspring, mothers and fathers were presented for the 2 cohorts separately (no additional stratification is used). The unit of analysis was the offspring and their paternal/maternal characteristics; for this reason, the same mother/father appeared more than once in the descriptive analysis if they had more than one offspring included in the study cohorts. In case the same mother/father was included in the study with more than one offspring, their characteristics were described in relationship to the exposure window for each individual offspring. For example, age of father at index date was calculated separately for each offspring included in the study, and the same father was included in the descriptive analysis as many times as the number of their offspring, which were included in the study cohorts.

All the potential risk factors and confounders for each outcome were presented. Since the population used in this analysis also included offspring paternally exposed to AEDs polytherapy during the 3

months lookback from LMP2, in addition to all the risk factors and confounders, additional variables were also presented for fathers, describing the use of AEDs during the 3 months lookback from LMP2. Where percentages were presented, these were calculated over the total number of offspring in the cohort described; this was because the same father could have more than one offspring included in the study and in these cases, their exposure was considered separately for each offspring.

- Number and percentage of offspring paternally exposed to each individual AED in the 3 months lookback from LMP2 (regardless of whether it was in monotherapy or polytherapy).
- Number and percentage of offspring paternally exposed to AEDs polytherapy in the 3 months lookback from LMP2, i.e. the number of fathers receiving more than one AED during the 3 months (simultaneously of in sequence).
- Number and percentage of offspring paternally exposed to valproate in combination with other AEDs in the 3 months lookback from LMP2 (for definition of combination, see section 9.4).
- Number and percentage of offspring whose fathers switched to/from an AED other than valproate, lamotrigine, levetiracetam in the 3 months lookback from LMP2: these were all the fathers who experienced a switch during the 3 months lookback from LMP2, and who received only one treatment between valproate, lamotrigine, levetiracetam, and at least another AED (for definition of switch, see section 9.4) during the same period.
- Number and percentage of offspring paternally exposed to monotherapy with valproate, lamotrigine, levetiracetam respectively in the 3 months lookback from LMP2.

Descriptive analyses

The population included in the Primary outcome cohort for descriptive analysis and Secondary outcome cohort for descriptive analysis contained offspring paternally exposed to valproate, lamotrigine/levetiracetam (monotherapy) in the 3 months lookback from LMP2.

This analysis described the Primary outcome cohort for descriptive analysis and Secondary outcome cohort for descriptive analysis in terms of clinical characteristics, demographics and risk factors. Three separate tables were produced: fathers' table, mothers' and offspring tables. Results were presented overall and by paternal exposure group: valproate, lamotrigine, levetiracetam, and lamotrigine/levetiracetam (composite).

All the potential risk factors and confounders for each outcome were presented.

In addition to the risk factors and confounders, paternal and maternal exposure to AEDs during the 3 months lookback from LMP2 (and also during pregnancy for mothers) were described in the paternal and maternal tables by using the K-means clusters method. Although maternal history of epilepsy was not considered a risk factor for CM, this characteristic was summarised in both cohorts.

In addition to the risk factors and confounders, the following offspring characteristics were presented:

- Gestational age (<28; 28-31; 32-36; 37-41; ≥42 weeks)
- Birth weight (<1000; 1000-1499; 1500-2499; ≥2500 g)
- Gender
- Year of birth (Primary outcome cohort for descriptive analysis only)
- Frequency of ASD (Primary outcome cohort for descriptive analysis only): this included the total number of unique offspring with at least one diagnosis of ASD in their entire follow-up, not only those whose first diagnosis for the primary outcome was ASD

(offspring with a first diagnosis of NDD, and a later diagnosis of ASD was included in this summary) but also, those with ASD as a 1st diagnosis
- Frequency of NDD including ASD (Primary outcome cohort for descriptive analysis only)
- Frequency of NDD including ASD ICD-10 codes: this was the total number of unique offspring with each ICD-10 code in their entire follow-up. Since each offspring might have more than one ICD-10 code related to the primary outcome during their follow-up, the sum of the totals for each ICD-10 code might exceed the total number of offspring experiencing the primary outcome
- Age (in years) at ASD diagnosis (Primary outcome cohort for descriptive analysis only): age at first diagnosis of ASD referred to the age at first record of ASD ever, independently if it occurred before or after another NDD, for offspring with both NDD and ASD outcomes
- Age (in years) at first diagnosis of NDD including ASD (Primary outcome cohort for descriptive analysis only)
- Frequency of CM: overall, and by major or minor CM, separately: while for the frequency of CM only one outcome per offspring was considered, for the description of major and minor CM codes, all records were evaluated and if the same offspring was diagnosed with both major and minor CM, they appear in both summary frequencies
- Frequency of stillbirth, spontaneous abortion, intrauterine growth retardation and perinatal mortality, associated to a diagnosis of CM

Incidence of Primary and Secondary outcomes

The population included in this analysis was the Primary outcome cohort for descriptive analysis and Secondary outcome cohort for descriptive analysis.

The cumulative incidence proportion, incidence rate and time to onset of primary and secondary outcome were explored separately by paternal exposure group. Results were presented overall (by cohort), and separately by paternal exposure group: valproate vs. lamotrigine/levetiracetam (composite and separately). Cumulative incidence proportion and rate were presented by year of follow-up.

The following analyses were conducted on the primary outcome:

- Cumulative incidence proportion of NDD including ASD, by follow-up year and for years 0-12
- Cumulative incidence rate of NDD including ASD, by follow-up year
- Time to NDD including ASD

On the secondary outcome, the following analysis was conducted:

- Cumulative incidence proportion of CM, by follow-up year and up to until 12 years. This was calculated as the total number of offspring experiencing the outcome during the entire follow-up (i.e. the sum of the number of events for the years 0 to 12) divided by the initial number of offspring included at the start of follow-up (i.e. population used in the analysis). Notably, considering that the index date in the CM cohort started before or on date of birth and that patients were followed-up until 12 years of age at maximum, there were patients with a follow-up longer than 12 years, and therefore cumulative incidence proportion for the entire follow-up included a longer period than 12 years (but shorter than 13 years).

The following sections describe the methodology that was used to conduct each of these analyses.

- **Cumulative incidence proportion (risk)**

The cumulative incidence proportion (or risk) of both the primary and secondary outcomes were calculated by follow-up year and reported with 95% confidence intervals (CI). Cumulative incidence proportion were calculated overall by cohort, and separately by paternal exposure groups, as follows:

- Valproate
- Lamotrigine/levetiracetam (composite)
- Lamotrigine
- Levetiracetam

For each follow-up year, the cumulative incidence proportion was calculated according to the formula below:

$$Cumulative\ incidence\ proportion_{year-i} = (Offspring\ with\ newly\ diagnosed\ outcome\ during\ year\ i / Offspring\ at\ risk\ at\ start\ of\ year\ i) x 100$$

Follow-up time was divided into 365-days intervals starting on the index date until the earliest between the date of first diagnosis of the outcome of interest, the end of the study period, death, emigration (where available) or reaching the age of 12 years. Where index date coincided with offspring birth, each year of follow-up coincided with a year of age, but not if index date did not coincide with offspring birth.

The numerator for each follow-up year contained the number of offspring for whom the incident outcome were recorded in that year and excluded offspring who had an outcome previously within the study period. The denominator for each follow-up year included offspring at risk at the beginning of that year of follow-up; these were all offspring who weren't lost to follow-up or experienced the outcome in the preceding years of follow-up.

In addition, cumulative incidence proportion for the entire period 0-12 years was presented; this was calculated as the total number of offspring experiencing the outcome (NDD and CM, separately) during the entire follow-up (i.e. the sum of the number of events for the years 0 to 12) divided by the initial number of offspring included at the start of follow-up (i.e. population used in the analysis).

- **Cumulative incidence rate**

The cumulative incidence rate was calculated only for the primary outcome and was expressed as number of cases per 1000 patients-years at risk (+95% CI).

Cumulative incidence rate was calculated overall by cohort, and separately by paternal exposure groups, as follows:

- Valproate
- Lamotrigine/levetiracetam (composite)
- Lamotrigine
- Levetiracetam

Cumulative incidence rate was calculated cumulatively over follow-up time (i.e. 0-1 year; 0-2 years […] 0-12 years). Follow-up time was divided into 365-days intervals starting on the index date until the earliest between the date of first diagnosis of the outcome of interest, the end of the study period, death, emigration (where available) or reaching the age of 12 years.

Each rate was calculated as the fraction between number of incident cases between index date and the end of the period considered, divided by the total person-years at risk in the period considered. For example, at 2 years, the cumulative incidence rate was calculated as:

$$Cumulative\ incidence\ rate_{2years} = (New\ cases\ between\ index\ and\ 2years / Person - years\ at\ risk\ between\ index\ and\ 2years) x 1000$$

The cumulative incidence rate of the primary outcome was expressed as number of cases per 1000 person-years at risk (+95% CI).

- **Time-to-event analysis**

A time-to-event analysis was conducted on the primary outcome. Kaplan-Meier non-parametric methods was applied in order to estimate:

- 25th percentile, median, 75th percentile of time-to-event (in months)
- Kaplan-Meier survival function curve with CI

The number and percentage of total events and censored offspring was presented. This analysis was conducted overall and separately by paternal exposure groups, as follows:

- Valproate
- Lamotrigine/levetiracetam (composite)
- Lamotrigine
- Levetiracetam

For this analysis, the observation period started on index date and continued until the date of first diagnosis of the outcome of interest for offspring experiencing the outcome ("events") or until the earliest between the end of the study period, death, emigration (where available) or reaching the age of 12 years for offspring not experiencing the outcome of interest ("censored"). Time-to-event was expressed in months. In the Kaplan-Meier curve, only the valproate and the composite lamotrigine/levetiracetam groups were plotted.

9.9.2.2 Comparative Analyses

9.9.2.2.1 Univariate Analyses

The population included in this analysis was the Primary outcome cohort for comparative analysis and Secondary outcome cohort for comparative analysis.

Univariate analyses for each cohort were performed to characterise exposure groups (valproate and lamotrigine/levetiracetam (composite and separately) in monotherapy) with respect to potential risk factors and confounders. Additionally, univariate analyses were used to assess the association of any potential confounders or risk factor with the primary (NDD including ASD) and secondary (CM) outcomes.

The adjusted models for the comparative analyses were reported in the following analysis, whose risk factors and confounders in the multivariate models were identified in the univariate analyses.

The risk factors and confounders that were explored in the univariate analysis were presented in section 9.4.4. The list of risk factors and confounders did not include those considered as exclusion criteria.

Association between potential confounders and risk factors, and paternal exposure

The first univariate analysis described potential confounders and risk factors in terms of their distribution overall and by paternal exposure group.

The population included in this analysis was the Primary outcome cohort for comparative analyses and the Secondary outcome cohort for comparative analyses. Results were presented overall (by cohort), and separately by paternal exposure group: valproate vs. lamotrigine/levetiracetam (composite and separately).

Differences in the distribution of the risk factors and confounders among the exposure groups was tested statistically. Difference between categorical variables was tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5, Fisher's exact test was used. Differences between continuous variables was tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

The following groups were tested for differences:

- Valproate vs. lamotrigine/levetiracetam (composite)
- Valproate vs. lamotrigine
- Valproate vs. levetiracetam

Test statistics and p-values were presented; a 0.05 significance level was used, and tests were conducted using 2-sided testing.

Association between covariates and outcomes

The strength of the relationship between each confounder or risk factor and the Primary and Secondary outcome were assessed in a crude analysis. The population included in this analysis was the Primary outcome cohort for comparative analyses and the Secondary outcome cohort for comparative analyses. The list of covariates that were analysed was different for the 2 outcomes; details can be found in section 9.4.4.

This analysis was conducted by assessing the frequency (number and percentage) of the 2 outcomes in the different subgroups represented by different values of the confounders and risk factors. Frequency tables of the number of "events" and "non-events" by the different levels of categorical variables were created; for continuous confounders/risk factors (i.e. maternal and paternal age, maternal and paternal polypharmacy index) the mean and median value of the confounder/risk factor in the "events" and "non-events" were calculated.

In order to test the strength of the association between each variable and the outcome, a crude logistic regression model was estimated for each variable separately, and the Odds Ratios (OR) with 95% CI, as well as the results of the Wald test were reported to evaluate which variables were significantly associated with the outcomes. The reference category was indicated in the tables.

9.9.2.2.2 Multivariate Analyses

Multivariate analyses were conducted to estimate the effect of exposure groups on the risk of primary and secondary outcomes.

The primary analysis was conducted in the Primary outcome cohort for comparative analyses to investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy)

compared to lamotrigine/levetiracetam treatment at the time of conception. All the analyses on NDD, including ASD, only draws conclusions about NDD, including ASD, as a composite outcome, however a sensitivity analysis (sensitivity analysis 2) focused specifically on ASD diagnoses (ever, not only as 1st NDD diagnosis prior to/on exit date) (please refer to section 9.9.4.2). The secondary analysis was conducted in the Secondary outcome cohort for comparative analyses to investigate the risk of CM in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment at the time of conception.

Crude and propensity score (PS) weighted regression models were estimated and better detailed in the following subsections.

9.9.2.2.2.1 Propensity score

In order to model the PS for the analyses, 3 different PS models were performed separately for the Primary and Secondary outcome cohorts. The population included for these analyses were the Primary outcome cohort for comparative analyses and the Secondary outcome cohort for comparative analyses, and the models were PS estimation model 1: *logistic regression*; PS estimation model 2: *random forest model;* and PS estimation model 3*: logistic regression informed by random forest.*

Each PS model reflected the probability of an offspring being assigned to valproate or lamotrigine/levetiracetam group, given a set of observed covariates (these are different for the primary and secondary outcomes and different across the countries). All variables listed were considered for inclusion in the PS estimation models 1 and 2 and were included based on their univariate association with the outcome of interest (NDD including ASD for the primary cohort, and CM for the secondary cohort), as described in section 9.9.2.2.1. Both risk factors and confounders were included in the PS models, since the confounders may address confounding bias and the risk factors may correct for small amounts of chance bias or empirical confounding existing within each realisation of the dataset, thereby improving the precision of the estimator. For PS models 1 and 2, candidate covariates were also considered to enter the models if the OR in a single association with the outcome was higher than 1.1 or lower than 0.9 or if the Wald test was significantly associated with the outcome, for categorical variables with more than 2 categories (i.e. more than one OR estimated). PS model 3 (logistic regression informed by random forest) consisted in incorporating the interactions identified by model 2 (random forest) into model 1 (logistic regression).

The distributions of estimated PS were visually compared across the 3 models, separately for the primary and secondary outcome. Only the best PS model (PS model 1, model 2 or model 3) for the primary and Secondary outcome cohorts was used to apply inverse probability of treatment weights in the multivariate analysis. The selection of the best model for the Primary and Secondary outcome cohorts were based on the balance achieved in the weighted exposure groups after using inverse probability of treatment weights. Once the propensity scores were estimated (separately for the Primary and Secondary outcome cohorts), inverse probability of treatment weights were obtained based on each set of propensity scores and propensity score estimation models 1, 2 and 3 are detailed in the following subsections.

Propensity score estimation Model 1 – logistic regression

The first approach consisted of a logistic regression model with all potential confounders and risk factors associated with the study outcomes. Candidate covariates were considered to enter the PS model if the OR for the univariate association with the outcome was higher than 1.1 or lower than 0.9 or, if the Wald test for that variable was significant for variables with more than 2 categories. The PS models included exposure group (valproate vs. lamotrigine/levetiracetam) as the dependent variable.

For continuous covariates, the distribution was analysed and appropriate transformations applied if needed; these variables were categorised based on the quartiles of the distribution, or included in the model using restricted cubic splines. Restricted cubic splines were a transformation of continuous predictors which allowed for non-linearity and behaves robustly at the tails of variables' distribution. This approach was detailed in the Statistical Analyses Plan dated 22 December 2022.

Additionally, two-way interactions were included in the PS model, only for variables which were identified by a clinician as clinically meaningful.

To identify outlying values of variables, such as gestational age and weight, the Cook's distance was calculated for each offspring after fitting the PS model. Offspring presenting a Cook's distance >4 times the mean was classified as influential and excluded from the model (and subsequent PS weighting), before re-estimating the model. This assessment was repeated for each PS model, and the number of offspring excluded from the PS model due to the Cook's distance criterion was reported.

Two separate models were estimated for the primary and secondary outcomes.

Propensity score estimation Model 2 – random forest model

The second modelling approach to estimate PS was a random decision forest model. The random forest non-parametric method was described in the Statistical Analyses Plan dated 22 December 2022.

The propensity score estimation model was specified as a Breiman's (20) random forest classification model where valproate vs. lamotrigine/levetiracetam was the outcome variable, and the candidate list of covariates were based on the results of the crude analyses. Potential covariates were selected if the OR in the univariate association with the outcome was higher than 1.1 or lower than 0.9; for categorical variables with more than 2 categories (i.e. more than one OR estimated) the Wald test was evaluated to assess whether the variable was significantly associated with the outcome. For continuous covariates (or ordinal categorical variables), every possible cut-off point was considered in order to portion the data. All covariates' interactions were also considered and incorporated into the model.

PS model 2 was estimated as the conditional probability of the offspring being paternally exposed to valproate (compared to lamotrigine/levetiracetam) in the 3 months lookback from LMP2, given the defined set of covariates, for each offspring the using the fit of the random forest model.

Outliers and/or influential subjects identified in the random forest model, with outlying measure higher than 10 were excluded and the model re-estimated.

Two separate models were estimated for the primary and secondary outcomes.

Propensity score estimation Model 3 – logistic regression informed by random forest

The third model estimation was the logistic regression informed by the random forest model.

In this approach, data-driven identification of interactions identified by the random forest model (Model 2 described above) were incorporated into the logistic regression model (Model 1 described above).

The random forest propensity score model 2 was used to identify important two-way interactions to include in the PS estimation model 3 - logistic regression informed by random forests. Results from the random forest (model 2) were ranked by importance, and the inclusion or not of which two-way interactions from the model 2 in the logistic regression (model 1) was based on the difference metric. The top features and two-way feature interactions from the fitted random forest were included in a new logistic regression propensity score model to predict paternal exposure to valproate (compared to lamotrigine/levetiracetam).

To identify outlying values of variables, such as gestational age and weight, the Cook's distance was calculated for each offspring after fitting the PS model. Offspring presenting a Cook's distance >4 times the mean was classified as influential and excluded from the model (and subsequent PS weighting), before re-estimating the model. This assessment was repeated for each PS model, and the number of offspring excluded from PS model and matching due to the Cook's distance criterion was reported.

Two separate models were estimated for the primary and secondary outcome.

Inverse probability of treatment weighting using propensity scores

As the different PS models were estimated (refers to the subsections above of Propensity score estimation Model 1, 2 and 3), inverse probability of treatment weights were obtained based on each set of propensity scores. PS weighting was used instead of matching for increased generalisability and to avoid the exclusion of patients from the adjusted analyses due to lack of matches, since the outcome of interest was relatively rare or infrequent.

Values of the standardised difference below 0.1 was interpreted as evidence of good balance achievement between weighted valproate and comparator groups for each covariate. In addition, variance ratios (i.e. the fraction of the sample variance of each covariate for the weighted valproate and comparator group) was used to compare the variance of the covariates between the weighted groups; values between 0 and 2 were interpreted as further evidence of good balance. Standardised difference and variance ratio between weighted valproate and comparator groups were also calculated for those variables that were not retained in each PS model, to assess whether there was imbalance in prognostically important variables that were not included in the PS models, as these might be included in the effect estimation models as covariates.

Additionally, the resulting distributions of each covariate were assessed by plotting side-by-side the valproate group against the reference group as box plots (for binary covariates) or as Q-Q plots for the valproate group against the reference group (for continuous covariates) in the weighted population. For each cohort, the best PS model was chosen based on the balance achieved in the exposure groups after weighting (based on covariates included in each PS model).

9.9.2.2.2.2 Effect estimation for NDD including ASD

The effect of paternal exposure to valproate (compared with lamotrigine/levetiracetam) on NDD including ASD was evaluated through multivariate Cox proportional hazard models.

Different approaches were used and compared, as described in the sections below. For each approach, the proportionality assumption was tested using statistical tests and graphical diagnostics based on the scaled Schoenfeld residuals, as well as log-log plots.

Effect estimation for NDD – crude model

The first approach to estimate the effect of paternal exposure to valproate on NDD including ASD in comparison with the composite of lamotrigine/levetiracetam was the crude Cox proportional hazards regression model. The population included in this analysis was the Primary outcome cohort for comparative analyses.

The crude model did not include any covariates other than the 2 exposure groups of valproate and lamotrigine/levetiracetam, and thus, the inverse probability of treatment weighting was not applied between the 2 exposure groups. In this model, offspring was followed from index date (i.e. birth) until first diagnosis of NDD including ASD, or censoring. Offspring not experiencing the outcome was censored at the earliest between the end of the study period (31 December 2017 or last available date), death, emigration (where available) or reaching the age of 12 years. Offspring age was the underlying timescale since the observation period starts at birth.

The effect of each individual on the coefficients of the crude model was measured by deleting each observation of the estimates. Offspring that presented the coefficient (*dfbetas*) for the exposure of interest outside the specified range (i.e. plus-minus 2 divided by the square root of the sample size $[\pm 2/\sqrt{(n)}]$) were classified as influential and excluded from the model. The crude model was re-estimated until no influential subject was identified. This assessment was repeated for each crude model, and the number of offspring excluded due to the coefficient criterion was reported.

The crude estimated HR (with 95% CI) of NDD including ASD in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam was presented.

Effect estimation for NDD – PS-weighted model

The second approach to estimate the effect of paternal exposure to valproate on NDD including ASD in comparison with the composite of lamotrigine/levetiracetam was the multivariate Cox proportional hazards regression model adjusted for the PS-weighted.

In the PS-weighted model, offspring was followed from index date (i.e. birth) until first diagnosis of NDD including ASD, or censoring. Offspring not experiencing the outcome was censored at the earliest between the end of the study period (31 December 2017 or last available date), death, emigration (where available) or reaching the age of 12 years. Offspring age was the underlying timescale since the observation period starts at birth.

All the confounders and/or risk factors retained in the PS models that were still unbalanced after weighting were considered for inclusion. The imbalance between the 2 exposure groups was assessed as described in "*Inverse probability of treatment weighting using propensity scores*".

The adjusted HR (with 95% CI) of NDD including ASD in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam were presented.

Effect estimation for NDD – PS-weighted model adjusted for K-means exposure cluster

As the PS-weighted offspring in the 2 paternal exposure groups might present very different intensity of exposure (to valproate and lamotrigine/levetiracetam), an additional PS-weighted Cox proportional hazard model was estimated and adjusted by exposure clusters.

This model included as confounders variables retained in the PS that were still unbalanced after weighting, and the K-means cluster variable, was included in the PS-weighted model as an effect-modifier (i.e. the interaction cluster*exposure group).

The adjusted HR (with 95% CI) of NDD including ASD in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam were presented.

9.9.2.2.2.3 Effect estimation for CM

The effect of paternal exposure to valproate (compared with lamotrigine/levetiracetam) on CM was evaluated through logistic regression models, using the presence or absence of the outcome as the dependent variable. Different logistic regression models were estimated and compared, which are described in the sections below.

As multiple offspring per father was possible, within-family dependencies were introduced into the data, therefore paternal clustering was taken into account by correcting robust standard errors, as described in the SAP v2.0.

Effect estimation for CM – crude model

The first model to estimate the OR of CM in offspring paternally exposed to valproate monotherapy during the 3 months lookback from LMP2 compared to the reference group (offspring paternally exposed to lamotrigine/levetiracetam) was a crude logistic regression model. The population included in this analysis was the Secondary outcome cohort for comparative analyses.

In this logistic regression model, only the exposure group was included as a covariate; the comparator group (lamotrigine/levetiracetam, composite monotherapy) was used as reference in the model. Crude OR with 95% CI were estimated, and model coefficients were estimated using robust standard errors.

Effect estimation for CM – PS-weighted model

A second logistic regression model to estimate the OR of CM was computed, only including offspring from the Secondary outcome cohort for comparative analyses. In this model, inclusion of confounders retained in the PS model that were still unbalanced after weighting were considered for inclusion; imbalance between the 2 exposure groups was assessed using standardised difference and variance ratio as described in 9.9.2.2.2.1. Adjusted OR, 95% CI and model coefficients using robust standard errors were estimated.

Effect estimation for CM – PS-weighted **model adjusted for K-means exposure cluster**

As the PS-weighted offspring in the 2 paternal exposure groups might present very different intensity of exposure (to valproate and lamotrigine/levetiracetam), an additional PS-weighted logistic regression model was estimated, including the K-means cluster variable in the model as an effect-modifier (i.e. the interaction cluster*exposure group is included in the model).

Confounders retained in the PS but not balanced after weighting were considered for inclusion in this model. Adjusted OR, 95% CI and model coefficients using robust (i.e. sandwich) standard errors were estimated.

9.9.2.3 Meta-analyses

Country-specific results were pooled in a meta-analysis in order to achieve a summary estimate of the observed size effect and identify any country-specific patterns.

The following results related to the primary outcome were meta-analysed across all 3 countries:

- Ratio of cumulative incidence proportions of NDD including ASD in valproate group and lamotrigine/levetiracetam group (see section 9.9.2.1)
- Ratio of cumulative incidence rates of NDD including ASD in valproate group and lamotrigine/levetiracetam group (see section 9.9.2.1)
- HR of NDD including ASD in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam (see section 9.9.2.2.2.2)

For the secondary outcome analyses, the following results were meta-analysed for Norway and Denmark only (since for Sweden non-live offspring was not included in the population):

- Ratio of cumulative incidence rates of CM in valproate group and lamotrigine/levetiracetam group (see section 9.9.2.1)
- OR of CM in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam (see section 9.9.2.2.2.3)

Since country-level differences in the effect of exposure on the outcomes were expected, random effect meta-analysis models were applied, and Chi-square and I^2 statistics were used to assess the heterogeneity between country-specific estimates. Inverse variance weighting was applied; this was done by estimating the between-countries variance of the estimate and used it to weight the country-level estimates to obtain a pooled one: estimates with a lower variance were assigned a higher weight.

An overall random-effects estimate (21) of a parameter θ estimated in k studies/countries was calculated as:

$$\hat{\theta}_R = \frac{\sum_{i=1}^{k:} w_i^* \hat{\theta}_i}{\sum_{i=1}^{k:} w_i^*}$$

Where w_i^* were the study/country-specific weights, and they were obtained as:

$$w_i^* = \frac{1}{v_i + \hat{\tau}^2}$$

Where $v_i = [SE(\hat{\theta}_i)]^2$ and $\hat{\tau}^2$ was the estimated variance of the true effect θ_i. In this study, the DerSimonian and Laird method (22) was used to estimate τ^2, the between-countries variance of the true effect.

The following considerations were applied when conducting the meta-analyses for each estimate:

- Cumulative incidence proportion (NDD and CM): in order to meta-analyse cumulative incidence proportions (i.e. risks), the risk ratio was calculated for each follow-up year, by calculating the ratio between the risk of the outcome in the 2 exposure groups (valproate vs. lamotrigine/levetiracetam composite monotherapy). Risk ratios were meta-analysed using the inverse variance random effect method (DerSimonian and Laird)
- Cumulative incidence rate (NDD only): in order to meta-analyses cumulative incidence rates, the rate ratio (i.e. the ratio of the rate in the valproate paternal exposure group to the rate in the lamotrigine/levetiracetam paternal exposure group) was calculated, for each year of follow-up. The (natural) logarithms of the rate ratios were combined across countries using the generic inverse variance method
- Hazard ratio (NDD only): the country-level estimates of the log hazard ratios and standard errors obtained using Cox proportional hazard models in each country was meta-analysed using the inverse variance method
- OR (CM only): estimates of OR and standard errors from the logistic regression in each country was meta-analysed using the inverse variance method

The meta-analysis package in R (23) was used to conduct the random effect meta-analyses.

9.9.2.4 Exploratory Analyses

Four exploratory analyses were conducted in order to meet the study Exploratory Objectives 5, 6, 7, and 8; 2 of these analyses were performed in the Primary outcome cohort (exploratory analyses 5 and 6), and 2 explorative analysis focused on the secondary outcome (exploratory analyses 7 and 8).

Exploratory analysis 5: offspring paternally exposed to valproate compared with other antiepileptic drug polytherapy

For Exploratory Objective 5, 2 groups were compared for the primary outcome:

- Offspring paternally exposed to valproate in polytherapy with other AEDs (excluding lamotrigine or levetiracetam) during the 3 months lookback from LMP2, compared to
- Offspring paternally exposed to levetiracetam/lamotrigine in polytherapy (i.e. polytherapy including at least one of them, and excluding valproate) during the 3 months lookback from LMP2

The populations used in this analysis were the Primary outcome cohort for Explorative Objective 5. Results were stratified by the 2 groups defined above.

For these 2 groups, the cohort characteristics, and univariate analyses were reported as for the main analyses.

For the cohort characteristics analysis, as well as presenting the summaries described in section 9.9.2.1, the 2 exposure groups were characterised with regards to the polytherapy received (i.e. distribution of the different polytherapy in the 2 paternal exposure groups and K-means clustering) during the 3 months lookback from LMP2. For the univariate analysis, the association

between the variables and paternal exposure groups defined above were described and compared (please refer to section 9.9.2.2.1).

9.9.2.4.1 Exploratory analysis 6: paternal exposure to valproate or lamotrigine/levetiracetam in discordant siblings

To explore potential for unmeasured family-related confounding factors (such as genetic liability for neuropsychiatric conditions or congenital malformations and early post-natal environmental influences), an exploratory sibling-matched descriptive analysis was conducted on the primary composite outcome (NDD, including ASD) whereby only families with paternal valproate exposure-discordant siblings were included (at least one offspring with paternal valproate exposure and one offspring without valproate exposure [i.e. at least one offspring with paternal valproate exposure and one offspring exposed to lamotrigine/levetiracetam]).

In order to identify the population for this analysis, the following steps were followed:

- Offspring in the Primary outcome cohort for comparative analyses without any sibling in the same cohort was excluded
- "Groups" of siblings with the same mother and father were identified. Any "group" with one offspring only was excluded
- From the remaining population, only those offspring with at least one sibling whose paternal exposure was discordant were retained. This ensured that each retained offspring from the valproate paternal exposure group had at least one sibling in the lamotrigine/levetiracetam paternal exposure group

For this analysis, only families with at least 2 offspring in the Primary outcome cohort for comparative analyses were included; since these families might have more than 2 offspring, the 2 exposure groups might be different in size (e.g. one offspring in the valproate exposure group, 2 offspring from the same mother and father in the levetiracetam/lamotrigine exposure group).

Results were stratified by offspring paternally exposed to valproate vs. offspring paternally exposed to lamotrigine/levetiracetam in the 3 months lookback from LMP2.

For these 2 groups, the cohort characteristics (section 9.9.2.1) and univariate analyses (see sections 9.9.2.1 and 9.9.2.2.1) are repeated.

9.9.2.4.2 Exploratory analysis 7: risk of CM in live offspring in Sweden

Exploratory Objective 7 investigated the risk of CM in live offspring from Sweden who were paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment at the time of conception.

For this objective, the cohort characteristics (section 9.9.2.1), incidence (section 9.9.2.1), univariate (section 9.9.2.2.1) and multivariate (section 9.9.2.2.2) analyses were repeated for Sweden only; this was due to the fact that the Secondary outcome cohort only includes live births in Sweden, and was therefore systematically different to the cohorts for Norway and Denmark.

For this analysis 2 slightly different sub-populations were used for the descriptive and comparative analyses. For the descriptive analyses (section 9.9.2.1) the Secondary outcome cohort for Explorative Objective 7 (Descriptive Analyses) was used; for the comparative analyses (sections 9.9.2.2.1 and

9.9.2.2.2) the Secondary outcome cohort for Explorative Objective 7 (Comparative Analyses) was used. The same methods used for the analyses of Norway and Denmark were applied to Sweden; differences in the definition of the outcome were presented in section 9.4.1.

9.9.2.4.3 Exploratory analysis 8: CM by target body system organ class

In Exploratory Objective 8, the spectrum of CM sub-types by organ class were described, with stratification as major or minor CM whenever was feasible. The number and percentage of CM cases by sub-type were presented, overall and by paternal exposure group (valproate, levetiracetam/lamotrigine composite and separately).

The population for this analysis was the Secondary outcome cohort for Explorative Objective 8. Only offspring experiencing the secondary outcome were included in this analysis; for these offspring, the number and percentage of each CM sub-type were presented. All records of minor and major CM during the entire follow-up were considered, only considering each ICD-10 code once for each offspring but allowed for multiple CM records (based on distinct ICD-10 codes) for the same offspring. In this analysis, the percentage of each CM sub-type was calculated over the total number of CM records (i.e. distinct ICD-10 codes) detected among offspring included in the population.

***Of note*: Exploratory analysis 8 results were not available at the time of initial submission. Complete results of exploratory analysis 8 for Denmark and Norway are provided as an addendum alongside the present CSR v1.1.**

9.9.3 Missing Values

Missing data were those where a variable was directly reported as missing or unavailable, where a variable observation was blank, where the extracted data may not have been interpretable, or where the value must have been imputed to be missing because of data inconsistency or out-of-range results.

Regression models for the primary and secondary outcomes were estimated on complete cases only, and the number of cases included in each analysis was reported.

Missingness of relevant confounders and risk factors could have led to exclusion of some offspring from the adjusted analyses. For this reason, a missing data assessment analysis was conducted to explore which covariates have non-trivial proportions of missing data (>5%); for all risk factors and confounders considered in the study (see section 9.4.4 for full list), the degree of data completeness and patterns of missingness were summarized using a pattern of missingness matrix. This matrix can be found in Table 278 and Table 279 for the primary and secondary outcomes in Denmark, Table 280 and in Table 281 for the primary and secondary outcomes in Sweden, and in Table 282 and Table 283 for the primary and secondary outcomes in Norway (see Appendix section 15.5). The most frequent missingness patterns represented groups of patients with the same missing variables; these groups were sorted from the largest to the smallest. Please note, most of the risk factors and confounders considered in the study were defined as the presence in the patient's record of a specific code indicating a condition (e.g. paternal bipolar disorder); due to the nature of the data used in this study, it was assumed that the absence of a code indicating each condition reflected the absence of that condition, rather than missingness. For this reason, the only variables which could present missing values among those considered as potential risk factors or confounders were maternal smoking prior to LMP2, and maternal smoking during pregnancy. Since maternal smoking prior to LMP2 presented a very high degree of missingness in some of the countries included in the study, the multiple imputation was not performed, and this variable was forced out of the adjusted models as it would have led to the exclusion of the vast majority of the offspring. On the contrary, smoking during pregnancy was adjusted for, where relevant, as its missingness was much lower.

9.9.4 Sensitivity Analyses

9.9.4.1 Sensitivity analysis variation of exposure time window for primary outcome

In this analysis, the association between extended risk window of paternal valproate exposure (6 months) and NDD, including ASD in the offspring was examined to investigate if there was an effect of valproate exposure other than through the spermatogenic cycle. i.e., fathers exposed to the drugs in the 3 months period prior to LMP2. But those fathers were not excluded from this analysis. Therefore, we cannot isolate effect during spermatogenesis .

The population included in this analysis is the Primary outcome cohort for sensitivity analysis 1. Results were presented overall (by cohort), and separately by paternal exposure group: valproate vs. lamotrigine/levetiracetam (composite and separately).

From the primary cohort, only offspring from fathers exposed to valproate, lamotrigine or levetiracetam in monotherapy in the 6 months period prior to LMP2 were included. This population was larger than the population used in most analyses, since the exposure window was wider, therefore offspring from fathers exposed to any of the drugs of interest in the period between 6 and 3 months prior to LMP2 were included (even in the absence of exposure to the drugs in the 3 months period prior to LMP2). Exposure to valproate or lamotrigine/levetiracetam was defined as described in section 9.4.1; however, since the exposure window considered in this analysis was 6 months, all dispensations recorded in the 9 months period prior to LMP2 were considered to assess whether there was at least one intake of these drugs during the 6 months lookback period from LMP2; K-means method was re-applied to classify exposure to AEDs in the extended exposure window.

The cohort characteristics (section 9.9.2.1), incidence (section 9.9.2.1), univariate (section 9.9.2.2.1) and multivariate (section 9.9.2.2.2) analyses were repeated on this population. PS estimation and weighting were repeated since the population used in the analysis was different to the one used in the main analysis, and the approach followed outlined in section 9.9.2.2.2.1. The multivariate analysis follow the approach described in section 9.9.2.2.2.

9.9.4.2 Sensitivity analysis – Focus on ASD for primary outcome

A sensitivity analysis was conducted on the Primary outcome cohort to assess the risk of ASD in offspring paternally exposed to valproate compared to lamotrigine/levetiracetam monotherapy treatment in the 3 months lookback from LMP2. The population used in this analysis was the Primary outcome cohort for the comparative analyses. Results were presented overall (by cohort), and separately by paternal exposure group: valproate vs lamotrigine/levetiracetam (composite and separately).

The cohort characteristics (section 9.9.2.1), incidence (section 9.9.2.1), univariate (section 9.9.2.2.1) and multivariate (section 9.9.2.2.2) analyses were repeated on this population. PS estimation and weighting were repeated since the population used in the analysis was different to the one used in the main analysis. The approach outlined in section 9.9.2.2.2.1 was followed for the PS estimation and weighting. Multivariate analyses followed the approach described in section 9.9.2.2.2; however, the outcome of interest was ASD specifically in this sensitivity analysis; the definition of the outcome was different since only offspring with an ASD diagnosis (ever, not only as 1st NDD diagnosis prior to/on exit date) were considered to have experienced the outcome of interest.

***Of note*: Sensitivity analysis 2 complete results were not available at the time of initial submission. The complete results of this sensitivity analysis 2 for the three countries are provided as an addendum alongside the present report v1.1.**

9.9.4.3 Sensitivity analysis – Exclusion of offspring with low birth weight or born prior to 8th months

There were suggestions for evidence of association between preterm birth/low birth weight and NDD (24–26). If AEDs affect preterm birth and preterm birth affects NDD, this means that preterm birth could act as a mediator between AEDs and NDD. In the same way, if AEDs affect very low birth weight and very low birth weight affects NDD, this means that very low birth weight could act as a mediator between AEDs and NDD. Adjusting for a mediator introduces a bias, therefore this sensitivity analysis was performed excluding extremely low birth weight, very preterm and extremely preterm newborns to explore the potential impact introduced by inclusion of this sub-population of offspring on the point estimate.

The population used in this analysis was the Primary outcome cohort for sensitivity analysis 3. Results were presented overall (by cohort), and separately by paternal exposure group: valproate vs. lamotrigine/levetiracetam (composite and separately).

The cohort characteristics (section 9.9.2.1), incidence (section 9.9.2.1), univariate (section 9.9.2.2.1) and multivariate (section 9.9.2.2.2) analyses were repeated on this population. PS estimation and weighting were repeated since the population used in the analysis was different to the one used in the main analysis. The approach outlined in section 9.9.2.2.2.1 was followed for the PS estimation and weighting. Multivariate analyses followed the approach described in section 9.9.2.2.2.

9.9.4.4 Sensitivity analysis – Handling of missing CM diagnosis

This sensitivity analysis was conducted on the Secondary outcome cohort only. Since a lot of diagnosis for spontaneous abortions and stillbirth could be missing due to under-reporting, this sensitivity analysis investigates the risk of CM using a broader definition of the outcome. The population used in this analysis was the Secondary outcome cohort for the comparative analyses. Results were presented overall (by cohort), and separately by paternal exposure group: valproate vs. lamotrigine/levetiracetam (composite and separately).

In this analysis, using the broader definition of the outcome; the following cases were considered to have experienced CM:

- Live births with a diagnosis of CM
- Spontaneous abortions/stillbirths with a recorded diagnosis/reason of death for CM
- Spontaneous abortions/stillbirths without an ICD-10 code for the diagnosis/reason (all spontaneous abortions/stillbirth with at least one ICD-10 and no code for CM were considered to not have experienced the outcome)

The main advantage of this broader definition of the outcome was to include in the analysis under reported cases of CM; at the same time, inclusion of cases with different (unrecorded) diagnoses was possible.

The cohort characteristics (section 9.9.2.1), incidence (section 9.9.2.1), univariate (section 9.9.2.2.1) and multivariate (section 9.9.2.2.2) analyses were repeated using this updated definition of CM. PS estimation and weighting were not needed to be repeated since the population and exposures were the same as those used in the main analyses, and only the definition of the outcome was different.

9.9.4.5 Sensitivity analysis – Simple pairwise comparisons for the exposure groups

This sensitivity analysis was conducted on both the primary and Secondary outcome cohorts, separately. In this sensitivity analysis, the risk of NDD, including ASD, and CM (separately) in offspring paternally exposed to valproate (monotherapy) were assessed comparing these groups with offspring paternally exposed to lamotrigine (monotherapy), and levetiracetam (monotherapy), separately. The populations included in this analysis were the Primary outcome cohort for sensitivity analysis 5 (2 populations, one when studying valproate vs. lamotrigine, and one when studying valproate vs. levetiracetam) and the Secondary outcome cohort for sensitivity analysis 5 (2 populations, one when studying valproate vs. lamotrigine, and one when studying valproate vs levetiracetam).

Valproate, lamotrigine and levetiracetam are medications with similar indications but that may be systematically prescribed for different type of epilepsy and potentially other indications (valproate and lamotrigine might be prescribed for bipolar disorder and levetiracetam is not). In particular, valproate was the treatment of choice (or first-line drug) for male patients with idiopathic generalised epilepsy and generalised tonic-clonic seizures, a type of epilepsy known to have a genetic basis and that, as such, can be found in several members of the same family. On the other hand, lamotrigine and levetiracetam were used for a wide range of conditions, including focal epilepsy.

Moreover, they were licensed in different periods (levetiracetam since 2000; lamotrigine since early 1990s; and valproate since 1967 to treat epilepsy and since 1995 to treat bipolar disorder) resulting in systematic different in the treated populations. This analysis compared valproate paternal exposure to lamotrigine and levetiracetam paternal exposure separately, for the purpose of both NDD and CM outcome:

Two sub-populations were created (separately for each outcome):

- Offspring from fathers exposed to valproate or lamotrigine monotherapy in the 3 months lookback from LMP2 – all offspring whose fathers were exposed to levetiracetam in the 3 months lookback from LMP2 are excluded from this analysis
- Offspring from fathers exposed to valproate or levetiracetam monotherapy in the 3 months period prior to LMP2 – all offspring whose fathers were exposed to lamotrigine in the 3 months lookback from LMP2 are excluded from this analysis

The univariate analysis of association between risk factors/confounders and outcomes (section 9.9.2.2.1) and multivariate analyses (see section 9.9.2.2.2) were repeated, first on the population of offspring paternally exposed to valproate or lamotrigine, then on the population exposed to valproate or levetiracetam, separately by paternal exposure group.

Since the exposure groups used in this analysis differed from those in the main study analysis where lamotrigine and levetiracetam were considered combinedly, the PS estimation and weighting were repeated.

For the analysis evaluating the effect of paternal exposure to valproate vs. levetiracetam, the PS estimation were repeated using paternal exposure to valproate (vs. levetiracetam) as outcome in the PS models. The different modelling approaches described in section 9.9.2.2.2.1 were repeated in order to identify the best PS models (separately for Primary and Secondary outcome cohorts); PS weighting was re-applied and used in the multivariate analyses.

Similarly, for the analysis evaluating the effect of paternal exposure to valproate vs. lamotrigine, the PS models were re-estimated using paternal exposure to valproate (vs. lamotrigine) as outcome in the PS models, and PS weighting was re-applied.

The multivariate analyses were conducted using the approach described in sections 9.9.2.2.2.2 (for the Primary outcome cohort) and 9.9.2.2.2.3 (for the Secondary outcome cohort).

The cohort characteristics analysis (section 9.9.2.2.1), the association between risk factors/confounders and paternal exposure groups (section 9.9.2.2.1) and the incidence analysis (section 9.9.2.1) were not repeated in this case, since these results were already presented separately for lamotrigine and levetiracetam in the main analyses.

9.9.4.6 Sensitivity analysis – Comparison of PS-weighted model with covariate adjustment model

In this analysis, a different approach was proposed to estimate the effect on NDD including ASD and CM of paternal exposure to valproate (monotherapy) compared with lamotrigine/levetiracetam (composite monotherapy) in the 3 months period prior to LMP2. The populations included in this analysis were the Primary outcome cohort for comparative analyses and the Secondary outcome cohort for comparative analyses.

In this sensitivity analysis the multivariate analysis was repeated, however no PS weighting was done. All the confounders for each outcome were included in the respective models; potential risk factors were included only if associated with both the exposure and the outcome, based on the results of the univariate analyses (see section 9.9.2.2.1).

In the primary cohort, a Cox Proportional Hazard (PH) adjusted regression model was used to estimate the HR of NDD, including ASD, (using offspring's age in years as the underlying timescale) in offspring paternally exposed to valproate monotherapy in the 3 months lookback from LMP2 date compared to the reference group comprised of offspring paternally exposed to lamotrigine/levetiracetam in the same time period. HRs and 95% CI were presented for all covariates. Since no PS weighting was applied to this analysis, the dfbetas (statistics that indicate the effect that deleting each observation has on the estimates for the regression coefficients) for the exposure coefficient was calculated for each offspring after fitting the adjusted model in order to identify influential subjects. Offspring that had a dfbetas for the exposure of interest outside the range +/- 2/sqrt(n) were classified as influential and excluded from the model, before re-estimating the model (23). This assessment was repeated for each model, and the number of offspring excluded due to the dfbetas criterion was reported.

In the secondary cohort, a logistic adjusted regression model was used to estimate the OR of CM in offspring paternally exposed to valproate monotherapy within 3 months prior to LMP2 date compared to the reference group comprised of offspring paternally exposed to lamotrigine/levetiracetam in the same time period. ORs and 95% CI were presented for all covariates. To identify outlying values of variables, such as gestational age and weight, the Cook's distance was calculated for each offspring after fitting the adjusted model. Offspring that had a Cook's distance >4 times the mean were classified as influential and excluded from the model, before re-estimation. The number of offspring excluded due to the Cook's distance criterion was reported.

9.9.4.7 Sensitivity analysis – Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy

This sensitivity analysis was conducted on the primary cohort only. The neurodevelopmental effects of post-natal exposure to AEDs and/or diagnosis of epilepsy on risk of NDD were not completely understood, therefore, in the primary analysis such children were excluded. The population used in this analysis was the Primary outcome cohort for sensitivity analysis 7. Results were presented overall (by cohort), and separately by paternal exposure group: valproate vs lamotrigine/levetiracetam (composite and separately).

In this sensitivity analysis the impact on the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment in the 3 months lookback from LMP2 was explored by including offspring exposed to AEDs and/or diagnosed with epilepsy after birth.

The cohort characteristics (section 9.9.2.1), incidence (section 9.9.2.1), univariate (section 9.9.2.2.1) and multivariate (section 9.9.2.2.2) analyses were repeated. In the analyses of the cohort characteristics, number and percentage of offspring diagnosed with epilepsy and number of offspring treated with AEDs during follow-up were presented. In the multivariate analysis (section 9.9.2.2.2), offspring exposure to AEDs and diagnosis of epilepsy between birth and the exit date was each considered time dependent variables, and thus allowed to take place at any time during the follow-up period. In order to do this, these variables were set to "0" (i.e. absent) until a first diagnosis record (for epilepsy) or the first dispensation (for AEDs) was present in the data. Once these variables change because the offspring was diagnosed with epilepsy or because AED treatment was initiated, the offspring was considered exposed/diagnosed until the exit date. AEDs exposure and epilepsy were included in the adjusted models (including the "crude" Cox regression model) as covariates, rather than being used to estimate PS.

PS estimation and weighting were repeated since the population used in the analysis is different to the one used in the main analysis. The approach outlined in section 9.9.2.2.2.1 was followed for the PS estimation and weighting. Multivariate analyses followed the approach described in section 9.9.2.2.2.

9.9.4.8 Sensitivity analysis – Validation of the assumption that individuals are exposed to one DDD per day

WHO DDD (World Health Organisation Defined Daily Dose) is the assumed average maintenance dose per day for a drug used for its main indication (i.e. epilepsy for valproate, lamotrigine and levetiracetam) in adults. This does not necessarily reflect the recommended or Prescribed Daily Dose. Therapeutic doses for individual patients and patient groups often differed from the DDD as they are based on individual characteristics (such as indication, age, weight, ethnic differences, type and severity of disease) and pharmacokinetic considerations. A comparison (ratio) between the distribution of estimated treatment durations (expected) and time between prescriptions (observed) was provided with the caveat that this would necessarily be affected by the DDD methodology

approximation. In order to partially overcome this limitation, this comparison was provided separately for patients with and without an indication of epilepsy, as epilepsy was the main indication for the medicines at study therefore the indication used by WHO to estimate DDD. It was expected that the use of WHO DDD would be a better approximation of the observed treatment duration among patients with a diagnosis of epilepsy, with a ratio closer to 1 than for other indications. The distribution of estimated treatment durations (expected) was compared to the distribution of time between prescriptions (observed), separately for lamotrigine, levetiracetam, valproate and for patients with and without an indication for epilepsy, using the following formulas:

Observed time between paternal prescriptions for offspring-i was

$$\sum_{j=1}^{k-1} days\left(prescription_{j+1} - prescription_j\right)$$

where k was the number of prescriptions, in the period of interest (6 months lookback from LMP2).

Expected paternal treatment duration for offspring-i was

$$\frac{\sum_{j=1}^{k-1} n.\ pkg\ in\ prescription_j * n.dosage\ unit\ in\ each\ pkg}{WHO\ DDD}$$

where k was the number of prescriptions, in the period of interest (6 months lookback from LMP2).

The ratio of Observed over Expected for offspring-i was

$$\sum_{j=1}^{k-1} days\left(prescription_{j+1} - prescription_j\right) \Big/ \frac{\sum_{j=1}^{k-1} n.\ pkg\ in\ prescription_j * n.dosage\ unit\ in\ each\ pkg}{WHO\ DDD}$$

$$= \sum_{j=1}^{k-1} \frac{days\left(prescription_{j+1} - prescription_j\right) * WHO\ DDD}{n.\ pkg\ in\ prescription_j * n.dosage\ unit\ in\ each\ pkg}$$

The ratio for the population was

$$\sum_{i=1}^{n} \left(\sum_{j=1}^{k-1} \frac{days\left(prescription_{j+1} - prescription_j\right) * WHO\ DDD}{n.\ pkg\ in\ prescription_j * n.dosage\ unit\ in\ each\ pkg} \right) / n$$

where n was the number of offspring and k was the number of prescriptions per father, in the period of interest (6 months period prior to LMP2).

Under the assumption of perfect compliance of each patient, if the ratio for the overall population was between 0.8 and 1.2 then the WHO DDD was a good approximation of the reality; the more the ratio departed from the good approximation range the more the real daily dose prescribed diverged from the WHO defined daily dose. It was expected to have a good approximation to the reality for fathers with epilepsy indication for AEDs.

This measure was affected both from the approximation of using the WHO DDD and the compliance of fathers to the treatment. The lower the compliance, the more the ratio departed from good approximation (0.8-1.2). Since the dose prescribed was not available, it was not possible to assess what affected more the results.

The mean (SD) estimated and observed paternal treatment duration for all offspring was presented by paternal exposure group, as well as the ratio. All results were presented separately for offspring from fathers with and without an indication of epilepsy.

9.9.4.9 Sensitivity analysis – Narrow case definition for secondary outcome in Norway and Denmark

Since the population used for the secondary outcome analysis was only comprised of live births in Sweden, this sensitivity analysis repeated the main study analyses focusing on live births only from Norway and Denmark, to allow a comparison between the secondary outcome results in Sweden, and those in the other countries.

For this sensitivity analysis, the cohort characteristics (section 9.9.2.1), incidence (section 9.9.2.1), univariate (section 9.9.2.2.1) and multivariate (section 9.9.2.2.2) analyses were repeated in Norway and Denmark on the subset of live births from the Secondary outcome cohort. Two slightly different sub-populations were used for the descriptive and comparative analyses. For the descriptive analyses (section 9.9.2.1) the Secondary outcome cohort for sensitivity analysis 9 (descriptive analyses) was used; for the comparative analyses (sections 9.9.2.2.1, 9.9.2.2.2) the Secondary outcome cohort for sensitivity analysis 9 (comparative analyses) was used. PS estimation and weighting were repeated using the approach described in section 9.9.2.2.2.1.

9.9.4.10 Sensitivity analysis – Continuous measure of cumulative exposure

This sensitivity analysis investigated the risk of NDD including ASD, as well as CM, in offspring paternally exposed to monotherapy treatment with valproate, lamotrigine or levetiracetam at the time of conception, using a continuous measure of cumulative exposure to treatment. While in the main analyses exposure to valproate or lamotrigine/levetiracetam was defined as a dichotomous variable (with the intensity of exposure also taken into account in the PS-weighted model adjusted for K-means, see section 9.9.2.2.2.2), in this analysis paternal exposure to the drugs of interest was measured as a continuous variable describing cumulative drug intake during the 3 months lookback from LMP2. For this analysis, the Primary outcome cohort for comparative analysis and the Secondary outcome cohort for comparative analysis were used.

Cumulative drug exposure to the 3 drugs of interest (valproate, lamotrigine, levetiracetam, all in monotherapy) were calculated as the total amount of DDD intake during the 3 months lookback from LMP2, using the following approach:

- Prescriptions of lamotrigine, levetiracetam or lamotrigine recorded in the 3 months lookback from LMP2 and those received in the 3 months prior to this window that had resulted in an intake during the exposure window were considered. These included:
    - Prescriptions received before the start of the exposure window (in the 3 months period before), but whose estimated duration (based on days covered) overlaps with the exposure window (e.g. prescription received 26 days before the start of the exposure window and whose duration, i.e. number of days covered based on one DDD/day, would extend beyond the start of the exposure window), AND
    - Prescriptions received during the exposure window (regardless of whether their duration extended beyond the exposure window)

- For each relevant prescription the number of DDDs prescribed was translated into the number of days covered, counting one DDD per day and distributing all available DDDs to the days of follow-up, according to the formula below:

$$Days\ covered = \frac{n.\ pkg\ in\ prescription_j * n.\ dosage\ unit\ in\ each\ pkg}{WHO\ DDD}$$

- The total number of days covered (or total DDDs) were obtained by adding up the days covered for each prescription, not allowing for the use of accumulated DDDs over time. If a new prescription was found before the previous one's days covered elapsed, the previous prescription was "truncated" the day before the next one was recorded. For prescriptions received prior to the start of the 3-monhts lookback from LMP2 which were considered as they gave rise to an intake during this period, only the days covered which fall into the 3 months lookback from LMP2 interval were considered in the calculation of total number of days covered

This newly defined exposure was described with mean, SD, minimum-maximum and 25th-75th percentile overall and by paternal exposure group: valproate, lamotrigine/levetiracetam composite and separately. In each treatment group (valproate, lamotrigine, levetiracetam), the distribution of cumulative exposure was also be explored, and categorised empirically using the tertiles of each group's distribution to represent low, medium and high exposure to each of the 3 treatments. This analysis was conducted independently for each drug, therefore the categories differed in the 3 groups.

In addition, multivariate analyses were conducted, separately for the 2 outcomes, to assess the association between the cumulative exposure and the outcomes at study between different treatments. The multivariate models used a traditional covariate adjustment method.

For the primary outcome, the following multivariate analyses were conducted:

- A Cox PH model was used; the exposure variable (2 groups: valproate vs lamotrigine/levetiracetam), the continuous variable describing cumulative and the interaction between exposure group and cumulative exposure were included. All the confounders for the primary outcome were included in the model; potential risk factors were included only if associated with both the exposure and the outcome, based on the results of the univariate analyses (see section 9.9.2.2.1)
- For each treatment group (3 groups: valproate, lamotrigine and levetiracetam) separately, a within-group analysis was performed to study the dose-response relationship by comparing high and medium exposure to low exposure to treatment as the reference category
- Each model was estimated on offspring from fathers exposed to the same treatment (i.e. a valproate model, a lamotrigine model, a levetiracetam model); Cox PH models included the exposure variable (high, medium and the reference category low) and a pre-defined list of covariates based on the primary comparative analyses. Since the distribution of cumulative exposure and of relevant confounders within each treatment group could differ to those of the other treatment groups, the results from the 3 within-exposure group analyses were not directly comparable

For the secondary outcome, the following multivariate analyses were conducted:

- A logistic regression model was used; the exposure variable (2 groups: valproate vs lamotrigine/levetiracetam), the continuous variable describing cumulative exposure and the interaction between exposure group and cumulative exposure were included. All the confounders for the secondary outcome were included in the model; potential risk

factors were included if associated with both the exposure and the outcome, based on the results of the univariate analyses (see section 9.9.2.2.1)
- For each treatment group (3 groups: valproate, lamotrigine and levetiracetam) separately, a within-group analysis was performed to study the dose-response relationship by comparing high and medium exposure to low exposure to treatment as the reference category
- Each model was estimated on offspring from fathers exposed to the same treatment (i.e. a valproate model, a lamotrigine model, a levetiracetam model); logistic regression models were used which include the exposure variable (high, medium and the reference category low) and a pre-defined list of covariates based on the primary comparative analyses. Since the distribution of cumulative exposure and of relevant confounders within each treatment group could differ to those of the other treatment groups, the results from the 3 within-exposure group analyses were not directly comparable

9.9.4.11 Sensitivity analysis - Narrow case definition of NDD

This sensitivity analysis used a narrow NDD composite case definition, and was conducted in 3 parts:

- Replication of the primary objective, with descriptive and comparative analyses as applied to the Primary outcome cohort

- Replication of exploratory objective 5, with summary cohort characteristics and univariate analysis performed to describe the subgroups and the risk factors for the narrow NDD composite outcome for offspring paternally exposed to valproate in combination with other AEDs (AED polytherapy) and offspring paternally unexposed to valproate but exposed to other AEDs (any combination) at the time of conception

- Replication of exploratory objective 6, with an exploratory sibling-matched descriptive analyses conducted on the narrow NDD composite outcome whereby only families with paternal valproate exposure-discordant siblings were included (at least one offspring with paternal valproate exposure and one offspring without exposure)

The code list with the ICD-10 codes used for this sensititivity analysis was presented in the Protocol V6.0 (sensitivity analysis 11).

9.10 Quality Control

The study used existing databases, which are being used widely for research. The study was executed in line with all applicable regulations and guidelines – such as best-practice guidelines applicable to non-interventional PASS, including but not limited to the European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology, the ENCePP Checklist for Study Protocols, and the Guidelines for Good Pharmacoepidemiology Practices of the International Society of Pharmacoepidemiology as well as the specific IQVIA Standard Operating Procedures (SOPs) on retrospective analysis.

The quality control was conducted at several levels depending on the database. All study programmes, log files, and output files are stored on a secure server.

10. Results

In this final report, we present the results related to the primary outcome (NDD including ASD) in Denmark, Sweden, and Norway, and to the secondary outcome (CM) for Denmark and Norway. Note that for Sweden, the analyses relevant to the secondary outcome are not presented, since data on non-live offspring was not available, precluding the creation of the Secondary outcome cohort. Nevertheless, an exploratory analysis investigating the risk of CM in live offspring paternally exposed to valproate compared to lamotrigine/levetiracetam at the time of conception in Sweden was performed and is presented in section 10.4.2.1.

The results of cumulative incidence proportions ratio, cumulative incidence rates ratio, crude and PS-weighted Cox regression models, crude and PS-weighted logistic regression models for both outcomes cohorts were pooled in a meta-analysis, to which the study was powered, and presented in section 10.1.

Box 1 Summary of analysis performed by outcome, for Denmark, Sweden, and Norway

	Denmark		Sweden		Norway	
Analysis description	NDD	CM	NDD	CM	NDD	CM
Meta-analysis	x	x	x	NA	x	x
Main analysis - Cohort characteristics	x	x	x	NA	x	x
Main analysis - Cumulative incidence rate and time-to-event	x	NA	x	NA	x	NA
Main analysis - Cumulative incidence proportion	x	x	x	NA	x	x
Main analysis - Univariate Analyses of association of risk factors/confounders with exposure and/or outcome	x	x	x	NA	x	x
Main analysis - Effect estimation	x	x	x	NA	x	x
Main analysis - Propensity score	x	x	x	NA	x	x
Case assessment	x	NA	x	NA	x	NA
Exploratory objective analyses	x	x[1]	x	x	x	x[1]
Sensitivity analyses	X[1]	x	x	NA	X[1]	x

NDD: neurodevelopmental disorders cohort; CM: congenital malformation cohort; "x" indicates the analysis was performed and is presented in this final report; NA: not applicable

[1] The results for sensitivity analyses 2 (risk of ASD) for Denmark, Sweden, and Norway, and for exploratory analyses 8 (congenital malformation by target body system organ class) for Denmark and Norway are provided as an addendum alongside the present CSR v1.1

10.1 Meta-analysis

The results of the meta-analysis are presented as follows:

The meta-analysis of cumulative incidence proportions ratio, cumulative incidence rates ratio, crude, and adjusted Cox regression models for NDD including ASD in Sweden, Norway, and Denmark are presented in Table 9 to Table 12.

The meta-analysis of cumulative incidence proportions ratio, and crude and adjusted logistic regression models for CM in Norway and Denmark are presented in Table 13 to Table 15.

10.1.1 Neurodevelopmental disorders including autism spectrum disorder cohort

Table 9 presents the pooled risk ratios of the cumulative incidence proportions of the Primary outcome cohort. Chi-square with 95% confidence interval (95% CI) and I^2 statistic were used to assess the heterogeneity between country-specific estimates. No heterogeneity was observed between country-specific estimates for the overall period of study follow-up (I^2 = 0.0%, 95% CI: 0.0, 89.6; p=0.8288). Although heterogeneity varied according to the years of study follow-up, the I^2 statistic indicates that the meta-analysis was appropriate. However, the broad 95% CI observed may reflect some uncertainty due to the small number of countries involved in the meta-analysis. A higher risk of NDD including ASD was observed in offspring from fathers exposed to valproate when compared to lamotrigine/levetiracetam group in the meta-analysis considering both the overall period of study follow-up (0-12 years RR=1.67, 95% CI: 1.34, 2.08; p<0.0001), and the 7-8 years of follow-up (RR=2.79, 95% CI: 1.33, 5.84; p=0.0066).

Table 9 Meta-analysis of the cumulative incidence proportions; primary outcome

	Risk ratio (valproate vs lamotrigine/levetiracetam composite monotherapy)							
NDD	**Sweden**	**Norway**	**Denmark**	**I^2 (%) (95% CI), p-value**	**Meta-analysis (random effect)**	**P-value (random effect)**	**Meta-analysis (fixed effect)**	**P-value (fixed effect)**
Follow-up period								
0-1 years	0.38 (0.04, 3.42)	10.77 (0.52, 223.99)	0.19 (0.01, 3.75)	51.50 (0.00, 86.00), 0.1274	0.84 (0.09, 7.88)	0.8762	0.74 (0.16, 3.40)	0.7004
1-2 years	2.82 (0.52, 15.39)	1.04 (0.09, 11.50)	2.70 (0.49, 14.7)	0.00 (0.00, 89.60), 0.7757	2.28 (0.78, 6.65)	0.1326	2.28 (0.78, 6.65)	0.1326
2-3 years	0.44 (0.09, 2.18)	0.69 (0.14, 3.40)	5.19 (0.58, 46.3)	40.00 (0.00, 81.50), 0.1888	0.97 (0.26, 3.62)	0.9640	0.88 (0.32, 2.41)	0.8082
3-4 years	1.84 (0.52, 6.51)	0.58 (0.12, 2.78)	0.20 (0.02, 1.67)	41.90 (0.00, 82.40), 0.1788	0.74 (0.22, 2.50)	0.6324	0.86 (0.35, 2.09)	0.7343
4-5 years	0.58 (0.15, 2.32)	1.71 (0.62, 4.67)	2.65 (0.69, 10.2)	21.50 (0.00, 91.80), 0.2799	1.44 (0.65, 3.20)	0.3670	1.46 (0.73, 2.93)	0.2863
5-6 years	1.72 (0.56, 5.22)	2.41 (0.65, 8.93)	1.74 (0.41, 7.27)	0.00 (0.00, 89.60), 0.9176	1.92 (0.92, 3.97)	0.0805	1.92 (0.92, 3.97)	0.0805
6-7 years	0.59 (0.17, 2.00)	1.23 (0.35, 4.32)	0.64 (0.18, 2.27)	0.00 (0.00, 89.60), 0.6750	0.77 (0.38, 1.58)	0.4792	0.77 (0.38, 1.58)	0.4792
7-8 years	2.28 (0.59, 8.75)	4.49 (1.42, 14.20)	1.73 (0.43, 6.91)	0.00 (0.00, 89.60), 0.5498	2.79 (1.33, 5.84)	0.0066	2.79 (1.33, 5.84)	0.0066
8-9 years	0.65 (0.21, 2.01)	0.68 (0.18, 2.55)	0.60 (0.22, 1.97)	0.00 (0.00, 89.60), 0.9979	0.66 (0.34, 1.30)	0.2334	0.66 (0.34, 1.30)	0.2334
9-10 years	0.77 (0.22, 2.62)	1.33 (0.36, 4.90)	1.22 (0.36, 4.14)	0.00 (0.00, 89.60), 0.8056	1.07 (0.52, 2.20)	0.8579	1.07 (0.52, 2.20)	0.8579
10-11 years	2.68 (0.30, 23.79)	0.50 (0.05, 4.77)	1.04 (0.25, 4.32)	0.00 (0.00, 89.60), 0.5721	1.11 (0.39, 3.18)	0.8510	1.11 (0.39, 3.18)	0.8510
11-12 years	0.88 (0.15, 5.16)	1.26 (0.18, 8.85)	3.76 (0.46, 30.4)	0.00 (0.00, 89.60), 0.5695	1.49 (0.49, 4.52)	0.4817	1.49 (0.49, 4.52)	0.4817
Overall (0-12 years)	1.53 (1.05, 2.23)	1.68 (1.14, 2.48)	1.81 (1.22, 2.67)	0.00 (0.00, 89.60), 0.8288	1.67 (1.34, 2.08)	<.0001	1.67 (1.34, 2.08)	<.0001

NDD: neurodevelopmental disorders

Legend: Risk ratio, i.e. ratio of the cumulative incidence proportions of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) were presented for each country separately and combined (meta-analysis). 95% CI: 95% confidence intervals. I^2 estimates the proportion of the variance in study estimates that is due to heterogeneity and it ranges from 0 (no heterogeneity) to 1 (heterogeneity).

Table 10 presents the pooled ratios of the cumulative incidence rates of Primary outcome cohort. No heterogeneity was observed between country-specific estimates for the overall period of study follow-up (I^2 = 0.0%, 95% CI: 0.0, 89.6; p=0.6558). Although the heterogeneity varied according to the years of study follow-up, the I^2 statistic indicates that meta-analysis was appropriate. However, the broad 95% CI observed could reflect some uncertainty of the test due to the small number of countries involved in the meta-analysis. A higher cumulative incidence rate of NDD including ASD in offspring from fathers exposed to valproate was observed in comparison to the lamotrigine/levetiracetam group in the meta-analysis considering the overall period of study follow-up (0-12 years RR=1.32, 95% CI: 1.05, 1.66; p=0.0162), the 0-8 years of study follow-up (RR=1.39, 95% CI: 1.06, 1.84; p=0.0191), the 0-10 years of study follow-up (RR=1.28, 95% CI: 1.01, 1.63; p=0.0451), and the 0-11 years of study follow-up (RR=1.28, 95% CI: 1.02, 1.62; p=0.0366).

Table 10 Meta-analysis of the cumulative incidence rates; primary outcome

	Risk ratio (valproate vs lamotrigine/levetiracetam composite monotherapy)							
NDD	**Sweden**	**Norway**	**Denmark**	**I2 (%) (95% CI), p, value**	**Meta, analysis (random effect)**	**P, value (random effect)**	**Meta, analysis (fixed effect)**	**P, value (fixed effect)**
Follow, up period								
0, 1 years	0.37 (0.04, 3.29)	10.62 (0.51, 221.19)	0.19 (0.01, 3.74)	51.60 (0.00, 86.10), 0.1266	0.82 (0.09, 7.75)	0.8620	0.72 (0.16, 3.32)	0.6779
0, 2 years	1.19 (0.36, 3.89)	3.16 (0.53, 18.92)	1.07 (0.28, 3.98)	0.00 (0.00, 89.60), 0.5980	1.39 (0.63, 3.05)	0.4190	1.39 (0.63, 3.05)	0.4190
0, 3 years	0.81 (0.32, 2.05)	1.31 (0.43, 3.99)	1.75 (0.60, 5.04)	0.00 (0.00, 89.60), 0.5467	1.18 (0.65, 2.13)	0.5891	1.18 (0.65, 2.13)	0.5891
0, 4 years	1.09 (0.53, 2.27)	0.96 (0.39, 2.36)	0.96 (0.40, 2.28)	0.00 (0.00, 89.60), 0.9675	1.01 (0.63, 1.63)	0.9512	1.01 (0.63, 1.63)	0.9512
0, 5 years	0.95 (0.50, 1.81)	1.24 (0.64, 2.41)	1.33 (0.65, 2.69)	0.00 (0.00, 89.60), 0.7557	1.15 (0.78, 1.70)	0.4735	1.15 (0.78, 1.70)	0.4735
0, 6 years	1.13 (0.65, 1.96)	1.42 (0.79, 2.56)	1.41 (0.75, 2.66)	0.00 (0.00, 89.60), 0.8177	1.30 (0.93, 1.83)	0.1252	1.30 (0.93, 1.83)	0.1252
0, 7 years	1.03 (0.62, 1.70)	1.39 (0.82, 2.37)	1.22 (0.70, 2.14)	0.00 (0.00, 89.60), 0.7133	1.20 (0.88, 1.63)	0.2468	1.20 (0.88, 1.63)	0.2468
0, 8 years	1.16 (0.73, 1.84)	1.77 (1.11, 2.83)	1.31 (0.78, 2.19)	0.00 (0.00, 89.60), 0.4361	1.39 (1.06, 1.84)	0.0191	1.39 (1.06, 1.84)	0.0191
0, 9 years	1.10 (0.71, 1.68)	1.58 (1.02, 2.44)	1.20 (0.75, 1.91)	0.00 (0.00, 89.60), 0.4857	1.28 (0.99, 1.65)	0.0621	1.28 (0.99, 1.65)	0.0621
0, 10 years	1.09 (0.73, 1.63)	1.56 (1.03, 2.37)	1.24 (0.80, 1.91)	0.00 (0.00, 89.60), 0.4688	1.28 (1.01, 1.63)	0.0451	1.28 (1.01, 1.63)	0.0451
0, 11 years	1.14 (0.77, 1.70)	1.49 (0.99, 2.25)	1.24 (0.82, 1.88)	0.00 (0.00, 89.60), 0.6442	1.28 (1.02, 1.62)	0.0366	1.28 (1.02, 1.62)	0.0366
0, 12 years	1.16 (0.79, 1.70)	1.49 (1.00, 2.23)	1.35 (0.90, 2.01)	0.00 (0.00, 89.60), 0.6558	1.32 (1.05, 1.66)	0.0162	1.32 (1.05, 1.66)	0.0162

NDD: neurodevelopmental disorders

Legend: Rate ratio, i.e. ratio of the cumulative incidence rate of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) were presented for each country separately and combined (meta-analysis). 95% CI: 95% confidence intervals. I^2 estimates the proportion of the variance in study estimates that is due to heterogeneity and it ranges from 0 (no heterogeneity) to 1 (heterogeneity)

Table 11 and Table 12 presents, respectively, the meta-analysis of the crude and adjusted hazard ratios (HR), for NDD including ASD, obtained from Cox regression models comparing offspring from fathers exposed to valproate to offspring from lamotrigine/levetiracetam group. No heterogeneity was observed between country-specific estimates neither in the crude Cox regression models (I^2 = 0.0%, 95% CI: 0.0, 89.6; p=0.4605) nor in the adjusted Cox regression models (I^2 = 0.0%, 95% CI: 0.0, 89.6; p=0.9170). No higher HR was observed in the meta-analysis of crude Cox regression models (HR 1.15, 95% CI: 0.90, 1.48; p=0.2682). In the adjusted models, a significant higher risk of NDD including ASD among offspring from fathers exposed to valproate in comparison to the lamotrigine/levetiracetam group was observed (HR 1.47, 95% CI: 1.10, 1.96; p=0.0089).

Table 11 Meta-analysis of the hazard ratios obtained from the crude Cox regression model; primary outcome

	Hazard ratio (valproate vs lamotrigine/levetiracetam composite monotherapy) - Crude Cox regression model						
NDD -	**Sweden**	**Norway**	**Denmark**	**Meta-analysis (random effect)**	**P-value (random effect)**	**Meta-analysis (fixed effect)**	**P-value (fixed effect)**
Number of offspring in the valproate group	930	617	793				
Number of events in the valproate group	49	38	43				
Number of offspring in the lamotrigine/levetiracetam group	1425	1326	1157				
Number of events in the lamotrigine/levetiracetam group	41	49	41				
I^2 (%) (95% CI), p-value					0.00% (0.00%-89.60%),0.4605		
Paternal exposure: valproate vs lamotrigin/levetiracetam	1.16 (0.76, 1.76)	1.40 (0.90, 2.18)	0.94 (0.60, 1.46)	1.15 (0.90, 1.48)	0.2682	1.15 (0.90, 1.48)	0.2682

NDD: neurodevelopmental disorders

Legend: Hazard ratio of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) were presented for each country separately and combined (meta-analysis). 95% CI: 95% confidence intervals.

Table 12 Meta-analysis of the hazard ratios obtained from the PS-weighted Cox regression model; primary outcome

	Hazard ratio (valproate vs lamotrigine/levetiracetam composite monotherapy) [1] PS-weighted Cox regression model						
NDD -	**Sweden**	**Norway**	**Denmark**	**Meta-analysis (random effect)**	**P-value (random effect)**	**Meta-analysis (fixed effect)**	**P-value (fixed effect)**
Number of offspring in the valproate group	841	505	678				
Number of events in the valproate group	47	32	38				
Number of offspring in the lamotrigine/levetiracetam group	1334	1165	1118				
Number of events in the lamotrigine/levetiracetam group	34	42	36				
I^2 (%) (95% CI), p-value					0.00% (0.00%-89.60%),0.9170		
Paternal exposure: valproate vs lamotrigine/levetiracetam	1.54 (0.95, 2.51)	1.52 (0.93, 2.49)	1.34 (0.79, 2.25)	1.47 (1.10, 1.96)	0.0089	1.47 (1.10, 1.96)	0.0089

NDD: neurodevelopmental disorders

Legend: Hazard ratio of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) were presented for each country separately and combined (meta-analysis). 95% CI: 95% confidence intervals.

[1] **The logistic regression PS model includes all variables from Table 31, Table 73, Table 100, following described:**

Denmark - Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Substance abuse during pregnancy", "Smoking during pregnancy", "Maternal polypharmacy index prior LMP2", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of: "concomitant medications associated with neuropsychiatric adverse events prior LMP2", "year of offspring conception"

Sweden - Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior LMP2", fathers with at least one prescription of: "concomitant medications associated with neuropsychiatric adverse events prior LMP2", "year of offspring conception"

Norway - Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse 12 months prior LMP2", fathers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior LMP2", "concomitant medications associated with neuropsychiatric adverse events 12 months prior LMP2", "Year of offspring conception"

10.1.2 Congenital Malformation cohort

Table 13 presents the pooled risk ratios of cumulative incidence proportions of the Secondary outcome cohort. Chi-square with 95% confidence interval (95% CI) and I^2 statistic were used to assess the heterogeneity between country-specific estimates. Heterogeneity was observed between country-specific estimates for the overall period of study follow-up (I^2 = 86.6%, 95% CI: 47.0, 96.6; p=0.0063), and for 0-1 years of follow-up (I^2 = 81.5%, 95% CI: 21.3, 95.6; p=0.0202). However, no higher risk of CM in offspring from fathers exposed to valproate was observed in comparison to the lamotrigine/levetiracetam group in the meta-analysis considering both the overall period of study follow-up (0-12 years RR=0.86, 95% CI: 0.52, 1.42; p=0.5572), or the specific periods of follow-up.

Table 14 and Table 15 presents respectively the meta-analysis of the crude and adjusted OR for CM, obtained from logistic regression models comparing offspring from fathers exposed to valproate to offspring from the lamotrigine/levetiracetam group. Again, heterogeneity was observed between country-specific estimates in the crude logistic regression models (I^2 =64.6%, 95% CI: 0.0, 91.9 p=0.0926), and in the adjusted models (I^2 = 44.7%, 95% CI: not available; p=0.1788). However, no difference in the risk for CM was observed among offspring from fathers exposed to valproate group compared to the lamotrigine/levetiracetam in the meta-analysis of crude (OR 0.84, 95% CI: 0.48, 1.48, p=0.5487) or adjusted logistic regression models (OR 0.79, 95% CI: 0.49, 1.29, p=0.3503).

Table 13 Meta-analysis of the cumulative incidence proportions; secondary outcome

	Risk ratio (valproate vs lamotrigine/levetiracetam composite monotherapy)						
CM	**Norway**	**Denmark**	**I2 (%) (95% CI), p, value**	**Meta, analysis (random effect)**	**P, value (random effect)**	**Meta, analysis (fixed effect)**	**P, value (fixed effect)**
Follow, up period							
0, 1 years	1.04 (0.78, 1.39)	0.57 (0.38, 0.86)	81.50 (21.30, 95.60), 0.0202	0.79 (0.44, 1.40)	0.4170	0.85 (0.67, 1.07)	0.1719
1, 2 years	0.81 (0.39, 1.67)	0.83 (0.36, 1.89)	0.00 (,), 0.9639	0.82 (0.48, 1.41)	0.4741	0.82 (0.48, 1.41)	0.4741
2, 3 years	1.83 (0.71, 4.71)	1.20 (0.43, 3.37)	0.00 (,), 0.5618	1.51 (0.75, 3.03)	0.2455	1.51 (0.75, 3.03)	0.2455
3, 4 years	0.54 (0.18, 1.62)	0.34 (0.07, 1.56)	0.00 (,), 0.6372	0.46 (0.19, 1.13)	0.0897	0.46 (0.19, 1.13)	0.0897
4, 5 years	0.49 (0.10, 2.30)	0.54 (0.14, 1.99)	0.00 (,), 0.9210	0.52 (0.19, 1.41)	0.1980	0.52 (0.19, 1.41)	0.1980
5, 6 years	1.92 (0.56, 6.61)	0.50 (0.05, 4.79)	4.70 (,), 0.3056	1.39 (0.45, 4.30)	0.5695	1.41 (0.48, 4.17)	0.5322
6, 7 years	1.10 (0.26, 4.58)	0.34 (0.03, 3.10)	0.00 (,), 0.3874	0.78 (0.24, 2.58)	0.6852	0.78 (0.24, 2.58)	0.6852
7, 8 years	2.48 (0.79, 7.76)	1.28 (0.08, 20.4)	0.00 (,), 0.6658	2.26 (0.79, 6.47)	0.1301	2.26 (0.79, 6.47)	0.1301
8, 9 years	0.72 (0.14, 3.68)	NA	,	,	,	,	,
9, 10 years	1.70 (0.24, 11.98)	NA	,	,	,	,	,
10, 11 years	1.53 (0.10, 24.36)	0.31 (0.01, 7.81)	0.00 (,), 0.4675	0.78 (0.10, 6.34)	0.8190	0.78 (0.10, 6.34)	0.8190
11, 12+ years	1.45 (0.21, 10.17)	NA	,	,	,	,	,
Overall (0, 12+ years)	1.10 (0.89, 1.36)	0.65 (0.48, 0.88)	86.60 (47.00, 96.60), 0.0063	0.86 (0.52, 1.42)	0.5572	0.92 (0.78, 1.10)	0.3787

Legend: Risk ratio, i.e. ratio of the cumulative incidence proportions of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) were presented for each country separately and combined (meta-analysis). 95% CI: 95% confidence intervals. I^2 estimates the proportion of the variance in study estimates that was due to heterogeneity and it ranged from 0 (no heterogeneity) to 1 (heterogeneity). Notes:

- Several risk ratios for Denmark were missing due to the fact that both valproate and lamotrigine/levetiracetam groups had 0 events in the corresponding years. It was not possible to calculate the risk ratios and perform the meta-analysis in those years.
- For countries where the index date was the 12th or 22nd week of pregnancy, follow-up time in years were longer than age in years, therefore some offspring were >12 years of follow-up by the time they were censored upon 12th birthday. For this reason, the table showed '12+ years'.
- The confidence interval for I 2 statistic was not available for some groups.

Table 14 Meta-analysis of the Odds ratios obtained from the crude logistic model; secondary outcome

			Odds ratio (valproate vs lamotrigine/levetiracetam composite monotherapy) - Crude logistic model			
CM -	**Norway**	**Denmark**	**Meta-analysis (random effect)**	**P-value (random effect)**	**Meta-analysis (fixed effect)**	**P-value (fixed effect)**
Number of offspring in the valproate group	262	259				
Number of events in the valproate group	41	23				
Number of offspring in the lamotrigine/levetiracetam group	443	389				
Number of events in the lamotrigine/levetiracetam group	64	53				
I^2 (%) (95% CI), p-value				64.64% (0.00%-91.94%),0.0926		
Paternal exposure: valproate vs levetiracetam/lamotrigine	1.10 (0.72, 1.68)	0.62 (0.37, 1.04)	0.84 (0.48, 1.48)	0.5487	0.87 (0.63, 1.21)	0.4188

Legend: Odds ratio of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) were presented for Norway and Denmark separately and combined (meta-analysis). 95% CI: 95% confidence intervals.

Table 15 Meta-analysis of the Odds ratios obtained from the PS-weighted logistic model; secondary outcome

CM - PS-weighted logistic model	Norway	Denmark	Odds ratio (valproate vs lamotrigine/levetiracetam composite monotherapy) [1] Meta-analysis (random effect)*	P-value (random effect)	Meta-analysis (fixed effect)*	P-value (fixed effect)
Number of offspring in the valproate group	222	238				
Number of events in valproate group	32	21				
Number of offspring in the lamotrigine/levetiracetam group	383	381				
Number of events in the lamotrigine/levetiracetam group	54	52				
I^2 (%) (95% CI), p-value				44.68% (-),0.1788		
Paternal exposure: valproate vs lamotrigine/levetiracetam	1.00 (0.62, 1.61)	0.61 (0.36, 1.06)	0.79 (0.49, 1.29)	0.3503	0.81 (0.56, 1.15)	0.2348

Legend: Odds ratio of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) were presented for Norway and Denmark separately and combined (meta-analysis). 95% CI: 95% confidence intervals.
Note: the confidence interval for I^2 statistic was not available.
[1] **The logistic regression PS model included all variables from Table 53, Table 123, following described:**
Denmark - Offspring risk factors/confounders: "Foetal alcohol syndrome"; **Maternal risk factors/confounders:** "Alcohol abuse prior to LMP2", "Alcohol abuse during pregnancy", "Substance abuse prior LMP2", "Substance abuse during pregnancy", "Smoking during pregnancy", "Gestational diabetes"
Norway - Maternal risk factors/confounders: "Substance abuse 2-months lookback from LMP2", "Smoking during pregnancy", "Varicella during pregnancy"

10.2 Country Results

Table 16 presents the summary of the main results of this study, by country and outcome cohort. For the NDD including ASD cohort, are presented the overall cumulative incidence proportion (0-12 years of follow-up), overall cumulative incidence rate of NDD including ASD (0-12 years of follow-up), crude and adjusted Cox regression models, and Cox regression model adjusted for cluster of exposure (please see Section 9.9.2.2.2.2), in Denmark, Sweden, and Norway.

For the CM cohort, the overall cumulative incidence proportion of CM (0-12 years of follow-up), crude and adjusted logistic regression models, and logistic regression model adjusted for cluster of exposure are presented in Denmark and Norway (please see Section 9.9.2.2.2.3).

Table 16 Summary results by country for neurodevelopmental disorders (NDD) and congenital malformations (CM) cohorts.

Summary of results of Neurodevelopmental Disorders (NDD) including Autism Spectrum Disorders (ASD) cohort			
	Denmark	**Sweden**	**Norway**
Overall Cumulative incidence proportion of NDD including ASD (0-12 years)[a]			
N (Overall)	2031	2451	2019
n	99	104	98
Overall population	4.87 (3.94, 5.81)	4.24 (3.45, 5.04)	4.85 (3.92, 5.79)
N (Valproate)	832	968	640
n	55	52	43
Valproate	6.61 (4.92, 8.30)	5.37 (3.95, 6.79)	6.72 (4.78, 8.66)
N (Lamotrigine/levetiracetam)	1199	1483	1379
n	44	52	55
Lamotrigine/levetiracetam	3.67 (2.61, 4.73)	3.51 (2.57, 4.44)	3.99 (2.96, 5.02)
Overall Cumulative incidence rate of NDD including ASD (0-12 years) [a]			
N (Overall)	99	104	98
Overall population	6.34 (5.16, 7.72)	7.44 (6.08, 9.02)	7.5 (6.09, 9.14)
N (Valproate)	55	52	43
Valproate	7.15 (5.39, 9.31)	8.02 (5.99, 10.52)	9.57 (6.93, 12.90)
N (Lamotrigine/levetiracetam)	44	52	55
Lamotrigine/levetiracetam	5.56 (4.04, 7.46)	6.94 (5.18, 9.10)	6.41 (4.83, 8.34)
Crude Cox regression model[b]			
N (Valproate)	793	930	617
n	43	49	38
Valproate	0.94 (0.60, 1.46)	1.16 (0.76, 1.76)	1.40 (0.90, 2.18)
N (Lamotrigine/levetiracetam)	1157	1425	1326
n	41	41	49
Lamotrigine/levetiracetam	Ref	Ref	Ref
Adjusted Cox regression model[b]			
N (Valproate)	678	841	505
n	38	47	32
Valproate	1.34 (0.79, 2.25)	1.54 (0.95, 2.51)	1.52 (0.93, 2.49)
N (Lamotrigine/levetiracetam)	1118	1334	1165
n	36	34	42
Lamotrigine/levetiracetam	Ref	Ref	Ref
Adjusted Cox regression model -			

Summary of results of Neurodevelopmental Disorders (NDD) including Autism Spectrum Disorders (ASD) cohort

	Denmark	Sweden	Norway
cluster[b]			
Cluster A			
N (Valproate)	368	355	349
n	21	23	24
Valproate	1.38 (0.69, 2.74)	1.63 (0.83, 3.20)	1.60 (0.90, 2.85)
N (Lamotrigine/levetiracetam)	644	577	877
n	22	15	30
Lamotrigine/levetiracetam	Ref	Ref	Ref
Cluster B			
N (Valproate)	310	258	156
n	17	11	8
Valproate	1.30 (0.60, 2.83)	1.40 (0.54, 3.62)	1.36 (0.53, 3.47)
N (Lamotrigine/levetiracetam)	474	445	288
n	14	11	12
Lamotrigine/levetiracetam	Ref	Ref	Ref
Cluster C			
N (Valproate)		228	
n		13	
Valproate	NA	1.54 (0.58, 4.13)	NA
N (Lamotrigine/levetiracetam)		312	
n		8	
Lamotrigine/levetiracetam	NA	Ref	Ref

Summary of results of CM

	Denmark	Sweden	Norway
Overall Cumulative incidence proportion of CM (0-12 years)[c]			
N (Overall)	1655		2027
n	207		316
Overall population	12.51(10.91, 14.10)	-	15.59(14.01, 17.17)
N (Valproate)	549		644
n	51		107
Valproate	9.29(6.86, 11.72)	-	16.61(13.74, 19.49)
N (Lamotrigine/levetiracetam)	1106		1383
n	156		209
Lamotrigine/levetiracetam	14.10(12.05, 16.16)	-	15.11(13.22, 17.00)
Crude logistic regression model[d]			
N (Valproate)	259		262
n	23		41
Valproate	0.62 (0.37, 1.04)	-	1.10 (0.72, 1.68)
N (Lamotrigine/levetiracetam)	389		443
n	53		64
Lamotrigine/levetiracetam	Ref	-	Ref
Adjusted logistic regression model[d]			
N (Valproate)	238		222
n	21		32
Valproate	0.61 (0.36, 1.06)	-	1.00 (0.62, 1.61)
N (Lamotrigine/levetiracetam)	381		383
n	52		54
Lamotrigine/levetiracetam	Ref	-	Ref
Adjusted logistic regression model - cluster[d]			
Cluster A		-	

N (Valproate)	138		349
n	10		24
Valproate	0.68 (0.31, 1.48)	-	0.55 (0.20, 1.51)
N (Lamotrigine/levetiracetam)	250		877
n	32		30
Lamotrigine/levetiracetam	Ref	-	Ref
Cluster B		-	
N (Valproate)	100		156
n	11		8
Valproate	0.54 (0.26, 1.12)	-	1.21 (0.70, 2.09)
N (Lamotrigine/levetiracetam)	131		288
n	20		12
Lamotrigine/levetiracetam	Ref	-	Ref

ASD: Autism Spectrum Disorders; CM: Congenital alformations; NDD: neurodevelopmental disorders; N: number of offspring in the considered subgroup; n: number of event in the considered subgroup; Ref: Reference; NA: Not applicable. Notes:

- **Primary outcome cohort**: Denmark: Cluster A: constant high exposure; Cluster B: constant low exposure; Sweden: Cluster A: constant high exposure; Cluster B: low-to-high exposure and Cluster C: high-to-low exposure; Norway: Cluster A: constant high exposure; Cluster B: constant low exposure;
- **Secondary outcome cohort:** Denmark: Cluster A: constant high exposure; Cluster B: constant low exposure, Norway: Cluster A: constant high exposure; Cluster B: constant low exposure

a: estimated in offspring selected in the Primary outcome cohort for descriptive analysis
b: estimated in offspring selected in the Primary outcome cohort for comparative analysis
c: estimated in offspring selected in the Secondary outcome cohort for descriptive analysis
d: estimated in offspring selected in the Secondary outcome cohort for comparative analysis

10.3 Results for Denmark

After applying all the inclusion and exclusion criteria, a total of 85201 pregnancies were identified in databases in Denmark. Subsequently additional exclusion criteria, not mutually exclusive, were applied to obtain the populations used for the descriptive and comparative analysis for each outcome, separately.[13]

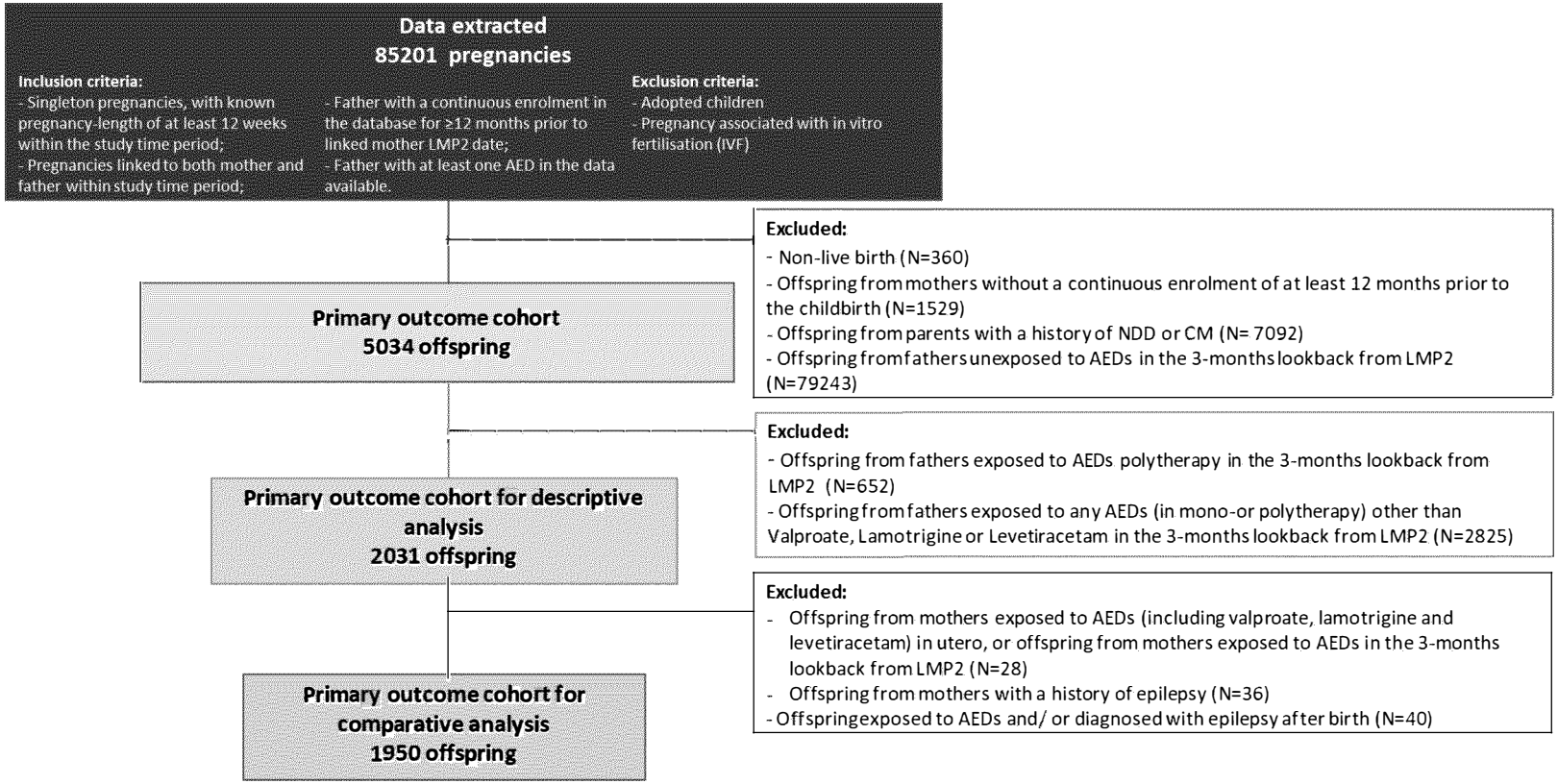
Please note that during stepwise exclusions from the cohorts post data extraction (Primary outcome cohort and Secondary outcome cohort) some characteristics were absent as they were either one of the exclusion criteria or characteristics associated with the exclusion criteria. Offspring with epilepsy, fathers exposed to other AEDs than those of interest and mothers exposed to AEDs or with a history of epilepsy are examples of these characteristics. Although these populations were described in this report, they were not part of the comparative analysis.

The selection of the Primary outcome cohort is presented in Figure 9.

From the 85201 pregnancies identified, the following were excluded: non-live births (N=360), offspring from a mother without a continuous enrolment in database of at least 12 months prior to the childbirth (N=1529), offspring from parents with a history of NDD or CM (N=7092), offspring paternally unexposed to AEDs in the 3 months lookback period from LMP2 (N=79243). Thus, the Primary outcome cohort consisted of 5034 offspring. There were 2031 offspring included in the Primary outcome cohort for descriptive analyses, and 1950 offspring in the Primary outcome cohort for comparative analyses.

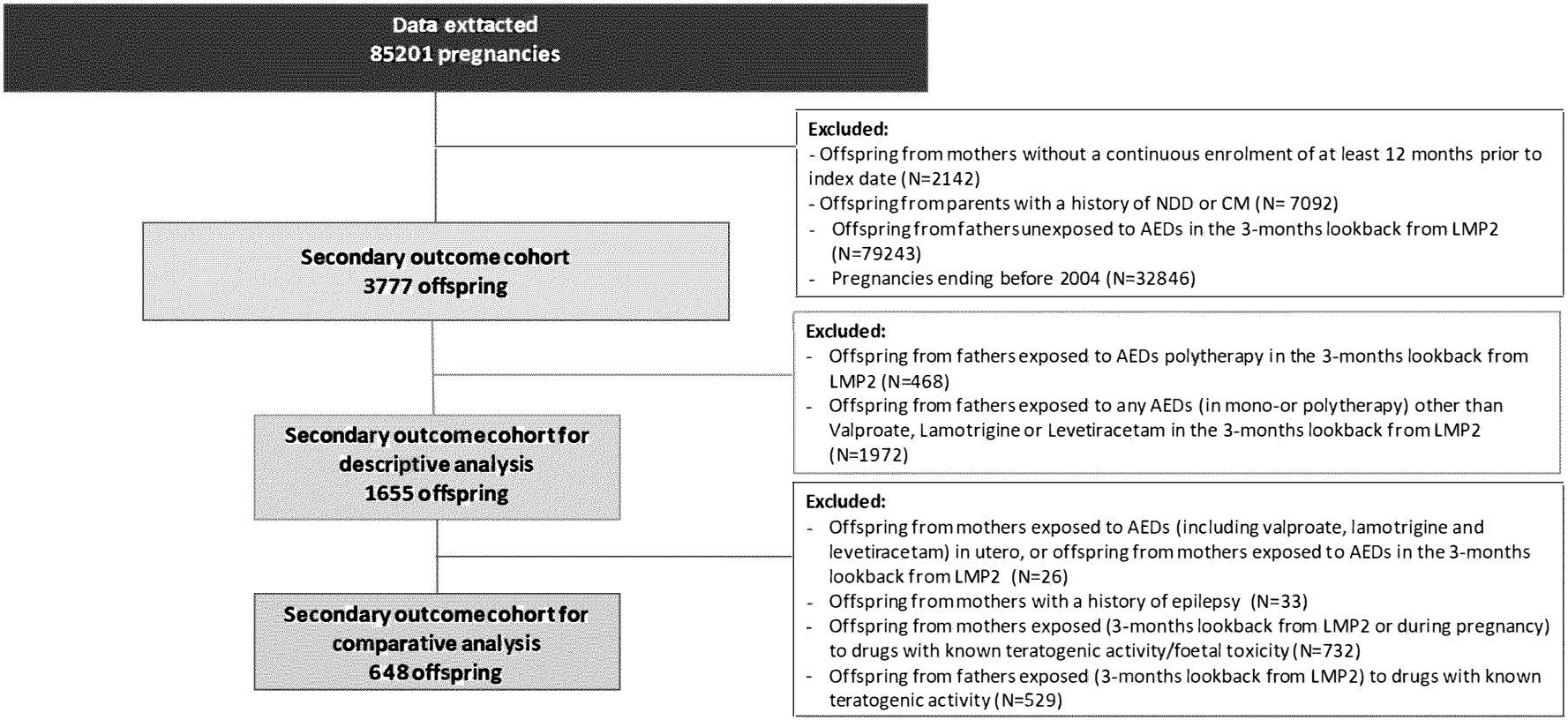
The selection of the Secondary outcome cohort, used to assess the risk of CM, is depicted in Figure 10. The Secondary outcome cohort for descriptive analyses consisted of 1655 offspring, while the Secondary outcome cohort for comparative analyses consisted of 648 offspring.

[13] In Denmark, data were masked for disclosure limitation in case a small number of observations (0< n <5) was found, or to preclude recalculation of values that leads to a small number of observations (e.g. in case the total is the sum of a small number and another number, both values would have been masked).



Legend: The exclusion criteria are not mutually exclusive.
AEDs: antiepileptic drug; CM: congenital malformations; LMP2: last menstrual period + 2 weeks; NDD: neurodevelopmental disorders

Figure 9 Study population of the Primary outcome cohort in Denmark



Legend: The exclusion criteria are not mutually exclusive.
AEDs: antiepileptic drug; CM: congenital malformations; LMP2: last menstrual period + 2 weeks; NDD: neurodevelopmental disorders

Figure 10 Study population of the Secondary outcome cohort in Denmark

10.3.1 Neurodevelopmental disorders including autism spectrum disorder

10.3.1.1 Description of the offspring, maternal and paternal characteristics by paternal exposure group

This section presents demographic and clinical characteristics of offspring, mothers, and fathers according to paternal exposure in monotherapy to valproate, lamotrigine or levetiracetam, and the comparator group of composite lamotrigine/levetiracetam monotherapy. This analysis was performed in the Primary outcome cohort for descriptive analyses, which is described in Figure 9.

Most of the offspring were male (52.2%), born at term between 37-41 weeks of gestational age (89.6%), and weighing ≥2500 g (96.5%). The highest proportions of offspring paternally exposed to valproate were conceived in the years 2001-2006, in contrast to the lamotrigine/levetiracetam group where the highest proportions were observed in the more recent years of the study, from 2009. The total offspring-years of follow-up was 15605.7 (7691.6 for valproate and 7914.1 for lamotrigine/levetiracetam group), and the mean follow-up in years per offspring was 9.2 for the valproate group and 6.6 for the lamotrigine/levetiracetam group (Table 17).

Regarding clinical characteristics of offspring by paternal exposure to valproate and lamotrigine/levetiracetam groups (832 vs. 1199 respectively), 2.5% of offspring paternally exposed to valproate and 1.4% paternally exposed to lamotrigine/levetiracetam were diagnosed with epilepsy. And 1.8% of offspring paternally exposed to valproate and 1.0% of offspring paternally exposed to lamotrigine/levetiracetam were exposed to AEDs between birth and exit date.

The diagnosis of NDD including ASD, occurred in 6.6% of offspring paternally exposed to valproate and in 3.7% of offspring paternally exposed to lamotrigine/levetiracetam. The median age in years at the first diagnosis of NDD including ASD was 7.1 (4.4, 9.1) for the valproate and 5.7 (3.5, 8.5) for the lamotrigine/levetiracetam group (Table 18).

ASD as the first NDD diagnosis, during all the study period, was observed in 1.4% of offspring paternally exposed to valproate and in 1.3% of offspring paternally exposed to lamotrigine/levetiracetam. All ASD diagnoses, ever and not only as a first NDD diagnosis, were observed in 1.4% of offspring paternally exposed to valproate and in 1.8% of offspring paternally exposed to lamotrigine/levetiracetam. The median (IQR) age in years at the first diagnosis of ASD was 6.1 (3.2, 8.0) for offspring paternally exposed to valproate and 7.5 (4.4, 10.2) for offspring paternally exposed to lamotrigine/levetiracetam.

Table 17 Offspring demographic characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Denmark (N=2031)

	Paternal exposure group									
NDD Number of offspring	**Valproate N=832**		**Lamotrigine/levetiracetam N=1199**		**Lamotrigine N=1034**		**Levetiracetam N=115**		**Total (valproate + lamotrigine/levetiracetam) N=2031**	
	N	%	N	%	N	%	N	%	N	%
Gestational age (weeks)										
<28 (extremely preterm)	***	***	***	***	***	***	***	***	***	***
28-31 (very preterm)	***	***	***	***	***	***	0	0	***	***
32-36 (moderate to late preterm)	49	5.89	39	3.25	***	***	***	***	88	4.33
37-41 (at term)	720	86.54	1100	91.74	994	91.7	106	92.17	1820	89.61
≥42 (post-term)	57	6.85	53	4.42	***	***	***	***	110	5.42
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	0	0.00	***	***	***	***	***	***	***	***
1000-1499 (very low)	***	***	***	***	***	***	0	0.00	***	***
1500-2499 (low)	16	1.92	37	3.09	***	***	***	***	53	2.61
≥2500	807	97	1152	96.08	1043	96.22	109	94.78	1959	96.45
Missing	***	***	***	***	***	***	***	***	9	0.44
Gender [a]										
Male	434	52.16	627	52.29	565	52.12	62	53.91	1061	52.24
Female	398	47.84	572	47.71	519	47.88	53	46.09	970	47.76
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of birth										
1997	31	3.73	6	0.5	6	0.55	0	0.00	37	1.82
1998	26	3.13	9	0.75	9	0.83	0	0.00	35	1.72
1999	33	3.97	7	0.58	7	0.65	0	0.00	40	1.97
2000	29	3.49	8	0.67	8	0.74	0	0.00	37	1.82

NDD Number of offspring	Paternal exposure group Valproate N=832		Lamotrigine/levetiracetam N=1199		Lamotrigine N=1034		Levetiracetam N=115		Total (valproate + lamotrigine/levetiracetam) N=2031	
	N	%	N	%	N	%	N	%	N	%
2001	54	6.49	21	1.75	21	1.94	0	0.00	75	3.69
2002	52	6.25	14	1.17	***	***	***	***	66	3.25
2003	61	7.33	28	2.34	***	***	***	***	89	4.38
2004	47	5.65	26	2.17	26	2.4	0	0.00	73	3.59
2005	58	6.97	44	3.67	***	***	***	***	102	5.02
2006	56	6.73	50	4.17	50	4.61	0	0.00	106	5.22
2007	50	6.01	54	4.50	***	***	***	***	104	5.12
2008	34	4.09	66	5.50	57	5.26	9	7.83	100	4.92
2009	47	5.65	73	6.09	67	6.18	6	5.22	120	5.91
2010	41	4.93	79	6.59	***	***	***	***	120	5.91
2011	29	3.49	86	7.17	81	7.47	5	4.35	115	5.66
2012	32	3.85	94	7.84	***	***	***	***	126	6.20
2013	30	3.61	94	7.84	84	7.75	10	8.70	124	6.11
2014	32	3.85	106	8.84	93	8.58	13	11.30	138	6.79
2015	37	4.45	98	8.17	86	7.93	12	10.43	135	6.65
2016	27	3.25	105	8.76	89	8.21	16	13.91	132	6.50
2017	20	2.40	72	6.01	54	4.98	18	15.65	92	4.53
2018	6	0.72	59	4.92	46	4.24	13	11.30	65	3.20
Total patient-years of follow-up	7691.63		7914.08		7402.33		511.75		15605.72	
Mean follow-up (years) per patient	9.24		6.60		6.83		4.45		7.68	

NDD: neurodevelopment disorder; g: grams

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at index (childbirth).

Table 18 Offspring clinical characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Denmark (N=2031)

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=832**		**N=1199**		**N=1084**		**N=115**		**N=2031**	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Congenital CMV [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital rubella [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Epilepsy [a]	21	2.52	17	1.42	17	1.57	0	0.00	38	1.87
Foetal alcohol syndrome [a]	0	0.00	***	***	***	***	0	0.00	***	***
Fragile X syndrome [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lejeune/cri du chat syndrome [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tuberous sclerosis [a]	***	***	0	0.00	0	0.00	0	0.00	***	***
Medication use										
Exposure to AEDs [a]	15	1.80	12	1.00	***	***	***	***	27	1.33
Outcomes										
ASD (ever, not only as 1st diagnosis)	12	1.44	22	1.83	***	***	***	***	34	1.67
ASD (as 1st diagnosis)	12	1.44	16	1.33	***	***	***	***	28	1.38
NDD including ASD	55	6.61	44	3.67	***	***	***	***	99	4.87
Outcomes (ICD-10 codes, ever) [b]										
Intellectual Disability – Mild	14	1.68	***	***	***	***	***	***	***	***
Intellectual Disability – Moderate	5	0.60	***	***	***	***	0	0.00	***	***
Intellectual Disability - Severe	***	***	***	***	***	***	0	0.00	***	***
Intellectual Disability - Profound	***	***	***	***	***	***	0	0.00	***	***
Other Intellectual Disability	***	***	0	0.00	0	0.00	0	0.00	***	***

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=832		N=1199		N=1084		N=115		N=2031	
	N	%	N	%	N	%	N	%	N	%
Unspecified Intellectual Disability	5	0.60	***	***	***	***	0	0.00	***	***
Specific developmental disorders of speech and language	***	***	5	0.42	***	***	***	***	***	***
Specific developmental disorders of scholastic skills	***	***	0	0.00	0	0.00	0	0.00	***	***
Mixed specific developmental delays	13	1.56	7	0.58	7	0.65	0	0.00	20	0.98
Pervasive developmental disorders	22	2.64	25	2.09	***	***	***	***	47	2.31
Other disorders of psychological development	***	***	***	***	***	***	0	0.00	***	***
Unspecified disorder of psychological development	***	***	0	0.00	0	0.00	0	0.00	***	***
Mental disorder, not otherwise specified	***	***	***	***	***	***	0	0.00	***	***
Dyslexia and other symbolic dysfunctions, not elsewhere classified	***	***	***	***	***	***	0	0.00	***	***
Hyperkinetic disorders	14	1.68	18	1.50	***	***	***	***	32	1.58

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=832		N=1199		N=1084		N=115		N=2031	
	N	%	N	%	N	%	N	%	N	%
Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	***	***	***	***	***	***	0	0.00	7	0.34
Tic disorders	***	***	6	0.50	6	0.55	0	0.00	***	***
Specific developmental disorder of motor function	***	***	***	***	***	***	0	0.00	7	0.34
Stereotyped movement disorders	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Essential tremor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other specified forms of tremor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Myoclonus	0	0.00	***	***	***	***	0	0.00	***	***
Other chorea	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other specified extrapyramidal and movement disorders	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Extrapyramidal and movement disorder, unspecified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Idiopathic nonfamilial dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Spasmodic torticollis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Idiopathic orofacial dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blepharospasm	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=832**		**N=1199**		**N=1084**		**N=115**		**N=2031**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Other dystonia	***	***	0	0.00	0	0.00	0	0.00	***	***
Dystonia, unspecified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Extrapyramidal and movement disorders in diseases classified elsewhere	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Age at the first diagnosis (years)										
ASD (ever, not only as 1st diagnosis) [c,d]										
0-1	***	***	0	0.00	0	0.00	0	0.00	***	***
2-3	***	***	***	***	***	***	0	0.00	6	0.30
4-5	***	***	***	***	***	***	0	0.00	***	***
6-7	***	***	***	***	***	***	0	0.00	7	0.34
8-9	***	***	***	***	***	***	***	***	5	0.25
10-11	***	***	***	***	***	***	0	0.00	5	0.25
Total (offspring with the outcome)	12	1.44	16	1.33	***	***	***	***	28	1.39
Offspring without a diagnosis	820	98.56	1183	98.67	1069	98.62	114	99.13	2003	98.62
Mean (SD)	5.83 (3.11)		7.55 (3.03)		7.39 (3.07)		9.88 (.)		6.81 (3.13)	
Median (25th – 75th percentile)	6.09 (3.20, 7.99)		7.79 (4.76, 10.14)		7.58 (4.42, 10.40)		9.88 (9.88, 9.88)		6.81 (4.05, 9.62)	
Min, max	***		***		***		***		***	
NDD including ASD [c,d]										
0-1	5	0.60	5	0.42	***	***	***	***	10	0.49
2-3	8	0.96	8	0.67	***	***	***	***	16	0.79
4-5	6	0.72	11	0.92	11	1.01	0	0.00	17	0.84
6-7	12	1.44	7	0.58	***	***	***	***	19	0.94

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=832**		**N=1199**		**N=1084**		**N=115**		**N=2031**	
	N	%	N	%	N	%	N	%	N	%
8-9	14	1.68	7	0.58	***	***	***	***	21	1.03
10-11	10	1.20	6	0.50	6	0.55	0	0.00	16	0.79
Total (offspring with the outcome)	55	6.6	44	3.67	***	***	***	***	99	4.88
Offspring without an NDD diagnosis	777	93.39	1155	96.33	1044	96.31	111	96.52	1932	95.13
Mean (SD)	6.74 (3.03)		6.03 (3.32)		6.13 (3.27)		5.08 (4.25)		6.42 (3.17)	
Median (25th – 75th percentile)	7.1(4.45, 9.10)		5.7(3.51, 8.51)		5.7 (3.68, 8.51)		4.99 (1.62, 8.53)		6.54 (3.81, 8.89)	
Min, max	***		***		***		***		***	

AED: antiepileptic drug; ASD: autism spectrum disorders; CMV: cytomegalovirus; Min: Minimum, Max: Maximum; NDD: neurodevelopmental disorders; SD: standard deviation
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between index (childbirth) and exit date; b) ICD-10 codes refer to all records of NDD including ASD during the entire follow-up. Since offspring might have more than one distinct ICD-10 code, the sum of the distinct ICD-10 codes might not coincide with the total number of offspring with the composite outcome; c) Categories might be adapted according to the data; d) denominator for the percentage was the number of offspring with the outcome.

Overall, the median (IQR) age of mothers from the Primary outcome cohort for descriptive analyses at childbirth was 30 (27, 34) years (Table 19), and it was similar in both exposure groups. The most prevalent maternal clinical characteristics prior to childbirth were neurotic disorder observed in 5.8% of mothers of offspring paternally exposed to valproate and in 7.5% of mothers of offspring paternally exposed to lamotrigine/levetiracetam, gestational diabetes was observed in 3.6% of mothers of offspring paternally exposed to valproate and in 3.8% of mothers of offspring paternally exposed to lamotrigine/levetiracetam, and affective disorder, observed in 2.6% of mothers of offspring paternally exposed to valproate and in 5.0% of mothers of offspring paternally exposed to lamotrigine/levetiracetam (Table 20).

Regarding the maternal characteristics of the 2031 offspring in the Primary outcome cohort for descriptive analyses, 16.1% had a record of smoking during pregnancy, 16.6% of mothers of offspring paternally exposed to valproate and 15.8% of mothers of offspring paternally exposed to lamotrigine/levetiracetam. Data on maternal smoking prior to LMP2 was deemed not reliable due to the high missingness (94.8% of missing data on the group of lamotrigine/levetiracetam) (Table 20).

A polypharmacy index between 1 and 4 during pregnancy was observed in 44% of mothers of offspring paternally exposed to valproate group, and in 51.6% of mothers of offspring paternally exposed to lamotrigine/levetiracetam group. Regarding the concomitant medications associated with neuropsychiatric adverse events during pregnancy, 39.1% of mothers of offspring paternally exposed to valproate, and 47.8% of mothers of offspring paternally exposed to lamotrigine/levetiracetam had at least one prescription. (Table 20).

Regarding paternal demographic characteristics, the overall median (IQR) age of fathers at childbirth was 33 (29, 36) years, and it was similar in both exposure groups. The highest proportion of offspring paternally exposed to valproate was conceived in 2005, during the earlier years of the study inclusion (1996-2007), in contrast to the lamotrigine/levetiracetam group where the highest proportions were observed in the more recent years of study inclusion (2008-2018) (Table 21). Regarding paternal clinical characteristics of the offspring from the Primary outcome cohort for descriptive analyses, in the group of offspring paternally exposed to valproate, 6.3% of fathers presented neurotic disorder, 3.7% presented affective disorder excluding bipolar and mania, and 2.6% presented bipolar affective disorder. Among offspring paternally exposed to lamotrigine/levetiracetam, proportions were generally higher with 13.0% of fathers presenting affective disorder excluding bipolar and mania, 11.3% presenting neurotic disorder and 7.5% presenting bipolar affective disorder (Table 22).

The most frequent indication for AED treatment was epilepsy for the total group of valproate and lamotrigine/levetiracetam (63.5%), the valproate group (70.0%), and the lamotrigine/levetiracetam group (59.0%) (Table 22) [14].

[14] Since indications for medications are not available in all the data sources used for this study, the indication for AEDs was estimated based on medical history. The following indications were considered for the three AEDs of interest (valproate, lamotrigine, levetiracetam): epilepsy, bipolar disorder and

Clusters of fathers with homogenous trajectories of drug intake during the assessment period were identified, using the number of DDDs in every 14-days interval and grouping fathers with similar "trajectories" of this metric over time. Since it was assumed that treated fathers were exposed to 1 WHO DDD per day, the number of DDDs in each 14-days interval also coincided with the number of days covered in the same period (e.g. 10 DDDs=10 days covered in a specific 14-days interval). The longitudinal K-means clustering algorithm was applied to create K-means clusters with homogenous trajectories. No assumption about the number of clusters was made prior to running the algorithm.

The K-means algorithm, analysing DDD trajectories in fathers exposed to AEDs 3 months prior conception (i.e. prior LMP2) identified 2 different clusters A and B (Figure 11), one with constant low exposure (i.e. a low quantity of DDDs of exposure in the 14-days intervals of the assessment period, Cluster B) and one with constant moderate exposure to AEDs (Cluster A) . Both groups of exposure to valproate and to lamotrigine/levetiracetam seemed to present higher proportions of fathers in cluster A (52.8% and 57.6%, respectively) than in cluster B (47.2% and 42.5%, respectively) (Table 22).

mania, other/unknown. The entire medical history for each father will be considered up to LMP2 (exclusive) to identify diagnosis records of epilepsy and bipolar disorder/mania. In case more than one diagnosis was found (e.g. epilepsy and bipolar disorder), only one indication was selected, with priority given to epilepsy, followed by bipolar disorder. In case none of these diagnoses are found in the medical history, the indication was considered "other/unknown".

Table 19 Maternal demographic characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Denmark (N=2031)

	Paternal exposure group									
Neurodevelopmental disorders (NDD)	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
	N=832		**N=1199**		**N=1084**		**N=115**		**N=2031**	
Number of offspring	N	%	N	%	N	%	N	%	N	%
Mother's age [a]										
≤20 years	12	1.44	19	1.58	***	***	***	***	31	1.53
21-25	143	17.19	166	13.84	***	***	***	***	309	15.21
26-30	301	36.18	414	34.53	371	34.23	43	37.39	715	35.20
31-35	273	32.81	401	33.44	354	32.66	47	40.87	674	33.19
36-40	91	10.94	166	13.84	157	14.48	9	7.83	257	12.65
>40	12	1.44	33	2.75	33	3.04	0	0.00	45	2.22
Mean (SD)	29.97 (4.71)		30.66 (5.02)		30.73 (5.10)		30.02 (4.14)		30.38 (4.90)	
Median (25th - 75th percentile)	30(26.00, 33.00)		31(27.00, 34.00)		31(27.00, 34.00)		30(27.00, 33.00)		30(27.00, 34.00)	
Min, max	***		***		***		***		***	
Missing	-		-		-		-		-	

NDD: neurodevelopmental disorders; Min: Minimum; Max: Maximum; SD: standard deviation

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics are described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.

a) at index (childbirth).

Table 20 Maternal clinical characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Denmark (N=2031)

	Paternal exposure group									
Neurodevelopmental disorders (NDD)	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=832**		**N=1199**		**N=1084**		**N=115**		**N=2031**	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Affective disorder [a]	22	2.64	60	5.00	***	***	***	***	82	4.04
Diabetes [a]	10	1.20	25	2.09	***	***	***	***	35	1.72
Epilepsy [a]	18	2.16	18	1.50	***	***	***	***	36	1.77
Neurotic disorder [a]	48	5.77	90	7.51	***	***	***	***	138	6.79
Schizophrenia, schizotypal and delusional disorders [a]	5	0.60	9	0.75	***	***	***	***	14	0.69
Obesity [b]	10	1.20	21	1.75	***	***	***	***	31	1.53
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gestational diabetes [c]	30	3.61	46	3.84	41	3.78	5	4.35	76	3.74
Rubella [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lifestyle characteristics										
Alcohol abuse prior to LMP2 [b]	***	***	***	***	***	***	***	***	6	0.30
Alcohol abuse during pregnancy [c]	***	***	***	***	***	***	***	***	***	***
Substance abuse prior to LMP2 [b]	0	0.00	5	0.42	***	***	***	***	5	0.25
Substance abuse during pregnancy [c]	***	***	***	***	***	***	***	***	6	0.30
Smoking prior to LMP2 [b]										
No	25	3.00	45	3.75	39	3.60	6	5.22	70	3.45
Yes	***	***	18	1.50	18	1.66	0	0.00	***	***
Missing	***	***	1136	94.75	1027	94.74	109	94.78	***	***
Smoking during pregnancy [c]										
No	637	76.56	985	82.15	887	81.83	98	85.22	1622	79.86
Yes	138	16.59	189	15.76	***	***	***	***	327	16.10
Missing	57	6.85	25	2.09	***	***	***	***	82	4.04
Medication use										
Exposure to AEDs prior to LMP2 [d]										
Valproic Acid	0	0.00	***	***	***	***	***	***	***	***
Lamotrigine	***	***	10	0.83	10	0.92	0	0.00	***	***

	Paternal exposure group									
Neurodevelopmental disorders (NDD)	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=832**		**N=1199**		**N=1084**		**N=115**		**N=2031**	
	N	%	N	%	N	%	N	%	N	%
Levetiracetam	0	0.00	***	***	***	***	***	***	***	***
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives[e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	***	***	***	***	***	***	***	***
Carboxamide derivatives	***	***	***	***	***	***	***	***	5	0.25
Fatty acid derivatives	0	0.00	***	***	***	***	***	***	***	***
Other antiepileptics	***	***	15	1.25	***	***	***	***	***	***
Exposure to AED during pregnancy [c]										
Valproic Acid	***	***	***	***	***	***	***	***	***	***
Lamotrigine	5	0.60	10	0.83	10	0.92	0	0.00	15	0.74
Levetiracetam	0	0.00	***	***	***	***	***	***	***	***
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives[e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	***	***	***	***	***	***	***	***	***	***
Carboxamide derivatives	***	***	***	***	***	***	***	***	***	***
Fatty acid derivatives	***	***	***	***	***	***	***	***	***	***
Other antiepileptics	5	0.60	14	1.17	***	***	***	***	19	0.94
K-means cluster prior to LMP2 [d]										
Unexposed	825	99.16	***	***	***	***	***	***	***	***
Cluster A[1]	***	***	10	0.83	10	0.92	0	0.00	***	***
Cluster B[1]	***	***	7	0.58	7	0.65	0	0.00	***	***
Cluster C[1]	***	***	***	***	***	***	***	***	***	***
K-means cluster during pregnancy [c]										
Unexposed	823	98.92	***	***	***	***	***	***	***	***
Cluster A[2]	***	***	10	0.83	10	0.92	0	0.00	***	***

Neurodevelopmental disorders (NDD)	Paternal exposure group: Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=832		N=1199		N=1084		N=115		N=2031	
	N	%	N	%	N	%	N	%	N	%
Cluster B[2]	***	***	5	0.42	5	0.46	0	0.00	***	***
Cluster C[2]	***	***	***	***	***	***	***	***	***	***
Maternal polypharmacy index prior to LMP2 [d]										
0	571	68.63	742	61.88	654	60.33	88	76.52	1313	64.65
1-4	255	30.65	438	36.53	411	37.92	27	23.48	693	34.12
5-10	6	0.72	19	1.58	19	1.75	0	0.00	25	1.23
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mean (SD)	0.50 (0.93)		0.69 (1.16)		0.72 (1.20)		0.36 (0.74)		0.61 (1.08)	
Median (25th - 75th percentile)	0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 0.00)		0 (0.00, 1.00)	
Min, max	***		***		***		***		***	
Maternal polypharmacy index during pregnancy [c]										
0	452	54.33	553	46.12	494	45.57	59	51.30	1005	49.48
1-4	366	43.99	619	51.63	***	***	***	***	985	48.50
5-10	***	***	26	2.17	***	***	***	***	***	***
>10	***	***	***	***	***	***	***	***	***	***
Mean (SD)	0.78 (1.15)		1.00 (1.31)		1.02 (1.33)		0.80 (1.03)		0.91 (1.25)	
Median (25th - 75th percentile)	0 (0.00, 1.00)		1 (0.00, 2.00)		1 (0.00, 2.00)		0 (0.00, 1.00)		1 (0.00, 1.00)	
Min, max	***		***		***		***		***	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	51	6.13	109	9.09	103	9.50	6	5.22	160	7.88
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	28	3.37	75	6.26	***	***	***	***	103	5.07

Neurodevelopmental disorders (NDD)	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=832		N=1199		N=1084		N=115		N=2031	
	N	%	N	%	N	%	N	%	N	%
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] - mothers with at least one prescription	586	70.43	853	71.14	781	72.05	72	62.61	1439	70.85
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	325	39.06	573	47.79	521	48.06	52	45.22	898	44.21

AED: antiepileptic drug; CMV: cytomegalovirus; LMP2: last menstrual period + 2 weeks; NDD: neurodevelopmental disorders; Min: Minimum; Max: Maximum; SD: standard deviation

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) all available data prior to index date (childbirth); b) 12 months lookback from LMP2; c) during pregnancy (from LMP2 until index date); d) 3 months lookback from LMP2;

Cluster A^1: constant moderate exposure, Cluster B^1: constant low exposure, Cluster C^1: high - moderate exposure

Cluster A^2: moderate-low exposure, Cluster B^2: constant low exposure, Cluster C^2: high to moderate exposure

Table 21. Paternal demographic characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Denmark (N=2031)

Neurodevelopmental disorders (NDD)	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=832		N=1199		N=1084		N=115		N=2031	
	N	%	N	%	N	%	N	%	N	%
Father's age [a]										
≤20 years	***	***	5	0.42	5	0.46	0	0.00	***	***
21-25	***	***	99	8.26	88	8.12	11	9.57	***	***
26-30	242	29.09	277	23.10	252	23.25	25	21.74	519	25.55
31-35	314	37.74	421	35.11	365	33.67	56	48.70	735	36.19
36-40	152	18.27	263	21.93	247	22.79	16	13.91	415	20.43
>40	68	8.17	134	11.18	127	11.72	7	6.09	202	9.95
Mean (SD)	32.68 (5.30)		33.38 (5.91)		33.50 (5.99)		32.28 (4.94)		33.09 (5.68)	
Median (25th - 75th percentile)	32 (29.00, 36.00)		33 (29.00, 37.00)		33 (29.00, 37.00)		32 (29.00, 35.00)		33 (29.00, 36.00)	
Min, max	***		***		***		***		***	
Year of offspring conception [b]										
1996	26	3.13	***	***	***	***	0	0.00	***	***
1997	22	2.64	***	***	***	***	0	0.00	***	***
1998	33	3.97	7	0.58	7	0.65	0	0.00	40	1.97
1999	32	3.85	7	0.58	7	0.65	0	0.00	39	1.92
2000	45	5.41	17	1.42	17	1.57	0	0.00	62	3.05
2001	55	6.61	20	1.67	***	***	***	***	75	3.69
2002	50	6.01	20	1.67	***	***	***	***	70	3.45
2003	52	6.25	29	2.42	29	2.68	0	0.00	81	3.99
2004	57	6.85	42	3.50	***	***	***	***	99	4.87
2005	61	7.33	47	3.92	***	***	***	***	108	5.32

	Paternal exposure group									
Neurodevelopmental disorders (NDD)	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of offspring	**N=832**		**N=1199**		**N=1084**		**N=115**		**N=2031**	
	N	%	N	%	N	%	N	%	N	%
2006	45	5.41	46	3.84	46	4.24	0	0.00	91	4.48
2007	39	4.69	67	5.59	59	5.44	8	6.96	106	5.22
2008	48	5.77	77	6.42	69	6.37	8	6.96	125	6.15
2009	44	5.29	71	5.92	***	***	***	***	115	5.66
2010	36	4.33	82	6.84	76	7.01	6	5.22	118	5.81
2011	21	2.52	91	7.59	***	***	***	***	112	5.51
2012	37	4.45	98	8.17	89	8.21	9	7.83	135	6.65
2013	26	3.13	104	8.67	92	8.49	12	10.43	130	6.40
2014	37	4.45	107	8.92	95	8.76	12	10.43	144	7.09
2015	35	4.21	98	8.17	84	7.75	14	12.17	133	6.55
2016	21	2.52	80	6.67	63	5.81	17	14.78	101	4.97
2017	***	***	56	4.67	41	3.78	15	13.04	***	***
2018	***	***	21	1.75	***	***	***	***	***	***

NDD: neurodevelopmental disorders; Min: Minimum; Max: Maximum; SD: standard deviation
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth); b) at mother's LMP2.

Table 22 Paternal clinical characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Denmark (N=2031)

	Paternal exposure group

Neurodevelopmental disorders (NDD) Number of offspring	Valproate N=832		Lamotrigine/levetiracetam N=1199		Lamotrigine N=1084		Levetiracetam N=115		Total (valproate + lamotrigine/levetiracetam) N=2031	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Affective disorder excl. bipolar disorder and mania [a]	31	3.73	156	13.01	***	***	***	***	187	9.21
Bipolar affective disorder [a]	22	2.64	90	7.51	90	8.30	0	0.00	112	5.51
Mania [a]	6	0.72	9	0.75	9	0.83	0	0.00	15	0.74
Neurotic disorder [a]	52	6.25	135	11.26	128	11.81	7	6.09	187	9.21
Schizophrenia, schizotypal and delusional disorders [a]	16	1.92	27	2.25	27	2.49	0	0.00	43	2.12
Lifestyle characteristics										
Substance abuse [b]	6	0.72	***	***	***	***	***	***	***	***
Medication use										
AED indication [d]										
Epilepsy	582	69.95	707	58.97	604	55.72	103	89.57	1289	63.47
Bipolar disorder	23	2.76	90	7.51	90	8.30	0	0.00	113	5.56
other/unknown	227	27.28	402	33.53	390	35.98	12	10.43	629	30.97
K-means cluster [c]										
Cluster A	439	52.76	690	57.55	611	56.37	79	68.70	1129	55.59
Cluster B	393	47.24	509	42.45	473	43.63	36	31.30	902	44.41
Paternal polypharmacy index [c]										
0	576	69.23	676	56.38	590	54.43	86	74.78	1252	61.64
1-4	242	29.09	498	41.53	469	43.27	29	25.22	740	36.44
5-10	14	1.68	25	2.09	25	2.31	0	0.00	39	1.92
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mean (SD)	0.54 (1.15)		0.81 (1.23)		0.86 (1.27)		0.32 (0.63)		0.70 (1.21)	
Median (25th - 75th percentile)	0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)	
Min, max	***		***		***		***		***	

	Paternal exposure group									
Neurodevelopmental disorders (NDD)	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=832**		**N=1199**		**N=1084**		**N=115**		**N=2031**	
	N	%	N	%	N	%	N	%	N	%
Concomitant medications associated with valproate-indicated psychiatric conditions [c] – fathers with at least one prescription	101	12.14	369	30.78	***	***	***	***	470	23.14
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription	410	49.28	671	55.96	622	57.38	49	42.61	1081	53.23

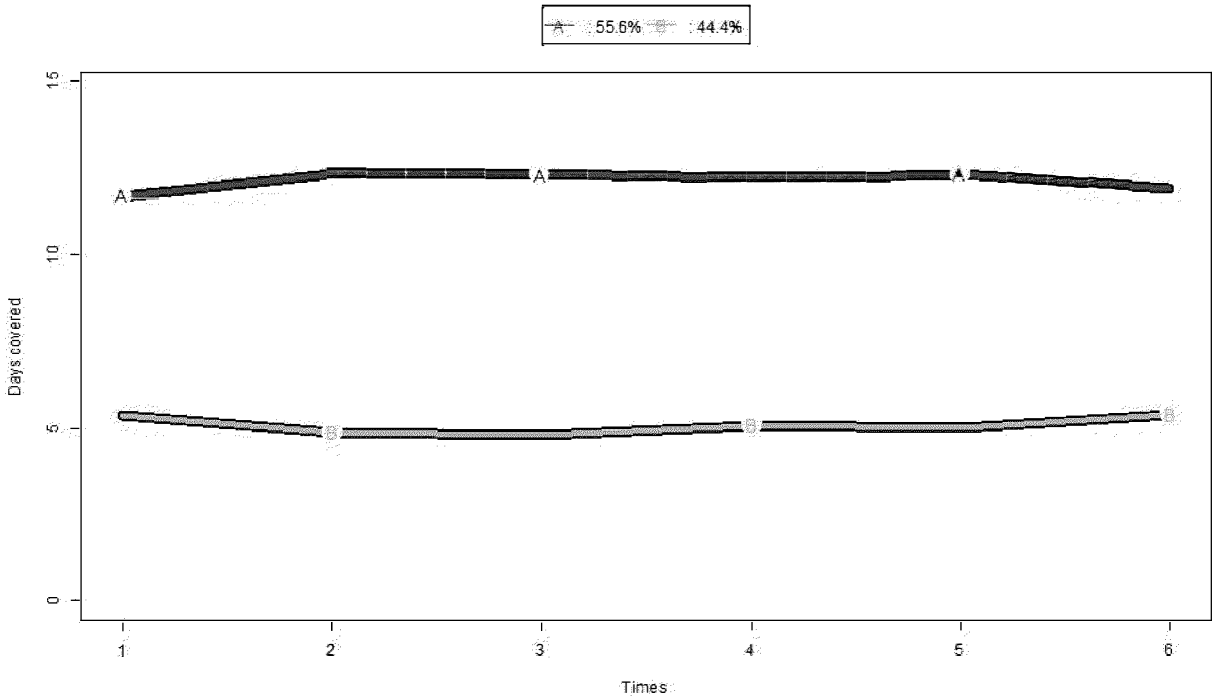
AED: antiepileptic drug; NDD: neurodevelopmental disorders; SD: standard deviation

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Cluster A: constant high exposure; Cluster B: constant low exposure

Comorbidities and AED indication: the same data were used for these 2 sets of categories (ICD-10 codes any time before index, i.e. child birthdate for the primary outcome). However, for "comorbidities" all records were considered and a patient with a record of mania and a record of bipolar affective disorder was counted in both categories, whereas for "AED indication", categories were mutually exclusive, based on the following priority order: 1) epilepsy 2) bipolar affective disorder and mania 3) other/unknown, meaning a patient with a record of epilepsy and a record of mania is counted only in the epilepsy category only.

a) all available data prior to index date (childbirth); b) 12 months lookback from LMP2; c) 3 months lookback from LMP2; d) Since indications for medications were not available in all the data sources used for this study, the indication for AEDs was estimated based on medical history. The entire medical history for each father was considered up to LMP2 (exclusive) to identify diagnosis records of epilepsy and bipolar disorder/mania. In case more than one diagnosis was found (e.g. epilepsy and bipolar disorder), only one indication was selected, with priority given to epilepsy, followed by bipolar disorder. In case none of these diagnoses was found in the medical history, the indication was considered "other/unknown".



Legend: Times refers to the 14-days interval during which exposure was assessed (in this case, 6 14 days interval [i.e.3 months]); Days covered refers to days covered in each 14-day interval; Defined Daily Dose (DDD) trajectories: Cluster A: constant moderate exposure; Cluster B: constant low exposure. The percentage showed the proportion of fathers exposed to valproate and lamotrigine/levetiracetam in each cluster.

Figure 11 Mean defined daily dose (DDD) trajectories for fathers exposed to Antiepileptic drugs (AEDs) in the 3 months lookback prior to Last menstrual Period Date Plus 2 weeks (LMP2) in Denmark

10.3.1.2 Cumulative incidence proportion

Cumulative incidence proportions (risk) of NDD by paternal exposure group are presented in Table 23, Table 136 and Table 137 (see Appendix), overall and stratified by gender. The overall cumulative incidence proportion of NDD (considering offspring diagnosed with NDD between the age of 0 and 12) appeared to be higher in offspring paternally exposed to valproate (6.6%, 95% CI: 4.9, 8.3) than offspring paternally exposed to lamotrigine/levetiracetam (3.7%, 95% CI: 2.6, 4.7) (Table 23).

Overall, considering the group exposed to valproate and lamotrigine/levetiracetam, the cumulative incidence proportion for 0-12 years of follow-up also appeared to be higher in male offspring (6.2%, 95% CI: 4.7, 7.6) than female offspring (3.5%, 95% CI: 2.4, 4.7). These proportions should be interpreted with caution since these are crude estimates and no adjustments were made. In addition, offspring diagnosed with epilepsy and/treated with AEDs and/or exposed to AEDs in utero were not excluded in the descriptive cohort (Table 136, Table 137).

Table 23 Cumulative incidence proportion (risk) of neurodevelopmental disorders (NDD) by paternal exposure group; Primary outcome cohort for descriptive analyses in Denmark (N=2031)

		Paternal exposure group				
Neurodevelopmental disorders (NDD)		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	832	1199	1084	115	2031
0-1 years	n	***	5	***	***	***
	n/N*100	***	0.42 (0.05, 0.78)	***	***	***
	N	822	1128	1027	101	1950
1-2 years	n	***	0	0	0	***
	n/N*100	***	0.0 0 (0.00, 0.00)	0.00 (0.00-0.00)	0.00 (0.00, 0.00)	***
	N	796	1049	967	82	1845
2-3 years	n	***	***	***	***	7
	n/N*100	***	***	***	***	0.38 (0.10, 0.66)
	N	766	943	877	66	1709
3-4 years	n	5	***	***	0	***
	n/N*100	0.65 (0.08, 1.22)	***	***	0.00(0.00, 0.00)	***
	N	723	835	782	53	1558
4-5 years	n	5	***	***	0	***
	n/N*100	0.69 (0.09, 1.30)	***	***	0.00(0.00, 0.00)	***
	N	685	730	690	40	1415
5-6 years	n	***	8	8	0	***
	n/N*100	***	1.10 (0.34, 1.85)	1.16 (0.36, 1.96)	0.00(0.00, 0.00)	***
	N	652	627	596	31	1279
6-7 years	n	8	***	***	0	***
	n/N*100	1.23 (0.38, 2.07)	***	***	0.00(0.00, 0.00)	***
	N	612	539	***	***	1151
7-8 years	n	***	6	***	***	***
	n/N*100	***	1.11 (0.23, 2.00)	***	***	***
	N	578	451	***	***	1029
8-9 years	n	9	***	***	0	***
	n/N*100	1.56 (0.55, 2.57)	***	***	0.00 (0.00, 0.00)	***
	N	529	374	356	18	903
9-10 years	n	5	***	***	***	***
	n/N*100	0.95 (0.12, 1.77)	***	***	***	***
	N	481	303	292	11	784
10-11 years	n	7	***	***	0	***
	n/N*100	1.46(0.39, 2.53)	***	***	0.00(0.00, 0.00)	***
	N	441	241	236	5	682

Neurodevelopmental disorders (NDD)		Paternal exposure group				
		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
11-12 years	n	***	***	***	0	6
	n/N*100	***	***	***	0.00(0.00, 0.00)	0.88 (0.18, 1.58)
	N	832	1199	1084	115	2031
Overall (0-12 years)	**n**	55	44	***	***	99
	n/N*100	6.61(4.92, 8.30)	3.67(2.61, 4.73)	***	***	4.87 (3.94, 5.81)

NDD: neurodevelopmental disorders
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) were presented.

10.3.1.3 Cumulative incidence rate and time to NDD diagnosis

The overall cumulative incidence rates of NDD by paternal exposure group are presented in Table 24 and stratified by offspring gender in Table 138 and Table 139 (see Appendix). Considering the overall study follow-up between 0 and 12 years of age, there appears to be a higher crude incidence rate of NDD among offspring paternally exposed to valproate (7.2, [95% CI: 5.4, 9.3] per 1000 Person-Year [PY]) than among offspring paternally exposed to lamotrigine/levetiracetam (5.6, [95% CI: 4.0, 7.5] per 1000 PY) although the 95%CIs for the 2 groups were overlapping. The same apparent difference was observed when stratifying crude cumulative incidence rates by gender (see Appendix Table 138 and Table 139). Also, considering the overall period of follow-up, the cumulative incidence rate in male offspring appears to be higher than in female offspring, in both paternal exposure groups, however the CI of the cumulative rates were overlapping.

Regarding the time to first diagnosis of NDD, the crude estimate for both exposure groups are presented as Kaplan-Meier curves in Figure 12. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th percentile of the time to diagnosis (time when 5% of the offspring were diagnosed) could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event.

The 5th percentile of the time to NDD was 100.7 (95% CI: 76.3, 135.0) months for the valproate and 105.5 (95% CI: 81.8, -) months for the lamotrigine/levetiracetam paternal exposure groups (Figure 12).

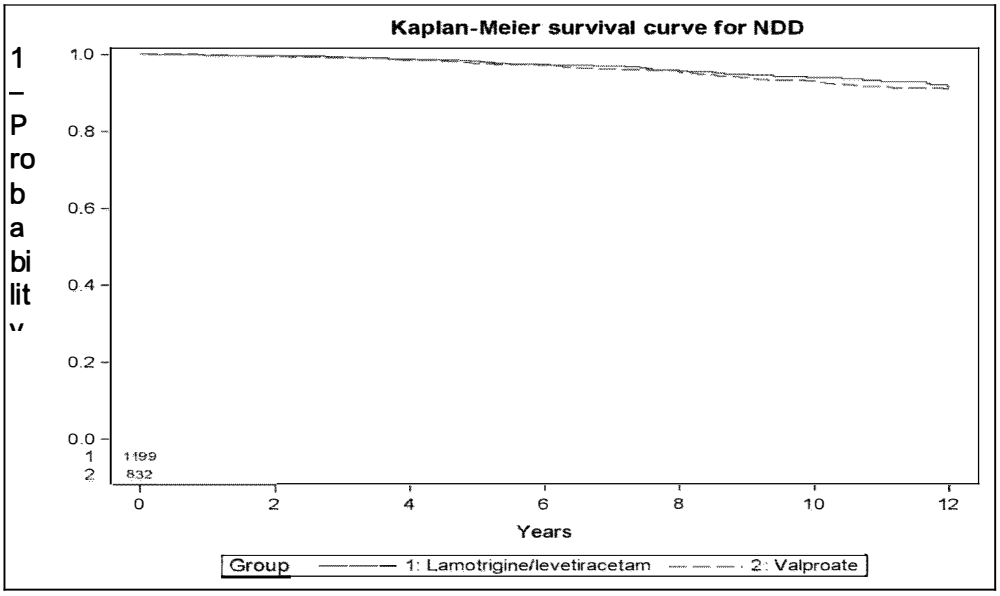
In the valproate paternal exposure group, for male offspring the 5th percentile of the time to NDD was 97.9 (95% CI: 57.5, -) months and for female offspring this was 122.3 (95% CI: 76.50, -) months. In lamotrigine/levetiracetam paternal exposure group the corresponding 5th percentile values were 92.5 (95% CI: 61.3, -) months and 142 (95% CI: 105.5, -) months. The crude estimate suggest that in both exposure groups time to diagnosis was shorter for males than females (Table 140).

Table 24 Cumulative incidence rate of neurodevelopmental disorders (NDD) by paternal exposure group; Primary outcome cohort for descriptive analysis in Denmark

		Paternal exposure group				
		Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
0-1 years	PY	828.15	1159.84	1052.9	106.94	1987.99
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-2 years	PY	1638.29	2248.93	2051.12	197.82	3887.22
	n	***	***	***	***	10
	n/PY*1000	***	***	***	***	2.57 (1.23, 4.73)
0-3 years	PY	2419.45	3246.29	2974.91	271.38	5665.74
	n	8	9	***	***	17
	n/PY*1000	3.31 (1.43, 6.52)	2.77 (1.27, 5.26)	***	***	3(1.75, 4.80)
0-4 years	PY	3163.16	4137.90	3808.02	329.87	7301.06
	n	13	***	***	***	***
	n/PY*1000	4.11 (2.19, 7.03)	***	***	***	***
0-5 years	PY	3866.05	4918.38	4543.21	375.17	8784.43
	n	***	16	***	***	***
	n/PY*1000	***	3.25 (1.86, 5.28)	***	***	***
0-6 years	PY	4534.72	5595.28	5184.34	410.94	10130.01
	n	19	***	***	***	***
	n/PY*1000	4.19 (2.52, 6.54)	***	***	***	***
0-7 years	PY	5164.07	6178.27	5738.43	439.84	11342.34
	n	***	25	***	***	***
	n/PY*1000	***	4.05 (2.62, 5.97)	***	***	***
0-8 years	PY	5763.57	6672.93	6208.50	464.42	12436.50
	n	31	31	***	***	62
	n/PY*1000	5.38 (3.65-7.63)	4.65 (3.16, 6.59)	***	***	4.99 (3.82, 6.39)
0-9 years	PY	6315.03	7087.28	6603.42	483.86	13402.31
	n	40	***	***	***	***
	n/PY*1000	6.33(4.53-8.63)	***	***	***	***
0-10 years	PY	6818.91	7426.33	6926.72	499.60	14245.24
	n	45	38	***	***	83
	n/PY*100	6.6 (4.81, 8.83)	5.12 (3.62,	***	***	5.83 (4.64,

		Paternal exposure group				
		Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	0		7.02)			7.22)
0-11 years	PY	7275.30	7697.21	7189.52	507.70	14972.51
	n	***	***	***	***	93
	n/PY*1000	***	***	***	***	6.21 (5.01, 7.61)
0-12 years	**PY**	7691.63	7914.08	7402.33	511.75	15605.72
	n	55	44	***	***	99
	n/PY*1000	7.15 (5.39, 9.31)	5.56 (4.04, 7.46)	***	***	6.34 (5.16, 7.72)

PY: person-year
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) were presented.



NDD	Valproate	Lamotrigine/ levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine/ levetiracetam)
Number of events	55	44	***	***	99
Number of censor	777	1155	***	***	1932
Survival time					
5th percentile	100.67 (76.27, 135.00)	105.50(81.83, -)	109.87(90.27, -)	87.53(5.40, -)	103.83(86.40, 130.27)
10th percentile	120.27(87.53, -)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
25th percentile	55	44	***	***	99
Median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)

NDD: neurodevelopmental disorders

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: some attrition figures below the curve were not provided for data privacy reasons. Due to low number of events the median time-to-event could not be calculated. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event

Figure 12 Kaplan-Meier survival curve for Neurodevelopmental Disorders (NDD) and distribution of time to NDD in Denmark

10.3.1.4 Association between potential risk factors/confounders for NDD including ASD and paternal exposure group

Association between potential covariates (risk factors and counfounders) for NDD including ASD and paternal exposure group was assessed in the Primary outcome cohort for descriptive analyses. Results of the crude associations are shown in Table 25 to Table 27.

Offspring exposed to AEDs and/or diagnosed with epilepsy after birth are included in the Primary outcome cohort for descriptive analyses but excluded from the Primary outcome cohort for comparative analyses, which explains the absence of a summary for epilepsy in Table 25. Epilepsy was an exclusion criterion for selecting the population for the comparative analyses because it was a strong risk factor for NDD (see Study Protocol v6.0, section 9.3.3.1) and offspring with epilepsy or receiving AEDs were already at risk of NDD regardless of paternal exposure.

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

For the offspring, none of the variables considered were associated with paternal exposure group (Table 25).

The maternal characteristics identified as risk factors (Table 4, Table 26) that were statistically significantly associated with paternal exposure were:

- Age (p=0.0036), younger maternal age in the valproate paternal exposure group
- Affective disorder (p=0.0074), lower percentage in the valproate paternal exposure group
- Polypharmacy index both prior to LMP2 (p=0.0002) and during pregnancy (p<0.0001), lower in the valproate paternal exposure group
- Concomitant medications associated with valproate-indicated psychiatric conditions both prior to LMP2 (p=0.0128) and during pregnancy (p=0.0022), a lower percentage in the valproate paternal exposure group
- Concomitant medications associated with neuropsychiatric adverse events during pregnancy (p<0.0001), a lower percentage in the valproate group

The paternal characteristics identified as risk factors or confounders (Table 27) that were statistically significantly associated with paternal exposure were:

- Affective disorder (excluding bipolar affective disorder and mania) (p<0.0001), bipolar affective disorder (p<0.0001), neurotic disorder (p<0.0001), all less frequent in the valproate exposure group
- Polypharmacy index (p<0.0001), lower in the valproate exposure group
- Concomitant medications associated with valproate-indicated psychiatric conditions (p<0.0001), a lower percentage in the valproate exposure group
- Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 (p=0.0017), a lower percentage in the valproate exposure group
- Age (p=0.0087), younger fathers in the valproate group

- Year of conception (p<0.0001), earlier years in the valproate group and more recent years in the lamotrigine/levetiracetam group.

Table 25 Association between potential offspring risk factors for Neurodevelopmental Disorders (NDD) and paternal exposure group; Primary outcome cohort for comparative analysis in Denmark (N=1950)

	Paternal exposure group										Comparison
NDD Number of offspring	**Valproate N=793**		**Lamotrigine/levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/levetiracetam) N=1950**		**Valproate vs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Offspring risk factors/confounders											
Gender [a]											
Male	412	51.95	606	52.38	545	52.20	61	53.98	1018	52.21	-
Female	381	48.05	551	47.62	499	47.80	52	46.02	932	47.79	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	0.03 (0.8545)
Congenital CMV [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Foetal alcohol syndrome [b]	0	0.00	***	***	***	***	0	0.00	***	***	1.00 (1.0000)*
Fragile X syndrome [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-

NDD: neurodevelopmental disorders

* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) at index (childbirth)

b) between index and exit date

Table 26 Association between potential maternal risk factors for Neurodevelopmental Disorders (NDD) and paternal exposure group; Primary outcome cohort for comparative analysis in Denmark (N=1950)

Paternal exposure group											**Comparison**
NDD **Number of offspring**	**Valproate** **N=793**		**Lamotrigine/levetiracetam** **N=1157**		**Lamotrigine** **N=1044**		**Levetiracetam** **N=113**		**Total (valproate + lamotrigine/levetiracetam)** **N=1950**		**Valproatevs Lamotrigine /levetiracetam** **-**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Maternal risk factors/confounders **Mother's age [a] (categorical)**											
≤20 years	10	1.26	19	1.64	***	***	***	***	29	1.49	-
21-25	136	17.15	156	13.48	***	***	***	***	292	14.97	-
26-30	288	36.32	399	34.49	356	34.10	43	38.05	687	35.23	-
31-35	260	32.79	391	33.79	345	33.05	46	40.71	651	33.38	-
36-40	87	10.97	160	13.83	152	14.56	8	7.08	247	12.67	-
>40	12	1.51	32	2.77	32	3.07	0	0.00	44	2.26	-
Test statistics	-	-	-	-	-	-	-	-	-	-	11.58 (0.0410)
Mother's age [a] (continuous)											
Mean (SD)	30.01 (4.70)	-	30.69 (4.99)	-	30.78 (5.07)	-	29.90 (4.07)	-	30.41 (4.88)	-	738118.50 (0.0036)*
Median (25th - 75th percentile)	30(27.00, 33.00)	-	31(27.00, 34.00)	-	31(27.00, 34.00)	-	30(27.00, 32.00)	-	30(27.00, 34.00)	-	-
Min, max	***	-	***	-	***	-	***	-	***	-	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Affective disorder [b]	19	2.40	55	4.75	***	***	***	***	74	3.79	7.16 (0.0074)
Diabetes [b]	9	1.13	25	2.16	***	***	***	***	34	1.74	2.89 (0.0891)
Gestational diabetes [c]	28	3.53	46	3.98	41	3.93	5	4.42	74	3.79	0.26 (0.6135)

Paternal exposure group											Comparison
NDD **Number of offspring**	**Valproate** **N=793**		**Lamotrigine/levetiracetam** **N=1157**		**Lamotrigine** **N=1044**		**Levetiracetam** **N=113**		**Total (valproate + lamotrigine/levetiracetam)** **N=1950**		**Valproatevs Lamotrigine /levetiracetam** **-**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Neurotic disorder [b]	44	5.55	83	7.17	***	***	***	***	127	6.51	2.04 (0.1531)
Schizophrenia, schizotypal and delusional disorders [b]	***	***	9	0.78	***	***	***	***	***	***	0.38 (0.3802)*
Obesity [d]	10	1.26	18	1.56	***	***	***	***	28	1.44	0.29 (0.5910)
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Rubella [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [d]	***	***	***	***	***	***	0	0.00	6	0.31	1.00 (1.0000)*
Alcohol abuse during pregnancy [c]	***	***	***	***	***	***	0	0.00	***	***	1.00 (1.0000)*
Substance abuse prior to LMP2 [d]	0	0.00	***	***	***	***	***	***	***	***	0.27 (0.2758)*
Substance abuse during pregnancy [c]	***	***	***	***	***	***	***	***	6	0.31	1.00 (1.0000)*
Smoking prior to LMP2 [d]											
No	25	3.15	43	3.72	37	3.54	6	5.31	68	3.49	-
Yes	***	***	16	1.38	16	1.53	0	0.00	***	***	-
Missing	***	***	1098	94.90	991	94.92	107	94.69	***	***	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	0.18 (0.1874)*
Smoking during pregnancy [c]											
No	606	76.42	954	82.45	857	82.09	97	85.84	1560	80.00	-
Yes	131	16.52	180	15.56	165	15.80	15	13.27	311	15.95	-
Missing	56	7.06	23	1.99	***	***	***	***	79	4.05	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	1.17 (0.2803)
Maternal polypharmacy index prior to LMP2 [e]**(categorical)**											

Paternal exposure group											Comparison
NDD **Number of offspring**	**Valproate** **N=793**		**Lamotrigine/levetiracetam** **N=1157**		**Lamotrigine** **N=1044**		**Levetiracetam** **N=113**		**Total (valproate + lamotrigine/levetiracetam)** **N=1950**		**Valproatevs Lamotrigine /levetiracetam** **-**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
0	549	69.23	716	61.88	629	60.25	87	76.99	1265	64.87	-
1-4	***	***	424	36.65	398	38.12	26	23.01	***	***	-
5-10	***	***	17	1.47	17	1.63	0	0.00	***	***	-
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	13.61 (0.0011)
Maternal polypharmacy index prior to LMP2 [e] (continuous)											
Mean (SD)	0.48 (0.89)	-	0.68 (1.13)	-	0.72 (1.16)	-	0.35 (0.74)	-	0.60 (1.04)	-	734926.00 (0.0002)*
Median (25^{th} - 75^{th} percentile)	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	0 (0.00, 0.00)	-	0 (0.00, 1.00)	-	-
Min, max	***	-	***	-	***	-	***	-	***	-	-
Maternal polypharmacy index during pregnancy [c](categorical)											
0	436	54.98	535	46.24	477	45.69	58	51.33	971	49.79	-
1-4	346	43.63	596	51.51	***	***	***	***	942	48.31	-
5-10	11	1.39	***	***	24	2.30	***	***	***	***	-
>10	0	0.00	***	***	***	***	0	0.00	***	***	-
Test statistics	-	-	-	-	-	-	-	-	-	-	15.48 (0.0014)
Maternal polypharmacy index during pregnancy[c] (continuous)											

Paternal exposure group											Comparison
NDD **Number of offspring**	**Valproate** **N=793**		**Lamotrigine/levetiracetam** **N=1157**		**Lamotrigine** **N=1044**		**Levetiracetam** **N=113**		**Total (valproate + lamotrigine/levetiracetam)** **N=1950**		**Valproatevs Lamotrigine /levetiracetam** -
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Mean (SD)	0.75 (1.07)	-	0.99 (1.29)	-	1.01 (1.32)	-	0.81 (1.03)	-	0.90 (1.21)	-	727169.50 (<.0001)*
Median (25th - 75th percentile)	0 (0.00, 1.00)	-	1 (0.00, 2.00)	-	1(0.00, 2.00)	-	0(0.00, 1.00)	-	1 (0.00, 1.00)	-	-
Min, max	***	-	***	-	***	-	***	-	***	-	-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	43	5.42	97	8.38	92	8.81	5	4.42	140	7.18	6.19 (0.0128)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	21	2.65	64	5.53	***	***	***	***	85	4.36	9.38 (0.0022)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] -mothers with at least one prescription	556	70.11	819	70.79	748	71.65	71	62.83	1375	70.51	0.10 (0.7488)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	304	38.34	552	47.71	501	47.99	51	45.13	856	43.90	16.79 (<.0001)

Paternal exposure group											Comparison
NDD Number of offspring	Valproate N=793		Lamotrigine/levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/levetiracetam) N=1950		Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	N	%	N	%	N	%	

NDD: neurodevelopmental disorders; CMV: Cytomegalovirus; SD- Standard Deviation; LMP2: Last Menstrual Period Date Plus 2 weeks

* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2

Table 27 Association between potential paternal risk factors/confounders for neurodevelopmental disorders (NDD) and paternal exposure group; Primary outcome cohort for comparative analysis in Denmark (N=1950)

Paternal exposure group											**Comparison**
NDD **Number of offspring**	**Valproate** **N=793**		**Lamotrigine/levetiracetam** **N=1157**		**Lamotrigine** **N=1044**		**Levetiracetam** **N=113**		**Total (valproate + lamotrigine/levetiracetam)** **N=1950**		**Valproate vs Lamotrigine/levetiracetam** -
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Paternal risk factors/confounders											
Affective disorder excluding bipolar affective disorder and mania [a]	30	3.78	150	12.96	***	***	***	***	180	9.23	47.34 (<.0001)
Bipolar affective disorder [a]	21	2.65	84	7.26	84	8.05	0	0.00	105	5.38	19.64 (<.0001)
Mania [a]	6	0.76	9	0.78	9	0.86	0	0.00	15	0.77	0.00 (0.9579)
Neurotic disorder [a]	48	6.05	130	11.24	123	11.78	7	6.19	178	9.13	15.24 (<.0001)
Schizophrenia, schizotypal and delusional disorders [a]	16	2.02	25	2.16	25	2.39	0	0.00	41	2.10	0.05 (0.8287)
Substance abuse [c]	5	0.63	***	***	***	***	***	***	***	***	0.12 (0.1281)*
Paternal polypharmacy index [d] (categorical)											
0	547	68.98	653	56.44	568	54.41	85	75.22	1200	61.54	-
1-4	234	29.51	480	41.49	452	43.30	28	24.78	714	36.62	-
5-10	12	1.51	24	2.07	24	2.30	0	0.00	36	1.85	-
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	31.26 (<.0001)
Paternal polypharmacy											

Paternal exposure group											**Comparison**
NDD **Number of offspring**	**Valproate** **N=793**		**Lamotrigine/levetiracetam** **N=1157**		**Lamotrigine** **N=1044**		**Levetiracetam** **N=113**		**Total (valproate + lamotrigine/levetiracetam)** **N=1950**		**Valproate vs Lamotrigine /levetiracetam** -
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
index [d] (continuous)											
Mean (SD)	0.54 (1.13)		0.81 (1.23)		0.86 (1.27)		0.32 (0.63)		0.70 (1.20)		710830.50 (<.0001)*
Median (25th - 75th percentile)	0(0.00, 1.00)		0(0.00, 1.00)		0(0.00, 1.00)		0(0.00, 0.00)		0(0.00, 1.00)		-
Min, max	***		***		***		***		***		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] – fathers with at least one prescription	96	12.11	360	31.11	***	***	***	***	456	23.38	94.90 (<.0001)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	387	48.80	648	56.01	600	57.47	48	42.48	1035	53.08	9.81 (0.0017)
Father's age [e] (categorical)											-
≤20 years	***	***	5	0.43	5	0.48	0	0.00	***	***	-
21-25	***	***	93	8.04	82	7.85	11	9.73	***	***	-
26-30	229	28.88	269	23.25	245	23.47	24	21.24	498	25.54	-
31-35	301	37.96	408	35.26	352	33.72	56	49.56	709	36.36	-
36-40	144	18.16	253	21.87	237	22.70	16	14.16	397	20.36	-
>40	65	8.20	129	11.15	123	11.78	6	5.31	194	9.95	-
Test statistics	-	-	-	-	-	-	-	-	-	-	15.89 (0.0072)
Father's age [e]											

Paternal exposure group											**Comparison**
NDD **Number of offspring**	**Valproate** **N=793**		**Lamotrigine/levetiracetam** **N=1157**		**Lamotrigine** **N=1044**		**Levetiracetam** **N=113**		**Total (valproate + lamotrigine/levetiracetam)** **N=1950**		**Valproate vs Lamotrigine /levetiracetam** -
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
(continuous)											
Mean (SD)	32.69 (5.32)		33.39 (5.89)		33.52 (5.98)		32.24 (4.88)		33.11 (5.67)		741569.00 (0.0087)*
Median (25th - 75th percentile)	32(29.00 , 36.00)		33(29.00, 37.00)		33(29.00 , 37.00)		32(30.00 , 35.00)		33(29.00, 36.00)		-
Min, max	***		***		***		***		***		-
Year of offspring conception [f,g]											
1996-2001	207	26.10	58	5.01	***	***	***	***	265	13.59	-
2002-2007	289	36.44	242	20.92	231	22.13	11	9.73	531	27.23	-
2008-2012	173	21.82	403	34.83	375	35.92	28	24.78	576	29.54	-
2013-2018	124	15.64	454	39.24	381	36.49	73	64.60	578	29.64	
Test statistics	-	-	-	-	-	-	-	-	-	-	311.08 (<.0001)

NDD: neurodevelopmental disorders; SD- Standard Deviation

* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father appeared more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) all available data prior to index date (childbirth); c) 12 months lookback from LMP2; d) 3 months lookback from LMP2; e) at index (childbirth); f) at mother's LMP2; g) calendar years were grouped in each country according to the length of the study period

10.3.1.5 Association between potential risk factors/confounders and outcome of NDD including ASD

Association between covariates (potential risk factors/confounders) and occurrence of NDD were assessed in the Primary outcome cohort for descriptive analyses. Results of the crude associations are shown in Table 28 to Table 30.

These variables were initially selected based on a review of the literature and clinical expert opinion, see section 9.4.3 for an overview.

For offspring characteristics, only gender (OR: 0.53, 95% CI: 0.34, 0.85; p=0.0075) was associated with the occurrence of NDD (Table 28); the proportion of events were significantly higher in males compared to the females.

For maternal characteristics identified as risk factors (see Table 4, Table 29) the following variables were statistically significantly associated with offspring having a NDD including ASD event:

- Age (OR: 4.24, 95% CI: 1.37, 13.10; p=0.0418), the risk of NDD was higher in women aged ≤20 years compared to the reference group of 26-30 years
- Affective disorder (OR: 2.87, 95% CI: 1.33, 6.19; p=0.0072)
- Smoking during pregnancy (OR: 2.49, 95% CI: 1.52, 4.07; p=0.0003)
- Use of polypharmacy before LMP2 (p=0.0366) or during pregnancy (p=0.0087) (as a continuous variable)
- Use of concomitant medications associated with valproate-indicated psychiatric conditions both prior (OR: 2.76, 95% CI: 1.51, 5.04; p=0.0009) and during pregnancy (OR: 3.65, 95% CI: 1.86, 7.17; p=0.0002)

For paternal characteristics identified as confounders or risk factors (see Table 4), the following variables were significantly associated with offspring having a NDD including ASD event (Table 30):

- Year of offspring conception (p<0.0001), offspring conceived in the period 2002-2007 (OR 2.05, 1.07-3.93) had a higher risk of having a NDD including ASD event compared to the reference category of 1996-2001 (years 2008-2012 OR: 0.64, 95% CI: 0.30, 1.36; 2013-2018 OR: 0.30, 95% CI: 0.12, 0.73).

Table 28 Association between potential offspring risk factors/confounders and neurodevelopmental disorders (NDD); Primary outcome cohort for comparative analysis in Denmark (N=1950)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Offspring risk factors/confounders								
Gender [a]								
Male	1018	52.21	56	5.50	962	94.50	Reference	-
Female	932	47.79	28	3.00	904	97.00	0.53 (0.34, 0.85)	-
Missing	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	7.15 (0.0075)
Congenital CMV [b]								
No	1950	100.00	84	4.31	1866	95.69	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital rubella [b]								
No	1950	100.00	84	4.31	1866	95.69	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Foetal alcohol syndrome [b]								
No	***	***	84	4.31	***	***	Reference	-
Yes	***	***	0	0.00	***	***	0.00 (0.00,I)	0.00 (0.9889)
Fragile X syndrome [b]								
No	1950	100.00	84	4.31	1866	95.69	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Lejeune/cri du chat syndrome [b]								
No	1950	100.00	84	4.31	1866	95.69	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Tuberous sclerosis [b]								

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
No	1950	100.00	84	4.31	1866	95.69	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-

NDD: neurodevelopmental disorders; CMV: Cytomegalovirus

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.

a) at index (childbirth)

b) between index and exit date

Table 29 Association between potential maternal risk factors/confounders and neurodevelopmental disorders (NDD); Primary outcome cohort for comparative analysis in Denmark (N=1950)

NDD	Overall	Event	Non-event	Association

	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Maternal risk factors/confounders								
Mother's age [a] (categorical)								
≤20 years	29	1.49	***	***	***	***	4.24 (1.37, 13.10)	-
21-25	292	14.97	17	5.82	275	94.18	1.64 (0.87, 3.08)	-
26-30	687	35.23	25	3.64	662	96.36	Reference	-
31-35	651	33.38	22	3.38	629	96.62	0.93 (0.52, 1.66)	-
36-40	247	12.67	12	4.86	235	95.14	1.35 (0.67, 2.73)	-
>40	44	2.26	***	***	***	***	2.65 (0.88, 7.98)	-
Wald test	-	-	-	-	-	-	-	11.53 (0.0418)
Affective disorder [b]								
No	1876	96.21	76	4.05	1800	95.95	Reference	-
Yes	74	3.79	8	10.81	66	89.19	2.87 (1.33, 6.19)	7.23 (0.0072)
Diabetes [b]								
No	1916	98.26	***	***	***	***	Reference	-
Yes	34	1.74	***	***	***	***	1.40 (0.33, 5.94)	0.21 (0.6483)
Gestational diabetes [c]								
No	1876	96.21	79	4.21	1797	95.79	Reference	-
Yes	74	3.79	5	6.76	69	93.24	1.65 (0.65, 4.20)	1.10 (0.2949)
Neurotic disorder [b]								
No	1823	93.49	75	4.11	1748	95.89	Reference	-
Yes	127	6.51	9	7.09	118	92.91	1.78 (0.87, 3.64)	2.48 (0.1153)
Schizophrenia, schizotypal and delusional disorders [b]								
No	1938	99.38	***	***	***	***	Reference	-
Yes	12	0.62	***	***	***	***	4.53 (0.98, 20.99)	3.72 (0.0537)
Obesity [d]								
No	1922	98.56	***	***	***	***	Reference	-
Yes	28	1.44	***	***	***	***	1.73 (0.40, 7.40)	0.54 (0.4622)
CMV [c]								

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
No	1950	100.00	84	4.31	1866	95.69	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Rubella [c]								
No	1950	100.00	84	4.31	1866	95.69	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse prior to LMP2 [d]								
No	1944	99.69	84	4.32	1860	95.68	Reference	-
Yes	6	0.31	0	0.00	6	100.00	0.00(0.00,I)	0.00 (0.9880)
Alcohol abuse during pregnancy [c]								
No	***	***	84	4.31	***	***	Reference	-
Yes	***	***	0	0.00	***	***	0.00(0.00,I)	0.00 (0.9895)
Substance abuse prior to LMP2 [d]								
No	***	***	***	***	***	***	***	-
Yes	***	***	***	***	***	***	***	***
Substance abuse during pregnancy [c]								
No	1944	99.69	84	4.32	1860	95.68	Reference	-
Yes	6	0.31	0	0.00	6	100.00	0.00(0.00,I)	0.00 (0.9880)
Smoking prior to LMP2 [d]								
No	68	3.49	***	***	***	***	Reference	-
Yes	20	1.03	***	***	***	***	3.67 (0.48, 27.86)	-
Missing	1862	95.49	***	***	***	***	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	1.58 (0.2092)
Smoking during pregnancy [c]								
No	1560	80.00	53	3.40	1507	96.60	Reference	-
Yes	311	15.95	25	8.04	286	91.96	2.49 (1.52, 4.07)	-
Missing	79	4.05	6	7.59	73	92.41	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	13.16 (0.0003)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Maternal polypharmacy index prior to LMP2 [e](categorical)								
0	1265	64.87	44	3.48	1221	96.52	Reference	-
1-4	664	34.05	40	6.02	624	93.98	1.78 (1.15, 2.76)	-
5-10	21	1.08	0	0.00	21	100.00	0.00(0.00,I)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	6.62 (0.0366)
Maternal polypharmacy index during pregnancy [c](categorical)								
0	971	49.79	37	3.81	934	96.19	Reference	-
1-4	942	48.31	40	4.25	902	95.75	1.12 (0.71, 1.77)	-
5-10	***	***	***	***	30	83.33	5.05 (1.98, 12.88)	-
>10	***	***	***	***	0	0.00	1.19806E10(0.00,I)	-
Wald test	-	-	-	-	-	-	-	11.64 (0.0087)
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription								
No	1810	92.82	70	3.87	1740	96.13	Reference	-
Yes	140	7.18	14	10.00	126	90.00	2.76 (1.51, 5.04)	10.95 (0.0009)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription								
No	1865	95.64	73	3.91	1792	96.09	Reference	-
Yes	85	4.36	11	12.94	74	87.06	3.65 (1.86, 7.17)	14.12 (0.0002)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription								
No	575	29.49	21	3.65	554	96.35	Reference	-
Yes	1375	70.51	63	4.58	1312	95.42	1.27 (0.77, 2.10)	0.85 (0.3577)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription								
No	1094	56.10	42	3.84	1052	96.16	Reference	-
Yes	856	43.90	42	4.91	814	95.09	1.29 (0.83, 2.00)	1.32 (0.2504)

NDD: neurodevelopmental disorders; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2

Table 30 Association between potential paternal risk factors/confounders and neurodevelopmental disorders (NDD); Primary outcome cohort for comparative analysis in Denmark (N=1950)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Paternal risk factors/confounders Affective disorder [a,b]								
No	1770	90.77	77	4.35	1693	95.65	Reference	-
Yes	180	9.23	7	3.89	173	96.11	0.89 (0.40, 1.96)	0.08 (0.7716)
Bipolar affective disorder [a]								
No	1845	94.62	***	***	***	***	Reference	-
Yes	105	5.38	***	***	***	***	0.42 (0.10, 1.72)	1.46 (0.2270)
Mania [a]								
No	1935	99.23	84	4.34	1851	95.66	Reference	-
Yes	15	0.77	0	0.00	15	100.00	0.00(0.00,I)	0.00 (0.9876)
Neurotic disorder [a]								
No	1772	90.87	79	4.46	1693	95.54	Reference	-
Yes	178	9.13	5	2.81	173	97.19	0.62 (0.25, 1.55)	1.05 (0.3060)
Schizophrenia, schizotypal and delusional disorders [a]								
No	1909	97.90	***	***	***	***	Reference	-
Yes	41	2.10	***	***	***	***	0.55 (0.07, 4.05)	0.34 (0.5573)
Substance abuse [c]								
No	1943	99.64	***	***	***	***	Reference	-
Yes	7	0.36	***	***	***	***	3.74 (0.44, 31.38)	1.47 (0.2249)
Paternal polypharmacy index [d] (categorical)								

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
0	1200	61.54	54	4.50	1146	95.50	Reference	-
1-4	714	36.62	***	***	***	***	0.87 (0.54, 1.38)	-
5-10	36	1.85	***	***	***	***	1.25 (0.29, 5.33)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	0.50 (0.7785)
Concomitant medications associated with valproate-indicated psychiatric conditions [c] -fathers with at least one prescription								
No	1494	76.62	64	4.28	1430	95.72	Reference	-
Yes	456	23.38	20	4.39	436	95.61	1.03 (0.61, 1.71)	0.01 (0.9246)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription								
No	915	46.92	37	4.04	878	95.96	Reference	-
Yes	1035	53.08	47	4.54	988	95.46	1.13 (0.73, 1.75)	0.29 (0.5895)
Father's age [e] (categorical)								
≤20 years	7	0.36	0	0.00	7	100.00	0.00 (0.00,I)	-
21-25	145	7.44	10	6.90	135	93.10	1.74 (0.83, 3.65)	-
26-30	498	25.54	21	4.22	477	95.78	1.03 (0.58, 1.83)	-
31-35	709	36.36	29	4.09	680	95.91	Reference	-
36-40	397	20.36	14	3.53	383	96.47	0.86 (0.45, 1.64)	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
>40	194	9.95	10	5.15	184	94.85	1.27 (0.61, 2.66)	-
Wald test	-	-	-	-	-	-	-	3.29 (0.6555)
Year of offspring conception [f,g]								
1996-2001	265	13.59	12	4.53	253	95.47	Reference	-
2002-2007	531	27.23	47	8.85	484	91.15	2.05 (1.07, 3.93)	-
2008-2012	576	29.54	17	2.95	559	97.05	0.64 (0.30, 1.36)	-
2013-2018	578	29.64	8	1.38	570	98.62	0.30 (0.12, 0.73)	-
Wald test	-	-	-	-	-	-	-	34.55 (<.0001)

NDD: neurodevelopmental disorders; OR: Odds ratio
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) all available data prior to index date (childbirth); b) all available data prior to index date; c) 12 months lookback from LMP2; d) 3 months lookback from LMP2; e) at index (date of childbirth); f) at mother's LMP2; g) calendar years were grouped in each country according to the length of the study period

10.3.1.6 Variable estimates from propensity score

Variables found to be associated with the outcome were included in the PS models for the analyses of the Primary outcome cohort. This means all specified confounders for which an association with both the outcome and the exposure was observed and all specified risk factors (associated with the outcome but not the exposure) were included in the PS models. Notably some maternal characteristics appeared to be associated with the exposure as well as the outcome; further evaluation of the impact of these variables were undertaken to minimise introduction of bias. If any of these above mentioned variables remained unbalanced after performing PS weighting, they were included in the final Cox regression model.
In the PS model estimated from logistic regression (Table 31), gender of the offspring was not associated with the paternal exposure to valproate or lamotrigine/levetiracetam (OR: 1.10, 95% CI: 0.88, 1.37, p=0.4138). Offspring with mothers with diabetes (OR: 0.21, 95% CI: 0.05, 0.90, p=0.0354), maternal polypharmacy index prior to LMP2 (categorical (1-4), OR 0.74, 95% CI: 0.57, 0.96, p=0.0225) and with mothers with at least one prescription concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy (OR: 0.27, 95% CI: 0.10, 0.71, p=0.0084), had lower probability of being in the valproate exposure group.

Offspring with fathers with affective disorders (OR: 0.12, 95% CI: 0.05, 0.27, p <0.0001), bipolar affective disorder (OR: 0.08, 95% CI: 0.02, 0.34, p=0.0006), and year of offspring conception 2002-2007 (OR: 0.37, 95% CI: 0.26, 0.55, p<0.0001), 2008-2012 (OR: 0.13, 95% CI: 0.09, 0.20; p<0.0001) and 2013-2018 (OR: 0.07, 95% CI: 0.05, 0.10 p<0.0001) compared to offspring conceived 1996-2001, had a lower probability of being in the valproate exposure group. On the other hand, offspring with fathers with schizophrenia, schizotypal and delusional disorders (OR: 3.12, 95% CI: 1.09, 8.93, p=0.0342), had a higher probability of being in the valproate exposure group.

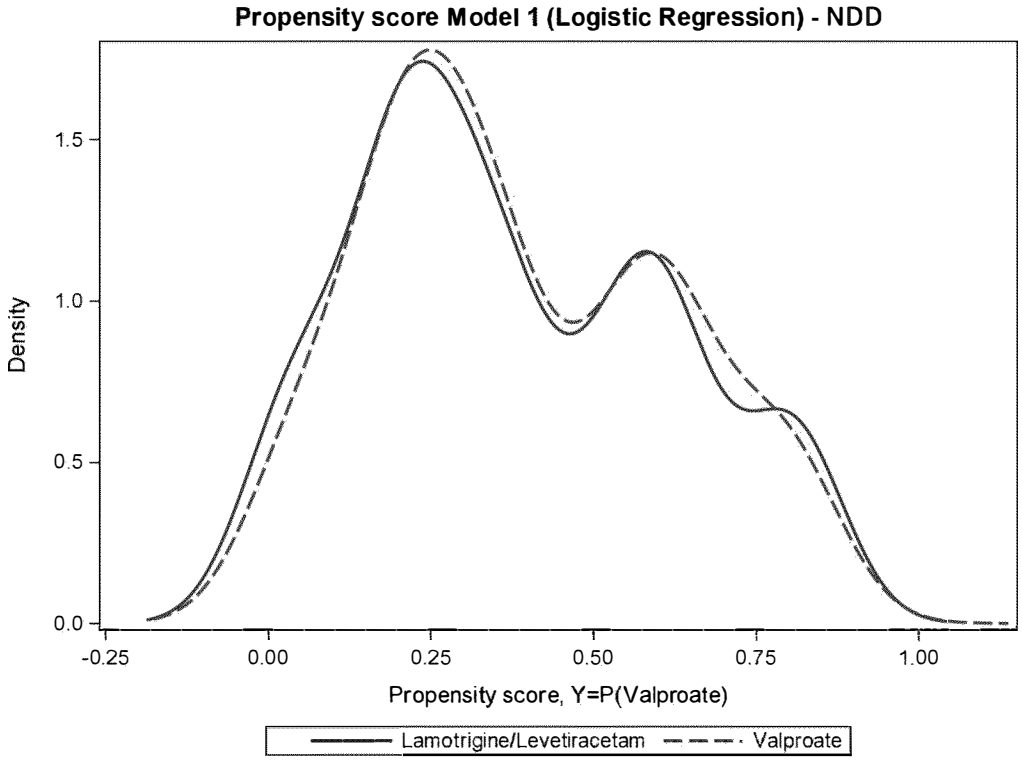
A random forest propensity score was performed to identify variable importance metrics, i.e. two-way interactions, and variables presenting low index importance were not included in the PS logistic informed by random forest model (Table 141). A random forest propensity score estimation was performed to identify variable importance metrics, i.e. two-way interactions, and variables presenting low index importance were not included in the PS logistic informed by random forest model.

Variables or interactions associated with NDD including ASD in the PS model from logistic regression informed by random forest (Table 142) were paternal concomitant medications associated with neuropsychiatric adverse events - fathers with at least one prescription (OR: 0.78, 95% CI: 0.64, 0.96 p=0.0182) and categories of calendar year of offspring conception 2002-2007 (OR: 0.31, 95% CI: 0.22, 0.44 p<0.0001), 2008-2012 (OR: 0.11, 95% CI: 0.08, 0.15 p<0.0001) and 2013-2018 (OR: 0.06, 95% CI: 0.04, 0.09 p<0.0001).

Plots of each PS model are depicted in Figure 13, Figure 27, and Figure 28.

The PS model that best achieved a balance in the weighted exposure groups after using inverse probability of treatment weights was the PS model estimated from logistic regression, as shown in Figure 13 and

Table 143. Thus, the logistic regression model was used to apply inverse probability of treatment weights in the effect estimation analysis (presented in Section 10.3.1.7).



NDD: neurodevelopmental disorders

Figure 13.Balance of Model 1 Logistic regression Primary outcome cohort in Denmark

Table 31. Variable estimates from logistic regression propensity score model; Primary outcome cohort in Denmark

NDD	**Estimate**		
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
Offspring risk factors/confounders			
Gender [b]			
Male	Reference	-	-
Female	1.10	(0.88, 1.37)	0.4138
Maternal risk factors/confounders			
Mother's age [b] (categorical)			
≤20 years	0.66	(0.27, 1.62)	0.3613
21-25	1.20	(0.86, 1.68)	0.2852
26-30	Reference	-	-
31-35	1.10	(0.84, 1.43)	0.5021

NDD	Estimate		
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
36-40	0.94	(0.65, 1.37)	0.7483
>40	0.54	(0.23, 1.31)	0.1739
Affective disorder [d]	0.63	(0.27, 1.48)	0.2883
Diabetes [d]	0.21	(0.05, 0.90)	0.0354
Gestational diabetes [e]	1.94	(0.91, 4.11)	0.0844
Neurotic disorder [d]	1.35	(0.81, 2.24)	0.2503
Obesity [f]	0.67	(0.23, 1.92)	0.4586
Substance abuse during pregnancy [e]	3.07	(0.07, 134.75)	0.5614
Smoking during pregnancy [e]			
No	Reference	-	-
Yes	0.92	(0.67, 1.26)	0.6148
Maternal polypharmacy index prior to LMP2 [h] (categorical)			
0	Reference	-	-
1-4	0.74	(0.57, 0.96)	0.0225
5-10	0.40	(0.09, 1.71)	0.2179
>10	-	-	-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.94	(0.50, 1.75)	0.8440
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.27	(0.10, 0.71)	0.0084
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] - mothers with at least one prescription	0.99	(0.76 - 1.29)	0.9519
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.87	(0.69, 1.09)	0.2251
Paternal risk factors/confounders			
Affective disorder [d,g]	0.12	(0.05, 0.27)	<.0001
Bipolar affective disorder [d]	0.08	(0.02, 0.34)	0.0006
Mania [d]	2.36	(0.25, 22.08)	0.4518
Neurotic disorder [d]	0.90	(0.54, 1.52)	0.7042
Schizophrenia, schizotypal and delusional disorders [d]	3.12	(1.09, 8.93)	0.0342
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with atleast one prescription	0.97	(0.77, 1.21)	0.7761
Year of offspring conception [i,j]			
1996-2001	Reference	-	-
2002-2007	0.37	(0.26, 0.55)	<.0001

NDD	Estimate		
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
2008-2012	0.13	(0.09, 0.20)	<.0001
2013-2018	0.07	(0.05, 0.10)	<.0001

NDD: neurodevelopmental disorders; OR: odds ratio; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Odds ratios (OR), 95% confidence intervals (CI) and p-values were represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.
a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.
b) at index (childbirth)
d) all available data prior to index date
e) during pregnancy (from LMP2 until index date)
f) 12 months lookback from LMP2
g) excluding bipolar affective disorder and mania
h) 3 months lookback from LMP2
i) at mother's LMP2
j) calendar years were grouped in each country according to the length of the study period

10.3.1.7 Effect estimation for NDD including ASD

The effect estimation for NDD including ASD was assessed by using crude Cox regression model as presented in Table 32. In this model 1950 subjects were included; 793 offspring in the valproate and 1157 in the lamotrigine/levetiracetam group, and no influential subjects were identified. Respectively, 5.4% (N=43) of offspring of the valproate group and 3.5% (N=41) of the lamotrigine/levetiracetam group presented a NDD including ASD event. In the crude analysis, no increased risk for NDD including ASD was observed in offspring of fathers exposed to valproate compared to offspring of fathers exposed to lamotrigine/levetiracetam group (HR: 0.94, 95% CI: 0.60, 1.46).

The effect estimation for NDD including ASD using a PS-weighted Cox regression model was assessed in a total of 1796 offspring; 678 offspring from the valproate and 1118 offspring from the lamotrigine/levetiracetam group. Respectively, 5.6% (N=38) of offspring of the valproate group and 3.2% (N=36) of the lamotrigine/levetiracetam group presented a NDD including ASD event. The PS-weighted Cox regression model was also adjusted for maternal affective disorders and maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy due to imbalance in PS weighting. No increased risk for NDD including ASD was observed comparing offspring of fathers exposed to valproate to offspring of fathers exposed to lamotrigine/levetiracetam group (HR: 1.34, 95% CI: 0.79, 2.25). However, there was a significant increased risk of NDD including ASD for maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy (HR: 3.29, 95% CI: 1.38, 7.78).

Table 34 presents the effect estimation for NDD using a PS-weighted Cox regression model adjusted for the K-means exposure cluster (Cluster A: constant high exposure; Cluster B: constant low exposure (for further details on the K-means cluster in the main analyses please check Figure 11 and Table 22). In order to obtain estimates of the effect of valproate vs lamotrigine/levetiracetam in each cluster identified by the K-means algorithm, an interaction term between the K-means clusters variable and the main exposure

variable was included in the model. The effect estimation was assessed in a total of 1796 offspring, and the no increased risk for NDD including ASD was observed in offspring of fathers exposed to valproate compared to offspring of fathers exposed to lamotrigine/levetiracetam, in the different clusters of exposure. Likewise, no interaction between exposure and paternal K-means cluster was observed.

In the analysis of effect estimation in cluster A (i.e. trajectories with constant higher exposure compared to cluster B) 368 offspring from the valproate group, of which 5.7% (N=21) presented a NDD including ASD event, and 644 from the lamotrigine/levetiracetam group, of which 3.4% (N=22) presented a NDD including ASD event, were considered. Similar size effects were observed for both clusters. There was no increased risk for NDD including ASD of offspring from fathers exposed to valproate compared to offspring from fathers exposed to lamotrigine/levetiracetam in cluster A (HR: 1.38, 95% CI: 0.69, 2.74) (Table 34). The effect estimated in cluster B (i.e. constant low exposure) considered 310 offspring from the valproate group, of which 5.5% (N=17) presented the event of NDD including ASD and 474 from the lamotrigine/levetiracetam group, of which 3.0% (N=14) presented the event of NDD including ASD. No increased risk for NDD including ASD of offspring from fathers exposed to valproate were observed compared to offspring from fathers exposed to lamotrigine/levetiracetam in cluster B (HR: 1.30, 95%CI: 0.60, 2.83) (Table 34).

Table 32. Effect estimation for NDD using crude Cox regression model; Primary outcome cohort in Denmark

Variable	**Total N**	**Number of events**	**Number of subjects included in the model (after excluding influential subjects)a**		**Model estimates**		
	N	**N**	**N**	**%**	**HR**	**95% CI**	**P-value**
Valproate	793	43					
Lamotrigine/levetiracetam	1157	41					
Paternal exposure: valproate vs lamotrigine/levetiracetam	1950		1950	100.00	0.94	(0.60, 1.46)	0.7792

NDD: neurodevelopmental disorders; CI: Confidence Interval; HR: Hazard Ratio
a) Influential subjects were identified using the dfbetas for the main exposure coefficient.

Table 33. Effect estimation for NDD using PS-weighted Cox regression model; Primary outcome cohort in Denmark

Variable	Total N	Number of events	Model estimates [1]		
			HR	95% CI	P-value
Valproate	678	38			
Lamotrigine/levetiracetam	1118	36			
Paternal exposure: valproate vs lamotrigine/levetiracetam	1796		1.34	(0.79, 2.25)	0.2741
Maternal affective disorder	-		1.84	(0.56, 6.11)	0.3246
Maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy - mothers with at least one prescription	-		3.29	(1.38, 7.83)	0.0073

NDD: neurodevelopmental disorders; PS: Propensity Score; HR: Hazard Ratio; CI: Confidence Interval
Legend: Hazard ratio (HR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders that were still unbalanced after weighting.
[1] **The logistic regression PS model includes all variables from Table 31, following described: Offspring risk factors/confounders**: "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder ", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Substance abuse during pregnancy", "Smoking during pregnancy", "Maternal polypharmacy index prior to LMP2, mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of: "concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "year of offspring conception"

Table 34. Effect estimation for Neurodevelopmental Disorders (NDD) using Propensity Score-weighted Cox regression model adjusted for K-means exposure cluster; Primary outcome cohort in Denmark

Variable	Total N	Number of events	Model estimates [1]		
			HR	95% CI	P-value
Valproate - cluster A	368	21			
Lamotrigine/levetiracetam - cluster A	644	22			
Valproate - cluster B	310	17			
Lamotrigine/levetiracetam - cluster B	474	14			
Paternal exposure: valproate vs lamotrigine/levetiracetam	1796		-	-	0.3662
K-means exposure cluster:					
K-means exposure cluster B	-		-	-	0.9358
Paternal exposure * cluster:					

Variable	Total N	Number of events	Model estimates [1]		
			HR	95% CI	P-value
Valproate * cluster B	-		-	-	0.9158
Effect of valproate across K-means cluster:					
Valproate vs lamotrigine/levetiracetam in cluster A	-		1.38	(0.69, 2.74)	-
Valproate vs lamotrigine/levetiracetam in cluster B	-		1.30	(0.60, 2.83)	-
Maternal affective disorder	-		1.84	(0.56, 6.06)	0.3139
Maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy - mothers with at least one prescription	-		3.28	(1.38, 7.80)	0.0070

NDD: neurodevelopmental disorders; PS: Propensity Score; HR: Hazard Ratio
Legend: Hazard ratio (HR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders that were still unbalanced after weighting.

[1] **The logistic regression PS model includes all variables from Table 31, following described: Offspring risk factors/confounders:** "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Substance abuse during pregnancy", "Smoking during pregnancy", "Maternal polypharmacy index prior to LMP2", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of: "concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "year of offspring conception".

Cluster A: constant high exposure

Cluster B: constant low exposure.

10.3.1.8 Case assessment

Overall, considering all the groups of paternal exposure, in 4.9% of the offspring were identified cases of NDD including ASD, of which the majority (64.7%) was considered as a probable case (meeting the criteria of multiple diagnoses for NDD including ASD recorded during the follow-up) in the case assessment. The same was observed considering valproate and lamotrigine/levetiracetam groups, with a higher percentage of NDD including ASD being observed in the valproate group. Considering the valproate group, in 6.6% of the offspring were identified cases of NDD including ASD, of which 60.0% were classified in the case assessment as probable cases. Considering the lamotrigine/levetiracetam group, in 3.7% of the offspring were identified cases of NDD including ASD, of which 70.5% were classified in the case assessment as probable cases (Table 35).

Table 35. Case assessment in Denmark

	Paternal exposure group									
NDD **Number of offspring**	**Valproate** **N=832**		**Lamotrigine/ levetiracetam** **N=1199**		**Lamotrigine** **N=1084**		**Levetiracetam** **N=115**		**Total (valproate + lamotrigine/ levetiracetam) N=2031**	
Nr of offspring identified as cases of NDD including ASD *	55	6.61%	44	3.67%	Disk	Disk	Disk	Disk	99	4.87%
Case assessment										
Possible **	22	40.00%	13	29.55%	Disk	Disk	Disk	Disk	35	35.35%
Probable **	33	60.00%	31	70.45%	Disk	Disk	Disk	Disk	64	64.65%

NDD: neurodevelopmental disorders
* percentages were calculated over the total pregnancies in each group
** percentages were calculated over the total number of offspring identified as cases of NDD including ASD in each group
Possible case: The offspring aged ≤12 years were considered a possible case if they satisfy the criteria that only one diagnosis record for NDD including ASD was recorded during follow-up.
Probable case: The offspring aged ≤12 years were considered a probable case if they satisfy the criteria that multiple diagnoses for NDD including ASD were recorded during follow-up, regardless of whether the same code was recorded multiple times or different codes were recorded

10.3.1.9 Exploratory analysis - NDD including ASD cohort

10.3.1.9.1 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Exploratory analysis 5 for NDD including ASD)

Results from exploratory analysis 5 are presented in Table 145 to Table 156, section 15.1.4. The analyses were performed in order to answer Exploratory Objective 5, which aimed to describe the risk factors and frequency of NDD, including ASD, in offspring paternally exposed to valproate (in polytherapy with other AEDs excluding lamotrigine/levetiracetam) and lamotrigine/levetiracetam (in polytherapy with other AEDs excluding valproate) at the time of conception. The analysis was performed in the Primary outcome cohort for Explorative Objective 5. Findings were compared to results obtained from the Primary cohort for comparative analysis (main analysis).
For exploratory analysis 5, the inclusion criterion was all offspring from the Primary outcome cohort (N=5034). After additional exclusions, a total of 335 offspring were included in this analysis, with 91 in the valproate and 244 in lamotrigine/levetiracetam group (Figure 29).

Many offspring, maternal, and paternal demographic and clinical characteristics were zero or masked when being different from zero (Table 145-Table 150).

None of the offspring was born extremely preterm (gestational age <28 weeks) or had extremely low (<1000 g) birth weight. Gestational age and birth weight were similarly distributed between the exposure groups. Compared with the valproate monotherapy in main analysis (Table 25), a higher proportion of females were observed in the valproate polytherapy group (57.1% vs 48.1% female in the main analyses) (Table 145).
Regarding offspring clinical characteristics, no comorbidities were reported in either group.

The cumulative proportion of NDD including ASD was similar in the offspring paternally exposed to valproate polytherapy compared to valproate monotherapy in the main analysis (5.5% vs 5.4%, respectively), but higher in the offspring paternally exposed to lamotrigine/levetiracetam polytherapy compared to lamotrigine/levetiracetam monotherapy in the main analysis (5.3% vs 3.5%, respectively) (Table 146, and section 10.3.1.7).

The maternal age at birth was similar as in the main analyses (median age of 30 years in valproate polytherapy [IQR 26, 35] and monotherapy [IQR 27, 33] and median age of 31 years in lamotrigine/levetiracetam polytherapy [IQR 28, 34] and monotherapy [IQR 27, 34]) (Table 26 and Table 147). As several comorbidities were masked in the exploratory analysis 5, comparison with the main analyses was not ideal. Nevertheless, the frequency of neurotic disorders amongst mothers were lower in lamotrigine/levetiracetam polytherapy compared to lamotrigine/levetiracetam monotherapy (5.7% vs 7.2%, respectively). In contrast to the main analyses, no maternal alcohol or substance abuse was reported in either group in the exploratory analysis 5. Table 26 and Table 147 shows that smoking during pregnancy was more common in valproate than lamotrigine/levetiracetam cohorts in monotherapy (16.5% vs 15.6%), but opposite results were observed in polytherapy (9.9% in valproate polytherapy vs 17.6% in lamotrigine/levetiracetam polytherapy). Mean polypharmacy index was lower in the time prior to LMP2 than during pregnancy in both valproate and lamotrigine/levetiracetam cohorts irrespective of monotherapy or polytherapy.

Regarding paternal demographic characteristics, fathers had a similar age in both exploratory analysis 5 and main analysis (median 33 [IQR 30, 38] years for exploratory analysis 5 and 32 [IQR 29, 36] years for the main analysis in the valproate group and median 33 years in both analyses in the lamotrigine/levetiracetam group [IQR 30, 36 in polytherapy; IQR 29, 37 in monotherapy]) (Table 27 and Table 149).

As several comorbidities were masked in the exploratory analysis 5, comparison of these comorbidities with the main analyses was not possible.

Epilepsy was the major indication for AED treatment in either valproate or lamotrigine/levetiracetam exposure groups in the exploratory analysis 5 (71.4% and 79.1%, respectively) (Table 150).

The distribution of potential risk factors and confounders for NDD including ASD by paternal exposure of polytherapy group were examined for the Primary outcome cohort for Explorative Objective 5. Results of univariate analyses are presented in Table 153.

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

As observed in the main analyses (Table 25), none of the potential offspring characteristics was associated with paternal polytherapy exposure (Table 151).

Less maternal characteristics were associated to paternal exposure in the exploratory analysis 5 (Table 152) when compared to the main analyses (Table 26). Only affective disorder (p=0.0205) was associated with paternal polytherapy exposure (the frequencies for affective disorders were masked, it was thus unknown in which exposure group affective disorders were more frequent amongst mothers). Affective disorder was also associated with paternal exposure group in the main analyses.

Regarding potential paternal characteristics associated to paternal exposure, differences in the association comparing paternal exposure to valproate vs. lamotrigine/levetiracetam were observed for categories of calendar year of offspring conception (p<0.001) (Table 153), which was also observed in the main analysis (Table 27). However, in the main analysis, differences in the association comparing the two exposure groups were observed for more variables (Table 27 and Table 153).

The distribution of potential risk factors and confounders were examined by NDD including ASD group in the Primary outcome cohort for Explorative Objective 5. Results of the univariate analyses are presented in Table 154-Table 156. All the variables examined were initially selected based on a review of the literature and clinical expert opinion, see section 9.4.4 for an overview.

None of the potential offspring risk factors were associated with NDD including ASD (Table 154). That was different from the main analyses, where gender was associated with NDD including ASD (Table 28).

Compared to the main analyses (Table 29), less potential maternal risk factors, only 2, were associated with higher risk of NDD including ASD in offspring in this exploratory analysis 5: neurotic disorder (OR: 5.38, 95% CI: 1.59, 18.20; p=0.0069) and smoking during pregnancy (OR: 3.59, 95% CI: 1.32, 9.76; p=0.0121) Table 155). In the main analyses smoking during pregnancy was also associated with a higher risk of NDD including ASD.

None of the potential paternal confounders/risk factors were associated with NDD including ASD (Table 156). This differed from the main analyses, as categories of calendar year of offspring conception was associated with NDD including ASD (Table 30).

10.3.1.9.2 Paternal exposure to valproate or lamotrigine/levetiracetam in discordant siblings (Exploratory analysis 6 for NDD including ASD)

Results from exploratory analysis 6 are presented in Table 157 to Table 165 in section 15.1.6. The analysis was performed in the Primary outcome cohort for explorative objective 6. This objective aimed to describe the risk factors and frequency of NDD including ASD, in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception. Findings were compared to results obtained from the Primary cohort for comparative analysis (main analyses).

For the exploratory analyses 6, the inclusion criterion was all offspring from the Primary outcome cohort for comparative analysis (N=1950). After additional exclusions, a total of 21 offspring were included in this analysis, with 11 in valproate and 10 in lamotrigine/levetiracetam group (Figure 31).

Many of offspring, maternal, and paternal demographic and clinical characteristics were zero or masked when being different from zero. There was no NDD including ASD event in this cohort, for exploratory analysis 6.

Gestational age was masked in the valproate group, and in lamotrigine/levetiracetam group all offspring were born at term. All offspring in both exposure groups had a birth weight ≥2500 g. The offspring gender distribution as well as year of birth were masked (Table 157).

None of the offspring had comorbidities and no event of NDD including ASD was reported (Table 158).

Median maternal age at birth was 26 (IQR 23, 29) for the valproate group and 29.5 (IQR 27, 32) for the lamotrigine/levetiracetam group (Table 159).

Regarding maternal comorbidities, neurotic disorder was reported in both groups, but number and frequency were masked. In lamotrigine/levetiracetam group but not in valproate group, gestational diabetes occurred. No alcohol or substance abuse and no smoking prior to LMP2 were reported in either group. Mean maternal polypharmacy index prior to LMP2 was 0.4 (SD 0.5) in the valproate group and 0.8 (SD 1.0) in the lamotrigine/levetiracetam group and during pregnancy, mean maternal polypharmacy index was 1.0 (SD 0.8) and 0.6 (SD 1.1), respectively (Table 160).

Similar to what was observed for maternal characteristics, fathers were younger in the valproate group with a median age of 29 (IQR 25, 33) whereas median paternal age in lamotrigine/levetiracetam group was 33.5 (IQR 31, 35). Year of offspring conception was masked (Table 161).

No paternal comorbidities were reported in the valproate group. In the lamotrigine/levetiracetam group, neurotic disorder was reported (numbers are masked). The main indication for AED treatment was epilepsy for all fathers regardless of exposure group. The mean paternal polypharmacy index was 0.5 (SD 0.7) in the valproate group and 0.9 (SD 1.2) in the lamotrigine/levetiracetam group (Table 162).

The distribution of potential risk factors and confounders for NDD including ASD by paternal exposure to valproate and levetiracetam were examined for the Primary outcome cohort for explorative objective 6. Results of univariable analyses are presented in Table 163 to Table 165.

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

Offspring gender was not associated with paternal exposure group. As no other offspring characteristics were observed in the cohort, analysing the impact of the paternal exposure was not possible (Table 163).

Only maternal age was associated with paternal exposure group was age (p=0.0220 for categorical age and p=0.0236 for continuous age) (Table 164).

None of the paternal characteristics were associated with the paternal exposure group (Table 165).

Since there was no NDD including ASD event in the cohort, the analysis for assess the association of risk factors with NDD including ASD was not performed.

10.3.1.10 Sensitivity analysis for NDD including ASD

Multiple sensitivity analyses were performed to examine the robustness of the main analysis findings. Summary tables of the main results for each of sensitivity analysis are presented in this section. All tables produced for each of the sensitivity analysis are presented in a separate document (Annex document).

Findings from extending the exposure window for the primary outcome to 6 months (sensitivity analysis 1), excluding offspring with low birth weight or born prior to 8th month for the primary cohort (sensitivity analysis 3), simple pairwise comparisons for the exposure groups (valproate vs lamotrigine, sensitivity analysis 5), comparing PS-matched model with covariate adjusted model for the primary cohort (sensitivity analysis 6), examining the effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy (sensitivity analysis 7) and using a narrow definition of the outcome (sensitivity analysis 11) were similar with the results observed in the main analyses (see Table 36).

Table 36. Summary of main analysis and sensitivity analyses for the Primary outcome cohort in Denmark

Analyses	Population considered	HR (95% CI) estimates		HR (95% CI) estimates by cluster of exposure	
		Crude*	Adjusted***	Cluster A	Cluster B
Main analysis N sample = 1950	Please check Section 9.3	0.94 (0.60, 1.46)	1.34 (0.79, 2.25)	1.38 (0.69, 2.74)	1.30 (0.60, 2.83)
Sensitivity analysis 1 N sample = 2049	Extended risk window of paternal valproate exposure (6 months)	0.86 (0.56, 1.32)	1.13 (0.68, 1.89)	1.51 (0.79, 2.87)	0.80 (0.35, 1.84)
Sensitivity analysis 3 N sample = 1931	Exclusion of offspring with low birth weight or born prior to 8th months	0.93 (0.59, 1.46)	1.36 (0.82, 2.27)	1.50 (0.80, 2.84)	1.19 (0.53, 2.69)
Sensitivity analysis 5A N sample = 2137	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	0.98 (0.62, 1.54)	1.51 (0.90, 2.53)	1.57 (0.81, 3.04)	1.42 (0.63, 3.20)
Sensitivity analysis 5B N sample = 906	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	**	0.59 (0.18, 1.95)	0.70 (0.16, 3.06)	0.43 (0.06, 3.30)
Sensitivity analysis 6 N sample = 2355	Comparison of PS-weighted model with covariate adjustment model	-	1.22 (0.77, 1.92)	-	-
Sensitivity analysis 7 N sample = 1987	Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy	1.03 (0.68,1.57)*	1.41 (0.84, 2.38)	1.42 (0.75, 2.67)	1.38 (0.59, 3.22)
Sensitivity analysis 11 N sample = 1950	Narrow definition of NDD	0.98 (0.61, 1.55)	1.59 (0.89, 2.86)	1.60 (0.75, 3.41)	1.55 (0.64, 3.78)

CI: Confidence Interval; HR: Hazard ratio; 5A analysis comparing valproate and lamotrigine; 5B analysis comparing valproate and levetiracetam;

*: for sensitivity analysis 7 the "crude" hazard ratio was adjusted for offspring epilepsy and offspring exposure AED.
** Due to the sample size, the estimated HR was not interpretable (>100,000). Crude and adjusted models do not always use the same population leading to differences in the sample size and number of events in the models.
***The logistic regression PS models used in sensitivity analysis include variables following described:
Sensitivity analysis 1: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", "Maternal polypharmacy index prior to LMP2", mothers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception". " In sensitivity analysis 1 the HR were further adjusted for "Maternal affective disorder".
Sensivity analysis 3: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", "Maternal polypharmacy index prior to LMP2", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Year of offspring conception at mother's LMP2"
Sensivity analysis 5[A]: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Substance abuse during pregnancy", "Smoking during pregnancy", mothers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception"
Sensivity analysis 5[B]: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Smoking during pregnancy", mothers with at least one prescription of "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2"
Sensitivity analysis 6: no PS weighting performed.
Sensivity analysis 7: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Obesity", "Substance abuse during pregnancy", "Smoking during pregnancy", "Maternal polypharmacy index prior to LMP2", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Year of offspring conception". In sensitivity analysis 7, the HR were further adjusted for offspring epilepsy and offspring exposure AED.
Sensitivy analysis 11: Maternal risk factors/confounders: "Mother's Age", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of: "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception". In sensitivity analysis 11 the HR were further adjusted for "Maternal affective disorder" and "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy".

Validation of the assumption that individuals were exposed to one DDD per day (sensitivity analysis 8) was performed among fathers who had prescriptions of AED for epilepsy, the estimated treatment durations (estimated from the number of prescriptions as described in section 9.9.4.8) were longer for fathers prescribed with lamotrigine, 119.4 (±94.3) days, followed by those with levetiracetam, 105.6 (±63.1) days, and 81.1 (45.9) days in those prescribed with valproate. Time between prescriptions (observed) was longer for fathers prescribed with lamotrigine, 109.3 (±30.4) days, followed by valproate, 104.0 (±30.1) days, and levetiracetam, 103.0 (±35.7) days. The ratio (observed vs estimated) was higher for valproate 1.57, followed by lamotrigine 1.54 and levetiracetam 1.40. Under the assumption of perfect compliance of each father, ratios depart from the approximation range 0.8-1.20, which indicate the real daily dose prescribed diverge from the WHO DDD (see Table 37 for further details).

Sensitivity analysis 8 was also performed among fathers who had dispenses of AED without indication for epilepsy, the estimated treatment durations (expected) was similar for fathers treated with lamotrigine, 75.0 (±63.1) days, and those on valproate, 73.1 (±40.3) days, while those in the levetiracetam group had an estimated shorter treatment duration of 54.8 (±15.9) days. Time between prescriptions (observed) was longer for fathers prescribed with valproate, 102.9 (±32.7) days, followed by fathers prescribed lamotrigine, 96.5 (±36.9) days, and levetiracetam, 78.6 (±42.4) days. The ratio (observed vs estimated) was higher for lamotrigine 2.51, followed by valproate 1.79 and levetiracetam 1.46 (Table 37). Under the assumption of perfect compliance of each father, ratios depart from the approximation range 0.8-1.20, which indicate the real daily dose prescribed diverge from the WHO DDD (see Table 37 for further details).

Table 37. Distribution of estimated treatment durations and time between prescriptions for fathers with/without an indication for epilepsy; Primary outcome cohort in Denmark

	Distribution of estimated treatment durations and time between prescriptions for fathers with an indication for epilepsy			Distribution of estimated treatment durations and time between prescriptions for fathers without an indication for epilepsy; primary outcome		
	Paternal exposure group			Paternal exposure group		
NDD	Valproate	Lamotrigine	Levetiracetam	Valproate	Lamotrigine	Levetiracetam
Number of offspring	N=582	N=604	N=103	N=250	N=480	N=12
Estimated treatment durations (expected)	81.06 (45.91)	119.43 (94.32)	105.59 (63.13)	73.10 (40.32)	75.00 (63.14)	54.76 (15.85)
Time between prescriptions (observed)	104.03 (30.11)	109.26 (30.39)	102.97 (35.68)	102.93 (32.73)	96.55 (36.86)	78.57 (42.39)
Ratio (observed vs expected)	1.57	1.54	1.40	1.79	2.51	1.46

NDD: neurodevelopmental disorders

In sensitivity analysis 10, the mean paternal cumulative exposure to valproate was 53.1 (±21.8) days, while in the lamotrigine/levetiracetam group mean paternal cumulative exposure was 54.5 (±26.0) days (See Annex document). Comparing paternal cumulative exposure to valproate with lamotrigine/levetiracetam at a specific cumulative exposure level (mean cumulative exposure 54.2 days) showed no difference in the risk of NDD in the offspring (HR: 0.58, 95% CI: 0.31, 1.08). At this particular mean cumulative exposure, the number of events reported in the valproate group and lamotrigine/levetiracetam group were 17 and 27, respectively. See Table 38 for further detail (NDD event data not shown).

Among fathers exposed to valproate, comparing medium cumulative exposure to low cumulative exposure to valproate, no NDD events (0 events) were observed in the medium cumulative exposure group while 14

events were reported for the low cumulative exposure to valproate group (HR: 0.00, 95% CI: 0.00, 0.00). Comparison between the high paternal cumulative exposure to valproate group and the low paternal cumulative exposure to valproate group showed no higher risk of NDD in the offspring from the high paternal cumulative exposure group (HR: 1.17, 95% CI: 0.59, 2.33). The number of NDD events reported to the high cumulative exposure to valproate group was 17. Results were masked for the lamotrigine group. See Table 39 for further description (NDD event not shown).

Table 38 Effect estimation for neurodevelopmental disorders (NDD) using Cox covariate adjustment model; Primary outcome cohort in Denmark

NDD	**Model estimates**		
Number of subjects included in analysis prior to exclusion influential subjects [a]	1950		
Number of subjects included in the model (after excluding influential subjects) [b]	1910 (97.95%)		
Variable	**HR**	**95% CI**	**P-value**
Paternal exposure: valproate vs lamotrigine/levetiracetam	-	-	0.3619
Paternal cumulative exposure to AEDs	-	-	0.0004
Paternal exposure * Paternal cumulative exposure to AEDs	-	-	0.9563
Effect of valproate at a specific cumulative exposure level:			
Valproate vs lamotrigine/levetiracetam at the mean cumulative exposure = 54.2171 days	0.58	(0.31- 1.08)	-

NDD: neurodevelopmental disorders; AED: antiepileptic drugs; CI: Confidence Interval
Legend: Hazard ratios (HR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders included in the covariate adjustment model. All variables potentially included in the model are listed here, however some of the variables might not be included in the final set of variables.
a) Number of subjects included represents the total number of subjects in the cohort of interest minus those subjects who had at least one missing value for any of the variables included in each model.
b) Influential subjects were identified using the dfbetas for the exposure coefficient.

Note: all the confounders were removed from the model due to the fact there were few NDD events left in the patient group after removing outliers.

Table 39 Effect estimation for neurodevelopmental disorders (NDD) using Cox covariate adjustment model for valproate and lamotrigine treatment group; Primary outcome cohort in Denmark

	Valproate			Lamotrigine		
	N	HR (95% CI)	P-value	N	HR (95% CI)	P-value
Number of subjects included in analysis prior to exclusion influential subjects [a]	793					
Number of subjects included in the model (after excluding influential subjects) [b]	781 (98.49%)					
Paternal cumulative exposure						
Low		Reference				
Medium		0.00 (0.00, 0.00)	<0.0001			
High		1.17 (0.59, 2.33)	0.6453	*	**	

Legend: Hazard ratios (HR), 95% confidence intervals (CI); NDD: neurodevelopmental disorders and p-values are represented for risk factors and confounders included in the covariate adjustment model. All variables potentially included in the model are listed here, however some of the variables might not be included in the final set of variables.
*: The number of NDD events is <20
**: The model has 2 parameters and requires at least 20 NDD events, thus the result could not be generated
a) Number of subjects included represents the total number of subjects in the cohort of interest minus those subjects who had at least one missing value for any of the variables included in each model.
b) Influential subjects were identified using the dfbetas for the exposure coefficient.

10.3.2 Congenital Malformations

10.3.2.1 Description of the offspring, maternal and paternal characteristics by paternal exposure group

The results presented below are from analyses performed in the Secondary outcome cohort for descriptive analyses (see Figure 10).

Overall, the majority of offspring were male (51.7%), similar in both exposure groups. Most of the offspring were born at term between 37-41 weeks of gestational age (90.3%) (87.2% in those paternally exposed to valproate and 91.9% in those paternally exposed to lamotrigine/levetiracetam) and weighing ≥2500 g (95.8%, similar in both exposure groups) (Table 40). Regarding clinical characteristics, overall, 12.5% were diagnosed with CM during the overall study follow-up. In the paternally exposed to valproate group, 6.7% had a diagnosis of minor CM while 3.5% had a diagnosis of major CM. In the lamotrigine/levetiracetam paternally exposed group, 10.5% had a diagnosis of minor CM while 4.5% had a diagnosis of major CM (Table 41). It should be noted that the major and minor CM groups are not mutually exclusive.

The most frequent adverse pregnancy outcome associated with a diagnosis of CM was intrauterine growth retardation, both for the valproate paternal exposure group (3.5%) and the lamotrigine/levetiracetam paternal exposure group (4.3%) (Table 41).

Overall, the median (IQR) age of mothers from the Secondary outcome cohort for descriptive analyses at childbirth was 30 (27, 34) years, similar in both exposure groups (Table 42).

The most prevalent clinical characteristics recorded in mothers prior to childbirth were gestational diabetes (observed in 3.6% of mothers of offspring paternally exposed to valproate and 3.4% of mothers of offspring paternally exposed to lamotrigine/levetiracetam), epilepsy (observed in 2.7% of mothers of offspring paternally exposed to valproate and 1.6% of mothers of offspring paternally exposed to lamotrigine/levetiracetam), and obesity (observed in 1.5% and 1.8% respectively) (Table 43).

Overall, 15.5% of mothers had a record of smoking during pregnancy, 16.0% of mothers of offspring paternally exposed to valproate and 15.3% of mothers of offspring paternally exposed to lamotrigine/levetiracetam; the proportion of missing values was 1.6%. Data on maternal smoking prior to LMP2 was deemed not reliable due to the high degree of missingness (94.9% of missing data in the lamotrigine/levetiracetam group).

Overall exposure to AEDs in mothers prior to LMP2 and during pregnancy was very low, and values were not disclosed for most of AEDs.

The proportion of mothers with concomitant medications associated with teratogenic activity/foetal toxicity prior to LMP2 was 25.9% and 30.8% in the valproate and lamotrigine/levetiracetam group, respectively. Correspondingly, the proportion of mothers with concomitant medications associated with teratogenic activity/foetal toxicity during pregnancy was 27% and 33.5% reported in the valproate and lamotrigine/levetiracetam group, respectively (Table 43). Nevertheless, these exposures were considered as risk factors for CM and excluded for the comparative analysis.

Regarding fathers' demographic characteristics, the overall median (IQR) age of fathers at childbirth was 33 (29-37) years, similar in both exposure groups. More offspring in the lamotrigine/levetiracetam group were conceived in the latest year of the study time period, compared with the valproate group (Table 44). Regarding indication for AED treatment for paternal exposure group, epilepsy was the most prevalent, with 75.4% in the valproate paternal exposed group and 58.3% in the lamotrigine/levetiracetam paternal exposed group (Table 45).

The K-means algorithm, analysing DDD trajectories in fathers exposed to AEDs 3 months prior to conception (i.e. prior to LMP2) identified 2 different clusters A and B (Figure 14) one with constant high exposure (A) and the other with constant low exposure to AEDs (B). Both groups of exposure to valproate and to either lamotrigine/levetiracetam seemed to present higher proportions of fathers in cluster A (53.9% and 57.7%) than in cluster B (46.1% and 42.3%). Paternal exposure to teratogenic activity/foetal toxicity for valproate and lamotrigine/levetiracetam groups was 24.2% and 35.8%, respectively.

Table 40 Offspring demographic characteristics by paternal exposure group; Secondary outcome cohort in Denmark (N=1655)

	Paternal exposure group									
CM	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=549**		**N=1106**		**N=996**		**N=111**		**N=1655**	
Gestational age (weeks)										
<28 (extremely preterm)	***	***	5	0.45	***	***	***	***	***	***
28-31 (very preterm)	***	***	5	0.45	5	0.50	0	0.00	***	***
32-36 (moderate to late preterm)	34	6.19	32	2.89	***	***	***	***	66	3.99
37-41 (at term)	479	87.25	1016	91.86	911	91.56	105	94.59	1495	90.33
≥42 (post-term)	30	5.46	48	4.34	***	***	***	***	78	4.71
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	0	0.00	***	***	***	***	***	***	***	***
1000-1499 (very low)	***	***	***	***	***	***	***	***	7	0.42
1500-2499 (low)	8	1.46	34	3.07	***	***	***	***	42	2.54
≥2500	529	96.36	1056	95.48	950	95.48	106	95.50	1585	95.77
Missing	***	***	10	0.90	***	***	***	***	***	***
Gender										
Male	280	51.00	575	51.99	515	51.76	60	54.05	855	51.66
Female	269	49.00	531	48.01	480	48.24	51	45.95	800	48.34
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM: congenital malformations; g: grams

*** Masked values indicated that data was calculated but not disclosed due to small number of participants

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father appeared more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

Table 41 Offspring clinical characteristics paternal exposure group; Secondary outcome cohort in Denmark (N=1655)

	Paternal exposure group									
CM	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=549**		**N=1106**		**N=995**		**N=111**		**N=1655**	
Comorbidities [a]										
Congenital CMV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital Herpes Simplex	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital varicella	***	***	***	***	***	***	***	***	***	***
Foetal alcohol syndrome	0	0.00	***	***	***	***	***	***	***	***
Outcomes										
CM	51	9.29	156	14.10	139	13.97	17	15.32	207	12.51
Major CM (at any time)	19	3.46	50	4.52	***	***	***	***	69	4.17
Minor CM (at any time)	37	6.74	116	10.49	102	10.25	14	12.61	153	9.24
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]										
Stillbirth	***	***	6	0.54	6	0.60	0	0.00	***	***
Spontaneous abortion	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Intrauterine growth retardation	19	3.46	48	4.34	***	***	***	***	67	4.05
Perinatal mortality	***	***	9	0.81	9	0.90	0	0.00	***	***

CM: congenital malformations; CMV: cytomegalovirus

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) between 22nd week of gestation and exit date; b) Denominator for the percentage is the number of offspring with CM.

Table 42 Maternal demographic characteristics by paternal exposure group; Secondary outcome cohort in Denmark (N=1655)

	Paternal exposure group									
CM Number of offspring	Valproate N=549		Lamotrigine/levetiracetam N=1106		Lamotrigine N=995		Levetiracetam N=111		Total (valproate + lamotrigine/levetiracetam) N=1655	
Mother's age [a]										
≤20 years	9	1.64	21	1.90	21	2.11	0	0.00	30	1.81
21-25	106	19.31	156	14.10	139	13.97	17	15.32	262	15.83
26-30	202	36.79	380	34.36	338	33.97	42	37.84	582	35.17
31-35	165	30.05	379	34.27	336	33.77	43	38.74	544	32.87
36-40	58	10.56	145	13.11	136	13.67	9	8.11	203	12.27
>40	9	1.64	25	2.26	25	2.51	0	0.00	34	2.05
Mean (SD)	29.68 (4.80)		30.43 (4.96)		30.50 (5.04)		29.81 (4.08)		30.18 (4.92)	
Median (25^{th} – 75^{th} percentile)	30(26.00, 33.00)		30(27.00, 34.00)		30(27.00, 34.00)		30(27.00, 32.00)		30(27.00, 34.00)	
Min, max	***		***		***		***		***	
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM: congenital malformations; SD: standard deviation

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at 22^{nd} week of gestation

Table 43 Maternal clinical characteristics by paternal exposure group; Secondary outcome cohort in Denmark (N=1655)

	Paternal exposure group				
CM **Number of offspring**	**Valproate** **N=549**	**Lamotrigine/levetiracetam** **N=1106**	**Lamotrigine** **N=996**	**Levetiracetam** **N=111**	**Total (valproate + lamotrigine/levetiracetam)** **N=1655**

CM	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=549		N=1106		N=996		N=111		N=1655	
Comorbidities										
Diabetes [a]	5	0.91	13	1.18	13	1.31	0	0.00	18	1.09
Epilepsy [a]	15	2.73	18	1.63	***	***	***	***	33	1.99
Obesity [b]	8	1.46	20	1.81	***	***	***	***	28	1.69
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Folate deficiency [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gestational diabetes [c]	20	3.64	38	3.44	33	3.32	5	4.50	58	3.50
Herpes simplex virus [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Rubella [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Toxoplasmosis [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Varicella [c]	***	***	***	***	***	***	***	***	***	***
Lifestyle characteristics										
Alcohol abuse prior to LMP2 [b]	***	***	0	0.00	0	0.00	0	0.00	***	***
Alcohol abuse during pregnancy [c]	0	0.00	5	0.45	5	0.50	0	0.00	5	0.30
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	6	0.54	***	***	***	***	6	0.36
Smoking prior to LMP2 [b]										
Yes	***	***	15	1.36	15	1.51	0	0.00	***	***
No	19	3.46	42	3.80	37	3.72	5	4.50	61	3.69
Missing	***	***	1049	94.85	943	94.77	106	95.50	***	***
Smoking during pregnancy [c]										
Yes	88	16.03	169	15.28	***	***	***	***	257	15.53
No	448	81.60	923	83.45	829	83.32	94	84.68	1371	82.84
Missing	13	2.37	14	1.27	***	***	***	***	27	1.63
Medication use										
Exposure to AEDs prior to LMP2 [d]										
Valproic Acid	0	0.00	***	***	***	***	***	***	***	***
Lamotrigine	5	0.91	10	0.90	10	1.01	0	0.00	15	0.91
Levetiracetam	0	0.00	***	***	***	***	***	***	***	***
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	***	***	***	***	***	***	***	***

	Paternal exposure group									
CM	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=549**		**N=1106**		**N=996**		**N=111**		**N=1655**	
Carboxamide derivatives	***	***	***	***	***	***	***	***	***	***
Fatty acid derivatives	0	0.00	***	***	***	***	***	***	***	***
Other antiepileptics	***	***	15	1.36	***	***	***	***	***	***
Exposure to AEDs during pregnancy [c]										
Valproic Acid	0	0.00	***	***	***	***	***	***	***	***
Lamotrigine	5	0.91	10	0.90	10	1.01	0	0.00	15	0.91
Levetiracetam	0	0.00	***	***	***	***	***	***	***	***
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	***	***	***	***	***	***	***	***	***	***
Carboxamide derivatives	***	***	***	***	***	***	***	***	***	***
Fatty acid derivatives	0	0.00	***	***	***	***	***	***	***	***
Other antiepileptics	5	0.91	14	1.27	***	***	***	***	19	1.15
K-means cluster prior to LMP2 [d]										
Unexposed	543	98.91	***	***	***	***	***	***	***	***
Cluster A[1]	***	***	10	0.90	10	1.01	0	0.00	***	***
Cluster B[1]	***	***	6	0.54	6	0.60	0	0.00	***	***
Cluster C[1]	***	***	***	***	***	***	***	***	***	***
K-means cluster during pregnancy [c]										
Unexposed	541	98.54	1090	98.55	***	***	***	***	1631	98.55
Cluster A[2]	***	***	10	0.90	10	1.01	0	0.00	***	***
Cluster B[2]	***	***	***	***	***	***	***	***	7	0.42
Cluster C[2]	***	***	***	***	***	***	***	***	***	***
Maternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [d] - mothers with at least one prescription	142	25.87	341	30.83	324	32.56	17	15.32	483	29.18
Maternal exposure to teratogenic activity/foetal toxicity during pregnancy [c] - mothers with at least one prescription	148	26.96	370	33.45	346	34.77	24	21.62	518	31.30

	Paternal exposure group				
CM	Valproate	Lamotrigine/levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine/levetiracetam)
Number of offspring	N=549	N=1106	N=996	N=111	N=1655

AED: antiepileptic drug; CM: congenital malformations; CMV: cytomegalovirus; LMP2: last menstrual period + 2 weeks; SD: standard deviation
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to 22nd week of gestation; b) 12 months lookback from LMP2; c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy); d) 3 months lookback from LMP2; e) Oxazolidine derivatives were not marketed in Denmark.
Cluster A[1]: constant moderate exposure, Cluster B[1]: constant low exposure, Cluster C[1]: constant high exposure
Cluster A[2]: constant moderate exposure, Cluster B[2]: constant low exposure, Cluster C[2]: constant high exposure

Table 44 Paternal demographic characteristics by paternal exposure group; Secondary outcome cohort in Denmark (N=1655)

	Paternal exposure group									
CM	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=549		N=1106		N=995		N=111		N=1655	
Father's age [a]										
≤20 years	***	***	5	0.45	5	0.50	0	0.00	***	***
21-25	***	***	95	8.59	85	8.54	10	9.01	***	***
26-30	145	26.41	263	23.78	233	23.42	30	27.03	408	24.65
31-35	215	39.16	396	35.80	343	34.47	53	47.75	611	36.92
36-40	99	18.03	236	21.34	224	22.51	12	10.81	335	20.24
>40	49	8.93	111	10.04	105	10.55	6	5.41	160	9.67
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mean (SD)	32.79 (5.50)		33.14 (5.77)		33.27 (5.87)		31.97 (4.73)		33.03 (5.69)	
Median (25th - 75th percentile)	33(29.00, 36.00)		33(29.00, 37.00)		33(29.00, 37.00)		32(30.00, 35.00)		33(29.00, 37.00)	
Min, max	***		***		***		***		***	

CM	Paternal exposure group									
	Valproate N=549		Lamotrigine/levetiracetam N=1106		Lamotrigine N=995		Levetiracetam N=111		Total (valproate + lamotrigine/levetiracetam) N=1655	
Number of offspring										
Father's age [a]										
Year of offspring conception [b]										
2003	30	5.46	19	1.72	19	1.91	0	0.00	49	2.96
2004	58	10.56	42	3.80	***	***	***	***	100	6.04
2005	61	11.11	47	4.25	***	***	***	***	108	6.53
2006	45	8.20	46	4.16	46	4.62	0	0.00	91	5.50
2007	39	7.10	67	6.06	59	5.93	8	7.21	106	6.40
2008	47	8.56	77	6.96	69	6.93	8	7.21	124	7.49
2009	44	8.01	71	6.42	***	***	***	***	115	6.95
2010	36	6.56	82	7.41	76	7.64	6	5.41	118	7.13
2011	22	4.01	90	8.14	***	***	***	***	112	6.77
2012	37	6.74	97	8.77	88	8.84	9	8.11	134	8.10
2013	26	4.74	105	9.49	93	9.35	12	10.81	131	7.92
2014	38	6.92	107	9.67	95	9.55	12	10.81	145	8.76
2015	35	6.38	99	8.95	85	8.54	14	12.61	134	8.10
2016	21	3.83	81	7.32	64	6.43	17	15.32	102	6.16
2017	***	***	56	5.06	41	4.12	15	13.51	***	***
2018	***	***	20	1.81	***	***	***	***	***	***

CM: congenital malformations; SD: standard deviation

*** Masked values indicated that data was calculated but not disclosed due to small number of participants

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at index (22nd week of gestation in Denmark); b) at mother's LMP2.

Table 45 Paternal clinical characteristics by paternal exposure group; secondary outcome cohort in Denmark (N=1655)

	Paternal exposure group									
CM	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=549**		**N=1106**		**N=995**		**N=111**		**N=1655**	
Medication use										
AED indication [a]										
Epilepsy	414	75.41	645	58.32	546	54.87	99	89.19	1059	63.99
Bipolar affective disorder and mania	22	4.01	88	7.96	88	8.84	0	0.00	110	6.65
Other/unknown	113	20.58	373	33.73	361	36.28	12	10.81	486	29.37
K-means cluster [b]										
Cluster A	296	53.92	638	57.69	562	56.48	76	68.47	934	56.44
Cluster B	253	46.08	468	42.31	433	43.52	35	31.53	721	43.56
Paternal exposure to teratogenic activity/foetal toxicity [b]	133	24.23	396	35.80	380	38.19	16	14.41	529	31.96

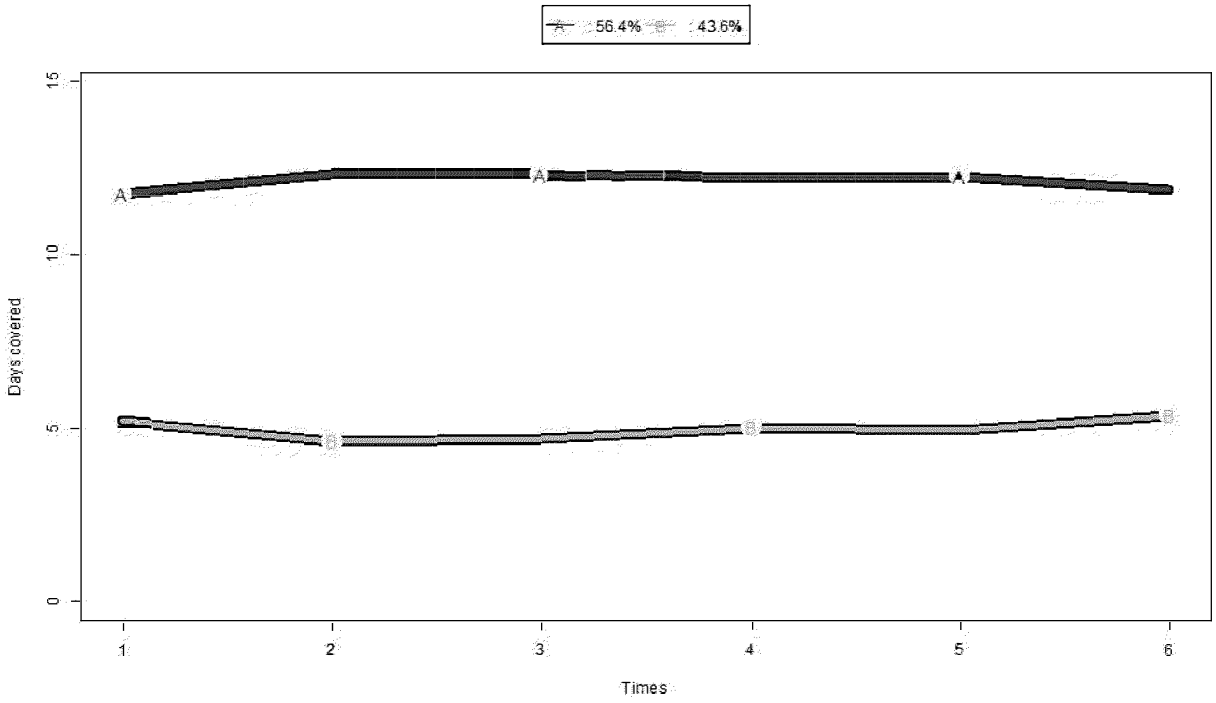
AED: antiepileptic drug; CM: congenital malformations

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Cluster A: constant high exposure; Cluster B: constant low exposure

Comorbidities and AED indication: the same data are used for these 2 sets of categories (ICD-10 codes anytime before index, i.e. child birthdate). However, for "comorbidities" all records were considered and a patient with a record of mania and a record of bipolar affective disorder was counted in both categories, whereas for "AED indication", categories were mutually exclusive, based on the following priority order: 1) epilepsy 2) bipolar affective disorder and mania 3) other/unknown, meaning a patient with a record of epilepsy and a record of mania was counted in the epilepsy category only.

a) Since indications for medications were not available in all the data sources used for this study, the indication for AEDs was estimated based on medical history. The entire medical history for each father was considered up to LMP2 (exclusive) to identify diagnosis records of epilepsy and bipolar disorder/mania. In case more than one diagnosis was found (e.g. epilepsy and bipolar disorder), only one indication was selected, with priority given to epilepsy, followed by bipolar disorder. In case none of these diagnoses were found in the medical history, the indication was considered "other/unknown". b) 3 months lookback from LMP2;



Legend: Times refers to the 14-days interval during which exposure was assessed (in this case, 6 14 days interval [i.e.3 months]); Days covered refers to days covered in each 14-day interval; Defined Daily Dose (DDD) trajectories: Cluster A: constant high exposure; Cluster B: constant low exposure. The percentage shows the proportion of fathers exposed to valproate and lamotrigine/levetiracetam in each cluster.

Figure 14 Mean Defined Daily Dose (DDD) trajectories for fathers exposed to Antiepileptic Drugs (AEDs) in the 3 months lookback prior to Last Menstrual Period Date Plus 2 weeks (LMP2) in Denmark

10.3.2.2 Cumulative incidence proportion

Considering the overall study follow-up, the incidence proportion of CM (major and minor as composite) among offspring paternally exposed to valproate (n=51, 9.3%, 95% CI: 6.9%,11.7%) appeared to be lower than those paternally exposed to lamotrigine/levetiracetam (n=156, 14.1%, 95% CI: 12.1%,16.2%). The CIs were slightly overlapping, which does not support differences between exposure groups (Table 46).

Table 46 Cumulative incidence proportion (risk) of CM by paternal exposure group; Secondar outcome cohort in Denmark (N=1655)

		Paternal				
CM		**Valproate**	**Lamotrigine /levetiracetam (composite)**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow, up period						
	N	549	1106	995	111	1655
0, 1 years	n	29	101	92	9	130
	n/N*100	5.28 (3.41, 7.15)	9.13 (7.43, 10.83)	9.25 (7.45, 11.05)	8.11 (3.03, 13.19)	7.85 (6.56, 9.15)
	N	513	960	867	93	1473
1, 2 years	n	8	18	***	***	26
	n/N*100	1.56 (0.49, 2.63)	1.88 (1.02, 2.73)	***	***	1.77 (1.09, 2.44)
	N	489	886	811	75	1375
2, 3 years	n	6	9	9	0	15
	n/N*100	1.23 (0.25, 2.20)	1.02 (0.36, 1.68)	1.11 (0.39, 1.83)	0.00 (0.00, 0.00)	1.09 (0.54, 1.64)
	N	458	790	730	60	1248
3, 4 years	n	***	10	***	***	***
	n/N*100	***	1.27 (0.49, 2.05)	***	***	***
	N	422	687	644	43	1109
4, 5 years	n	***	9	***	***	***
	n/N*100	***	1.31 (0.46, 2.16)	***	***	***
	N	390	586	553	33	976
5, 6 years	n	***	***	***	0	***
	n/N*100	***	***	***	0.00 (0.00, 0.00)	***
	N	359	500	474	26	859
6, 7 years	n	***	***	***	0	5

	n/N*100	***	***	***	0.00 (0.00, 0.00)	0.58 (0.07, 1.09)
7, 8 years	N	328	421	***	***	749
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00 (0.00, 0.00)	***
8, 9 years	N	303	342	325	17	645
	n	0	0	0	0	0
	n/N*100	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
9, 10 years	N	265	280	***	***	545
	n	0	0	0	0	0
	n/N*100	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
10, 11 years	N	223	214	203	11	437
	n	0	***	0	***	***
	n/N*100	0.00 (0.00,0.00)	***	0.00 (0.00,0.00)	***	***
11, 12+a years	N	189	159	154	5	348
	n	0	0	0	0	0
	n/N*100	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)
Overall (0, 12+ years)	**N**	549	1106	995	111	1655
	n	51	156	139	17	207
	n/N*100	9.29 (6.86, 11.72)	14.10 (12.05, 16.16)	13.97 (11.82, 16.12)	15.32 (8.62, 22.02)	12.51 (10.91, 14.10)

CM: congenital malformations

*** Masked values indicated that data was calculated but not disclosed

Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with 95% confidence interval (CI) are presented.

a: For countries where the index date is the 12th or 22nd week of pregnancy, follow-up time in years were longer than age in years, therefore some offspring were >12 years of follow-up by the time they were censored upon 12th birthday. For this reason, the table shows '12+ years'

10.3.2.3 Association between potential risk factors/confounders for CM and paternal exposure group

Association between potential covariates (risk factors and counfounders) for CM and paternal exposure group was assessed in the Secondary outcome cohort for comparative analyses. Results of the crude associations are shown in Table 47 to Table 49.

Most of the offspring characteristics considered were not observed in the sample. Congenital varicela and foetal alcohol syndrome were not associated with paternal exposure group, but values were not disclosed due to small sample (Table 47).

None of the maternal characteristics previously identified as a risk factor were significantly associated with paternal exposure to valproate or lamotrigine/levetiracetam (Table 48).

The only paternal characteristic identified as a risk factor (see Table 49) that was statistically significantly associated with paternal exposure was year of conception: earlier years of conception were more frequent in the valproate-exposed group and more recent years in the lamotrigine/levetiracetam exposed group ($p<0.0001$) (Table 49).

Table 47 Association between potential offspring risk factors/confounders for congenital malformations (CM) by paternal exposure group; Secondary outcome cohort in Denmark (N=648)

	Paternal exposure group										Comparison
CM **Number of offspring**	**Valproate** **N=259**		**Lamotrigine/levetiracetam** **N=389**		**Lamotrigine** **N=322**		**Levetiracetam** **N=67**		**Total (valproate + lamotrigine/levetiracetam)** **N=648**		**Valproate vs Lamotrigine /levetiracetam** **N=648**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Offspring risk factors/confounders[a]											
Congenital CMV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital Herpes Simplex	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital rubella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital toxoplasmosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital varicella	***	***	***	***	***	***	0	0.00	***	***	1.00 (1.0000)*
Foetal alcohol syndrome	0	0.00	***	***	***	***	0	0.00	***	***	1.00 (1.0000)*

CMV: cytomegalovirus; CM: Congenital Malformation

*** Masked values indicated that data was calculated but not disclosed due to small number of participants

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) between 22nd week of gestation and exit date

Table 48 Association between potential maternal risk factors for CM by paternal exposure group; Secondary outcome cohort in Denmark (N=648)

	Paternal exposure group	Comparison

CM Number of offspring	Valproate N=259		Lamotrigine/ levetiracetam N=389		Lamotrigine N=322		Levetiracetam N=67		Total (valproate + lamotrigine/ levetiracetam) N=648		Valproatevs Lamotrigine /levetiracetam N=648	Valproate vs Lamotrigine N=581	Valproate vs Levetiracetam N=326
											Test statistic (p-value)	Test statistic (p-value)	Test statistic (p-value)
Maternal risk factors													
Mother´s age [a](categorical)													
≤20 years	***	***	5	1.29	5	1.55	0	0.00	***	***	-	-	-
21-25	44	16.99	57	14.65	47	14.60	10	14.93	101	15.59	-	-	-
26-30	104	40.15	143	36.76	119	36.96	24	35.82	247	38.12	-	-	-
31-35	82	31.66	143	36.76	115	35.71	28	41.79	225	34.72	-	-	-
36-40	19	7.34	35	9.00	30	9.32	5	7.46	54	8.33	-	-	-
>40	***	***	6	1.54	6	1.86	0	0.00	***	***	-	-	-
Test statistics (p-value)	-	-	-	-	-	-	-	-	-	-	3.67 (0.5981)	2.80 (0.7311)	4.60 (0.4668)
Mother´s age [a](continuous)													
Mean (SD)	29.47 (4.49)		30.06 (4.58)		30.07 (4.71)		29.97 (3.91)		29.82 (4.55)		80332.00 (0.1109)[•]	72276.00 (0.1233)[•]	11575.00 (0.3661)[•]
Median (25th - 75th percentile)	29(26.00, 33.00)		30(27.00, 33.00)		30(27.00, 33.00)		30(27.00, 33.00)		30(27.00, 33.00)		-	-	-
Min, max	***		***		***		***		***		-	-	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-
Diabetes [b]	***	***	***	***	***	***	***	***	***	***	0.30 (0.3072)[•]	0.32 (0.3287)[•]	1.00 (1.0000)[•]
Obesity [c]	5	1.93	***	***	***	***	***	***	***	***	0.49 (0.4952)[•]	0.47 (0.4767)[•]	1.00 (1.0000)[•]
Alcohol abuse prior to LMP2 [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-
Alcohol abuse during pregnancy [d]	0	0.00	***	***	***	***	***	***	***	***	0.27 (0.2791)[•]	0.25 (0.2575)[•]	-
Substance abuse	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-

	Paternal exposure group										Comparison		
CM Number of offspring	Valproate N=259		Lamotrigine/ levetiracetam N=389		Lamotrigine N=322		Levetiracetam N=67		Total (valproate + lamotrigine/ levetiracetam) N=648		Valproatevs Lamotrigine /levetiracetam N=648	Valproate vs Lamotrigine N=581	Valproate vs Levetiracetam N=326
											Test statistic (p-value)	Test statistic (p-value)	Test statistic (p-value)
prior to LMP2 [c]													
Substance abuse during pregnancy [d]	0	0.00	***	***	***	***	***	***	***	***	0.51 (0.5194)[*]	1.00 (1.0000)[*]	0.20 (0.2055)[*]
Smoking prior to LMP2 [c]													
Yes	12	4.63	15	3.86	***	***	***	***	27	4.17	-	-	-
No	***	***	***	***	***	***	***	***	5	0.77	-	-	-
Missing	***	***	***	***	307	95.34	***	***	616	95.06	-	-	-
Test statistics (p-value) without 'Missing' category	-	-	-	-	-	-	-	-	-	-	1.00 (1.0000)[*]	1.00 (1.0000)[*]	1.00 (1.0000)[*]
Smoking during pregnancy [d]													
Yes	213	82.24	344	88.43	284	88.20	60	89.55	557	85.96	-	-	-
No	37	14.29	***	***	***	***	***	***	***	***	-	-	-
Missing	9	3.47	***	***	***	***	***	***	***	***	-	-	-
Test statistics (p-value) without 'Missing' category	-	-	-	-	-	-	-	-	-	-	1.88 (0.1701)	1.34 (0.2479)	1.45 (0.2289)
CMV [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-
Folate deficiency [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-
Gestational diabetes [d]	5	1.93	9	2.31	***	***	***	***	14	2.16	0.11 (0.7425)	0.12 (0.7279)	0.09 (0.0902)[*]
Herpes simplex virus [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-
Rubella [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-
Toxoplasmosis [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-	-	-

	Paternal exposure group										Comparison		
CM Number of offspring	Valproate N=259		Lamotrigine/ levetiracetam N=389		Lamotrigine N=322		Levetiracetam N=67		Total (valproate + lamotrigine/ levetiracetam) N=648		Valproatevs Lamotrigine /levetiracetam N=648	Valproate vs Lamotrigine N=581	Valproate vs Levetiracetam N=326
											Test statistic (p-value)	Test statistic (p-value)	Test statistic (p-value)
Varicella [d]	***	***	***	***	***	***	***	***	***	***	1.00 (1.0000)*	1.00 (1.0000)*	1.00 (1.0000)*

CMV: cytomegalovirus; LMP2: last menstrual period + 2 weeks; NDD: neurodevelopmental disorders; SD: standard deviation
*** Masked values indicated that data was calculated but not disclosed due to small number of participants
Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
Differences between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5, Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not Normal.
a) at 22nd week of gestation; b) all available data prior to index date; c) 12 months lookback from LMP2; d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy).

Table 49 Association between potential paternal risk factors/confounders for CM by paternal exposure group; Secondary outcome cohort in Denmark (N=648)

	Paternal exposure group					Comparison		
CM Number of offspring	Valproate N=259	Lamotrigine/levetiracetam N=389	Lamotrigine N=322	Levetiracetam N=67	Total (valproate + lamotrigine/ levetiracetam) N=648	Valproate vs Lamotrigine /levetiracetam N=648	Valproate vs Lamotrigine N=581	Valproate vs Levetiracetam N=326
						Test statistic (p-value)	Test statistic (p-value)	Test statistic (p-value)
Paternal risk factors/confounders								

CM Number of offspring	Paternal exposure group Valproate N=259		Lamotrigine/levetiracetam N=389		Lamotrigine N=322		Levetiracetam N=67		Total (valproate + lamotrigine/ levetiracetam) N=648		Comparison Valproate vs Lamotrigine /levetiracetam N=648	Valproate vs Lamotrigine N=581	Valproate vs Levetiracetam N=326
											Test statistic (p-value)	Test statistic (p-value)	Test statistic (p-value)
Father´s age [a](categorical)													
≤20 years	***	***	***	***	***	***	***	***	***	***	-	-	-
21-25	***	***	31	7.97	***	***	***	***	***	***	-	-	-
26-30	75	28.96	101	25.96	82	25.47	19	28.36	176	27.16	-	-	-
31-35	108	41.70	149	38.30	119	36.96	30	44.78	257	39.66	-	-	-
36-40	39	15.06	78	20.05	68	21.12	10	14.93	117	18.06	-	-	-
>40	18	6.95	***	***	***	***	***	***	***	***	-	-	-
Test statistics	-	-	-	-	-	-	-	-	-	-	4.47 (0.4835)	5.61 (0.3459)	1.21 (0.9437)
Father´s age [a] (continuous)													
Mean (SD)	32.32 (5.29)	-	32.77 (5.33)	-	32.85 (5.43)	-	32.40 (4.86)	-	32.59 (5.31)	-	81505.50 (0.2757)*	72993.00 (0.2366)*	11118.50 (0.8116)*
Median (25th - 75th percentile)	32(29.00, 35.00)	-	32(29.00, 36.00)	-	32(29.00, 36.00)	-	32(30.00, 35.00)	-	32(29.00, 36.00)	-	-	-	-
Min, max	***	-	***	-	***	-	***	-	***	-	-	-	-
Year of offspring conception [b,c]													
2003-2007	119	45.95	84	21.59	76	23.60	8	11.94	203	31.33	-	-	-
2008-2012	78	30.12	129	33.16	109	33.85	20	29.85	207	31.94	-	-	-
2013-2018	62	23.94	176	45.24	137	42.55	39	58.21	238	36.73	-	-	-
Test statistics	-	-	-	-	-	-	-	-	-	-	49.10 (<.0001)	36.49 (<.0001)	35.98 (<.0001)

	Paternal exposure group					Comparison		
CM Number of offspring	Valproate N=259	Lamotrigine/levetiracetam N=389	Lamotrigine N=322	Levetiracetam N=67	Total (valproate + lamotrigine/ levetiracetam) N=648	Valproate vs Lamotrigine /levetiracetam N=648	Valproate vs Lamotrigine N=581	Valproate vs Levetiracetam N=326
						Test statistic (p-value)	Test statistic (p-value)	Test statistic (p-value)

NDD: neurodevelopmental disorders; SD: standard deviation

*** Masked values indicated that data was calculated but not disclosed due to small number of participants

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

Differences between categorical variables are tested using Chi-square independence test; however, if the frequency of any of the categories analysed is <5, Fisher's Exact test is used. Differences between continuous variables are tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable is not Normal.

a) at 22nd week of gestation; b) at mother's LMP2; c) calendar years are grouped in each country according to the length of the study period.

10.3.2.4 Association between potential risk factors/confounders and CM

Association between covariates (potential risk factors / confounders) and occurrence of CM was assessed in the Secondary outcome cohort for comparative analyses. Results of crude associations are shown in Table 50 to Table 52.

None of the offspring, maternal or paternal characteristics were associated with CM in Denmark.

Table 50 Association between potential offspring risk factors and congenital malformations (CM); Secondary outcome cohort in Denmark

CM	Overall		Event		Non-event		Event vs non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Offspring risk factors/confounders [a]								
Congenital CMV								
No	648	100.00	76	11.73	572	88.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital Herpes Simplex								
No	648	100.00	76	11.73	572	88.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital rubella								
No	648	100.00	76	11.73	572	88.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital toxoplasmosis								
No	648	100.00	76	11.73	572	88.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital varicella								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00, I)	0.00 (0.9887)
Foetal alcohol syndrome								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00, I)	0.00 (0.9880)

CM: congenital malformations; CMV: cytomegalovirus

*** Masked values indicated that data was calculated but not disclosed due to small number of participants

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's Exact test were used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable is not normal.

a) between 22nd week of gestation and exit date

Table 51 Association between potential maternal risk factors and congenital malformations (CM); Secondary outcome cohort in Denmark

CM	Overall		Event		Non-event		Event vs Non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Maternal risk factors/confounders								
Mother's age [a] (categorical)								
<=20 years	11	1.70	0	0.00	11	100.00	0.00 (0.00,I)	-
21-25	101	15.59	13	12.87	88	87.13	1.31 (0.64,2.68)	-
26-30	247	38.12	25	10.12	222	89.88	Reference	-
31-35	225	34.72	28	12.44	197	87.56	1.26 (0.71,2.24)	-
36-40	54	8.33	***	16.67	45	83.33	1.78 (0.78,4.06)	-
>40	10	1.54	***	***	***	***	0.99 (0.12,8.11)	-
Wald test	-	-	-	-	-	-	-	2.07,0.8387
Diabetes [b]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00,I)	0.00,0.9895
Obesity [c]								
No	639	98.61	***	***	***	***	Reference	-
Yes	9	1.39	***	***	***	***	2.18 (0.44,10.70)	0.92,0.3363
Alcohol abuse prior to LMP2 [c]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	7.61 (0.47,122.95)	2.04,0.1528
Alcohol abuse during pregnancy [d]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00,I)	0.00,0.9880
Substance abuse prior to LMP2 [c]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00,I)	0.00,0.9880
Substance abuse during pregnancy [d]								

CM	Overall		Event		Non-event		Event vs Non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00,I)	0.00,0.9880
Smoking prior to LMP2 [c]								
No	27	4.17	***	***	***	***	Reference	-
Yes	5	0.77	0	0.00	5	100.00	-	-
Missing	616	95.06	***	***	***	***	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	0.00,0.9630
Smoking during pregnancy [d]								
No	557	85.96	67	12.03	490	87.97	Reference	-
Yes	80	12.35	***	***	***	***	0.81 (0.37,1.76)	-
Missing	11	1.70	***	***	***	***	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	0.28,0.5992
CMV [d]								
No	648	100.00	76	11.73	572	88.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Folate deficiency [d]								
No	648	100.00	76	11.73	572	88.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Gestational diabetes [d]								
No	634	97.84	***	***	***	***	Reference	-
Yes	14	2.16	Diskr	Diskr	Diskr	Diskr	2.10 (0.57,7.69)	1.25,0.2644
Herpes simplex virus [d]								
No	648	100.00	76	11.73	572	88.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Rubella [d]								
No	648	100.00	76	11.73	572	88.27	-	-

CM	Overall		Event		Non-event		Event vs Non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Yes	0	0.00	0	0.00	0	0.00	-	-
Toxoplasmosis [d]								
No	648	100.00	76	11.73	572	88.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Varicella [d]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00,I)	0.00,0.9887

CM: Congenital Malformation; LMP2: Last Menstrual Period Date Plus 2 weeks; CMV: Cytomegalovirus
*** Masked values indicated that data was calculated but not disclosed due to small number of participants
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at 22nd week of gestation
b) all available data prior to index date
c) 12 months lookback from LMP2
d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)

Table 52 Association between potential paternal risk factors/confounders and congenital malformations (CM); Secondary outcome cohort in Denmark

CM	Overall		Event		Non-event		Association	
							OR (95% CI)	Test statistic (p-value)
Paternal risk factors/confounders for CM								
Father's age [a] (categorical)								
≤20 years	***	***	***	***	***	***	3.93 (0.35, 44.72)	-
21-25	***	***	***	***	***	***	0.71 (0.24,2.13)	-
26-30	176	27.16	22	12.50	154	87.50	1.12 (0.62, 2.03)	-
31-35	257	39.66	29	11.28	228	88.72	Reference	-
36-40	117	18.06	13	11.11	104	88.89	0.98 (0.49, 1.97)	-

CM	Overall		Event		Non-event		Association	
							OR (95% CI)	Test statistic (p-value)
>40	47	7.25	7	14.89	40	85.11	1.38 (0.56, 3.35)	-
Wald test	-	-	-	-	-	-	-	2.34(0.8008)
Year of offspring conception [b,c]								
2003-2007	203	31.33	24	11.82	179	88.18	Reference	-
2008-2012	207	31.94	25	12.08	182	87.92	1.02 (0.56, 1.86)	-
2013-2018	238	36.73	27	11.34	211	88.66	0.95 (0.53, 1.71)	-
Wald test	-	-	-	-	-	-	-	0.06(0.9705)

CM: congenital malformation; OR: Odds ratio; CI: confidence interval

*** Masked values indicated that data was calculated but not disclosed due to small number of participants

Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome were examined by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported. The largest group (most frequent) in each of the age variables was used as a reference in order to increase quality of Odds ratio estimation. a) at 22nd week of gestation; b) at mother's LMP2; c) calendar years are grouped in each country according to the length of the study period.

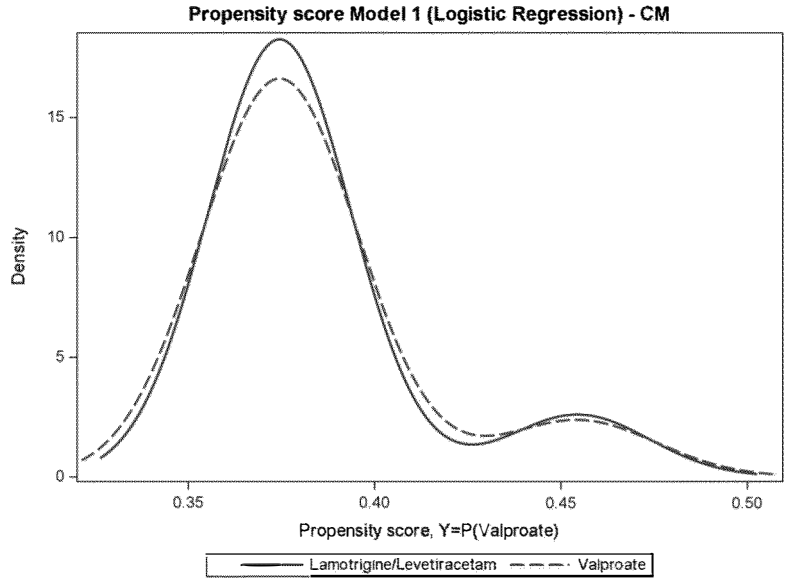
10.3.2.5 Variable estimates from propensity score

Variables pre-identified as risk factors/confounders in this study and associated with the study outcome in the univariate analyses were candidates for variable estimates from propensity score.

In the PS model estimated from logistic regression (Table 53), no offspring and maternal risk factors were associated with the paternal exposure to valproate or lamotrigine/levetiracetam.

Variable importance metric from random forest propensity score model and variable estimates from logistic regression informed by random forest propensity score model are not presented due to the fact that none of the offspring included in these models had any of the risk factors (i.e. offspring included had no risk factors and as a result the random forest propensity score and/or the logistic regression informed by random forest propensity score models could not be created and neither variable importance metric). Variable importance metric from random forest propensity score model and variable estimates from logistic regression informed by random forest propensity score model are not presented due to the fact that none of offspring included in these models had any of risk factors to construct to models (i.e. the offspring had no risk factor as a result cannot be created and neither variable importance metric).

The PS model that best achieved a balance in the weighted exposure groups after using inverse probability of treatment weights was the PS model estimated from logistic regression, as shown in in Figure 15 and Table 144. Thus, the logistic regression model was used to apply inverse probability of treatment weights in the effect estimation analysis.



CM: congenital malformation

Figure 15. Balance of Model 1 Logistic regression Secondary outcome in Denmark

Table 53. Variable estimates from logistic regression propensity score model; Secondary outcome cohort in Denmark

CM	Estimate		
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
Offspring risk factors/confounders			
Foetal alcohol syndrome [b]	0.00	0.00, I	0.9942
Maternal risk factors/confounders			
Alcohol abuse prior to LMP2 [c]	0.00	0.00, I	0.9918
Alcohol abuse during pregnancy [d]	-	-	-
Substance abuse prior to LMP2 [c]	0.00	0.00, I	0.9942
Substance abuse during pregnancy [d]	0.00	0.00, I	0.9942
Smoking during pregnancy [d]			
No	Reference	-	-
Yes	1.50	0.92, 2.45	0.1047
Gestational diabetes [d]	0.00	0.00, I	0.9850

Legend: Odds ratios (OR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.
a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.
b) between index and exit date
c) 12 months lookback from LMP2
d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)

10.3.2.6 Effect estimation for Congenital Malformation

The effect estimation for CM was assessed by using a crude logistic regression model as presented in (Table 54). In this model, 648 subjects were included, with 259 (40%) offspring in the valproate group and 389 (60%) in the lamotrigine/levetiracetam group, and no influential subjects were identified. The number of offspring with CM in the valproate and lamotrigine/levetiracetam group was 23 (8.9%) and 53 (13.6%), respectively. The OR of CM was 0.62 (95% CI: 0.37-1.04) between paternal exposure to valproate when compared to paternal exposure to lamotrigine/levetiracetam.

The effect estimation for CM using PS-weighted logistic model regression was assessed in a total of 619 offspring, with 238 (38.4%) offspring in the valproate group and 381 (61.6%) in the lamotrigine/levetiracetam group. The number of offspring with a CM in the valproate and lamotrigine/levetiracetam group was 21 (8.8%) and 52 (13.6%), respectively (data not shown). The OR of CM was 0.61 (95% CI: 0.36-1.06) between paternal exposure to valproate when compared to paternal exposure to lamotrigine/levetiracetam Table 55 presents the effect estimation for CM using PS-weighted logistic regression model adjusted for the K-means exposure cluster (i.e. trajectories with constant high exposure (A), and constant low exposure (B), for further details on the K-means cluster in the main analyses please see Figure 14. The estimate was assessed in a total of 619 offspring, with 388 in cluster

A (138 in valproate group and 250 in lamotrigine/levetiracetam group) and 231 (100 in valproate group and 131 in lamotrigine/levetiracetam group) in cluster B. The number of offspring with a CM in cluster A and cluster B was 42 (10 in the valproate group and 32 in the lamotrigine/levetiracetam group) and 31 (11 in the valproate group and 20 in the lamotrigine/levetiracetam group), respectively. The OR for CM was 0.68 (95% CI: 0.31, 1.48) for cluster A and 0.54 (95% CI: 0.26, 1.12) for cluster B, when comparing paternal exposure to valproate to those exposed to lamotrigine/levetiracetam. Likewise, no interaction between exposure and paternal K-means cluster was observed.

Table 54. Effect estimation for Congenital Malformations (CM) using crude logistic model; Secondary outcome cohort in Denmark

Variable	Total N	Number of events	Model estimates		
	N	N	OR	95% CI	P-value
Valproate	259	23			
Lamotrigine/levetiracetam	389	53			
Paternal exposure: valproate vs lamotrigine/levetiracetam	648		0.62	(0.37, 1.04)	0.0723

Table 55. Effect estimation for Congenital Malformations (CM) using Propensity Score-weighted logistic model; Secondary outcome cohort in Denmark

Variable	Total N	Number of events	Model estimates[1]		
			OR	95% CI	P-value
Valproate	238	21			
Lamotrigine/levetiracetam	381	52			
Paternal exposure: valproate vs lamotrigine/levetiracetam	619		0.61	(0.36, 1.06)	0.0810

Unbalanced variables after weighting were not entered in the model due to quasi-complete separation.

[1] **The logistic regression PS model includes all variables from table 54, following described: Offspring risk factors/confounders:** "Foetal alcohol syndrome"; **Maternal risk factors/confounders:** "Alcohol abuse prior to LMP2", "Alcohol abuse during pregnancy", "Substance abuse prior to LMP2", "Substance abuse during pregnancy", "Smoking during pregnancy", "Gestational diabetes"
LMP2: Last Menstrual Period Date Plus 2 weeks

Table 56. Effect estimation for Congenital Malformations (CM) using Propensity Score-weighted logistic model on offspring with concordant K-means exposure cluster; Secondary outcome cohort in Denmark

Variable	Total N	Number of events	Model estimates[1]		
			OR	95% CI	P-value
Valproate - cluster A	138	10			
Lamotrigine/levetiracetam - cluster A	250	32			
Valproate - cluster B	100	11			
Lamotrigine/levetiracetam - cluster B	131	20			
Paternal exposure: valproate vs lamotrigine/levetiracetam	619		-	-	0.0982

K-means exposure cluster:

Variable	Total N	Number of events	Model estimates[1]		
			OR	95% CI	P-value
K-means exposure cluster B	-		-	-	0.5004
Paternal exposure * cluster:					
Valproate * cluster B	-		-	-	0.6560
Effect of valproate across K-means cluster:					
Valproate vs lamotrigine/levetiracetam in cluster A	-		0.68	(0.31, 1.48)	-
Valproate vs lamotrigine/levetiracetam in cluster B	-		0.54	(0.26, 1.12)	-

OR: Odds ratio; CI: confidence Interval
Unbalanced variables after weighting were not entered in the model due to quasi-complete separation.
[1] **The logistic regression PS model includes all variables from table 54, following described: Offspring risk factors/confounders:** "Foetal alcohol syndrome"; **Maternal risk factors/confounders:** "Alcohol abuse prior to LMP2", "Alcohol abuse during pregnancy", "Substance abuse prior to LMP2", "Substance abuse during pregnancy", "Smoking during pregnancy", "Gestational diabetes"

Cluster A: constant high exposure, Cluster B: constant low exposure.

10.3.2.7 Exploratory Analyses – CM cohort

10.3.2.7.1 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Exploratory analysis 5 for CM)

Results from exploratory analysis 5 are presented in Table 166 to Table 171 in section 15.1.7. The analysis was performed in the Secondary outcome cohort for explorative objective 5, to answer Exploratory Objective 5, which aimed to describe the risk factors and frequency of CM in offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine/levetiracetam) and lamotrigine/levetiracetam (in combination with other AEDs excluding valproate) at the time of the conception.

For the exploratory analysis 5, the inclusion criterion was all offspring from the Secondary outcome cohort (N=3777). After additional exclusions, a total of 23 offspring were included in this analysis, with none in valproate and 23 in lamotrigine/levetiracetam group (Figure 32).

In exploratory analysis 5, the sample size was significantly lower than the main analysis, hence direct comparison with the main analysis was not possible. Majority of offspring in the lamotrigine/levetiracetam polytherapy group was male (56.5%) (Table 166). No comorbidities were reported in the lamotrigine/levetiracetam polypharmacy group (Table 167). Most of the offspring demographic and clinical characteristics were either zero or masked.

Median age of mothers at childbirth was 31 (IQR 28-34) years in the lamotrigine/levetiracetam polytherapy group (Table 168). No maternal comorbidities were reported in the lamotrigine/levetiracetam

polytherapy group (Table 169). Most of the maternal demographic and clinical characteristics were either zero or masked.

Median age of fathers was 34 (IQR 29-36) years in the lamotrigine/levetiracetam polypharmacy group (Table 170). Most of the paternal demographic and clinical characteristics were either zero or masked (Table 171).

10.3.2.7.2 Paternal exposure to valproate or lamotrigine/levetiracetam in discordant siblings (Exploratory analysis 6)

Results from exploratory analysis 6 are presented in Table 172 to Table 180 in section 15.1.8. The analysis was performed in the Secondary outcome cohort for explorative objective 6. This objective aimed to describe the risk factors and frequency of CM, in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception.

For the exploratory analyses 6, the inclusion criterion was all offspring from the Secondary outcome cohort for comparative analysis (N=648). After additional exclusions, <10 offspring were included in this analysis, with <5 in both the valproate and lamotrigine/levetiracetam groups (Figure 33). Therefore, frequencies and percentages for all offspring, maternal, and paternal characteristics were either zero or masked (Table 172-Table 180). No CM events were reported in this cohort (Table 173).

Results for exploratory analysis 8 are not reported in this final report. For further details please see section 9.9.2.4.3.

10.3.2.8 Sensitivity analyses for CM

Multiple sensitivity analyses were performed to examine the robustness of the main analysis finding. Summary tables of the main results for each of sensitivity analysis are presented in this section. All tables produced for each of the sensitivity analysis are presented in a separate document.

Overall, handling of missing CM diagnosis (sensitivity analysis 4), simple pairwise comparisons for the exposure groups (valproate vs lamotrigine, and valproate vs levetiracetam, sensitivity analysis 5), comparing PS-matched model with covariate adjusted model for the primary cohort (sensitivity analysis 6) and narrow case definition for secondary outcome (sensitivity analysis 9) were consistent with the results observed in the main analyses (see Table 57).

In sensitivity analysis 6, there were no patients with a CM after removing outliers, thus, it was not possible to perform logistic regression, and OR, 95%CI and p-values were not estimated.

In sensitivity analysis 10, the mean paternal cumulative exposure to valproate was 54.4 ±22.3 days, while in the lamotrigine/levetiracetam group mean paternal cumulative exposure was 59.3 ±23.8 days (see Table 58).

Table 57 Summary of main analysis and sensitivity analyses for the Secondary outcome cohort in Denmark

Analyses*	Population considered	OR (95% CI) estimates		OR (95% CI) estimates by cluster of exposure	
		Crude	Adjusted*	Cluster A	Cluster B
Main analysis N sample = 648	Please check Section 9.3	0.62 (0.37, 1.04)	0.61 (0.36, 1.06)	0.68 (0.31, 1.48)	0.54 (0.26, 1.12)
Sensitivity analysis 4 N sample = 648	Handling of missing CM diagnosis	0.62 (0.37, 1.04)	0.61 (0.36, 1.06)	0.68 (0.31, 1.48)	0.54 (0.26, 1.12)
Sensitivity analysis 5[A] N sample = 581	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	0.62 (0.36, 1.06)	0.61 (0.35, 1.07)	0.65 (0.29, 1.45)	0.54 (0.26, 1.16)
Sensitivity analysis 5[B] N sample = 326	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	0.62 (0.27, 1.42)	0.64 (0.27, 1.52)		
Sensitivity analysis 9 N sample =	Narrow case definition for secondary outcome	0.61 (0.34, 1.06)	0.61 (0.34, 1.06)	0.69 (0.32, 1.49)	0.51 (0.24, 1.10)

CI: Confidence Interval; OR: Odds ratio; **5[A]** analysis comparing valproate and lamotrigine; **5[B]** analysis comparing valproate and levetiracetam; *: the number of this event was 0 and **OR** could not be estimated***: The logistic regression PS models used in sensitivity analysis include variables following described: Sensitivyty analysis 1:** not applicable.
Sensitivyty analysis 4: Offspring risk factors/confounders: "Foetal alcohol syndrome"**; Maternal risk factors/confounders:** "Alcohol abuse prior to LMP2", "Alcohol abuse during pregnancy", "Substance abuse prior to LMP2", "Substance abuse during pregnancy", "Smoking during pregnancy", "Gestational diabetes"
Sensitivy analalysis 5[A]: Offspring risk factors/confounders: "Foetal alcohol syndrome"; **Maternal risk factors/confounders:** "Alcohol abuse prior to LMP2", "Alcohol abuse during pregnancy", Substance abuse prior to LMP2", "Smoking during pregnancy"
Sensitivy analalysis 5[B]: Offspring risk factors/confounders: "Congenital varicella" **Maternal risk factors/confounders:** "Diabetes", "Obesity", "Substance abuse during pregnancy", Varicella during pregnancy"
Sensitivy analysis 9: Offspring risk factors/confounders: "Foetal alcohol syndrome"; **Maternal risk factors/confounders:** "Alcohol abuse during pregnancy", "Substance abuse during pregnancy", "Smoking during pregnancy", "Gestational diabetes"

Table 58. Paternal cumulative exposure to Antiepileptic drugs (AEDs) by paternal exposure group; Secondary outcome cohort in Denmark

Paternal exposure group										
CM **Number of offspring**	**Valproate** **N=793**		**Lamotrigine/levetiracetam** **N=1157**		**Lamotrigine** **N=**		**Levetiracetam** **N=**		**Total (valproate + lamotrigine/levetiracetam)** **N=1950**	
Cumulative exposure to AEDs										
Low	86	33.20	130	33.42	108	33.54	22	32.84	215	33.18
Medium	87	33.59	128	32.90	107	33.23	23	34.33	216	33.33
High	86	33.20	131	33.68	107	33.23	22	32.84	217	33.49
Mean (SD)	54.35 (22.28)		59.27 (23.79)		59.05 (24.05)		60.30 (22.65)		57.30 (23.30)	
Median (25th - 75th percentile)	56(37.00, 75.00)		62.33(42.33, 84.00)		62.17(42.33, 84.00)		62.67(41.00, 84.00)		59.33(39.67, 82.50)	
Min, max	***		***		***		***		***	

AED: antiepileptic drugs; NDD: neurodevelopmental disorders; SD: Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
*** Masked values indicated that data was calculated but not disclosed

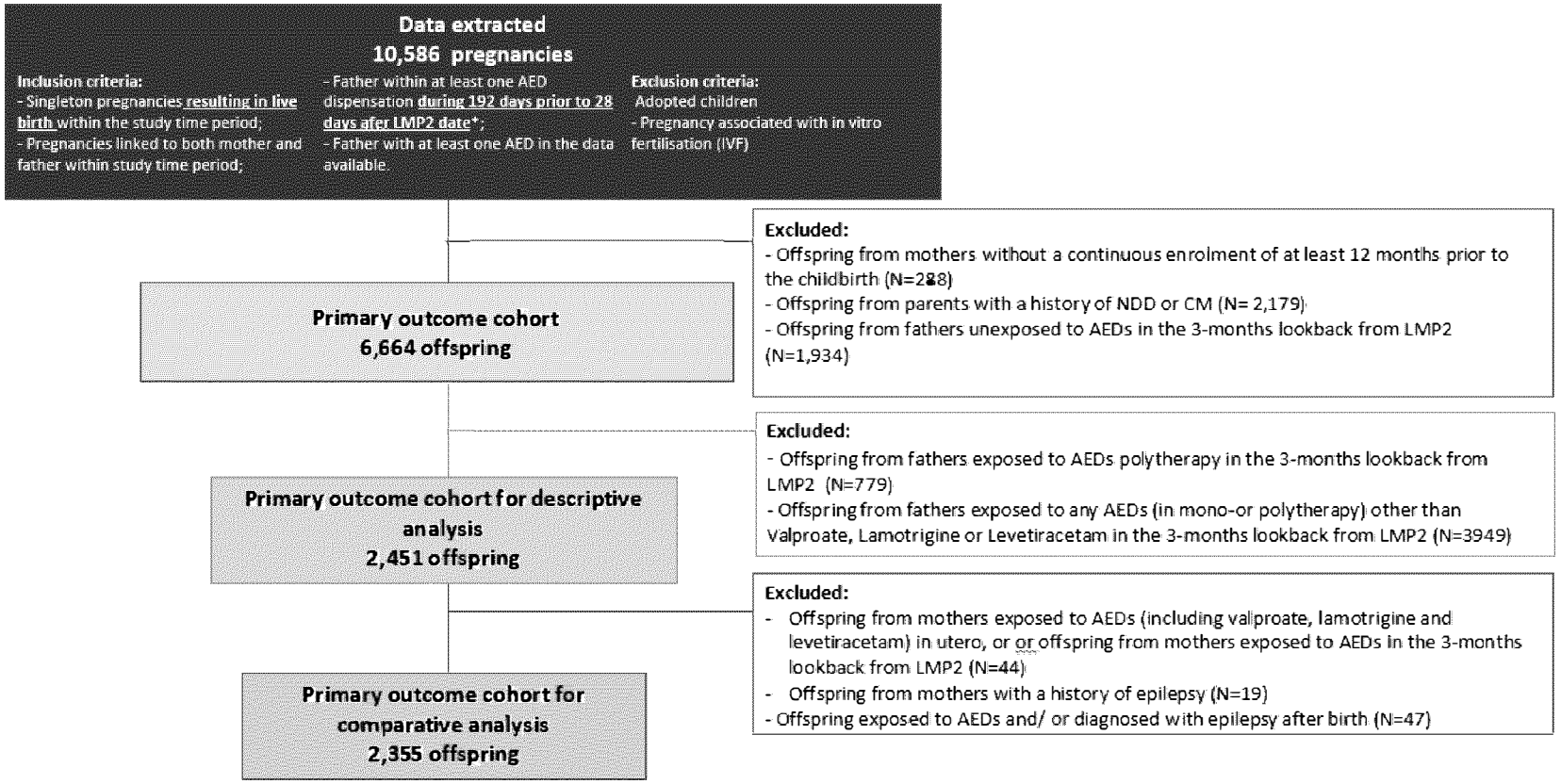
10.4 Results for Sweden

After applying all the inclusion and exclusion criteria, a total of 10,586 pregnancies were identified in databases in Sweden. Subsequently additional exclusion criteria, not mutually exclusive, were applied to obtain the populations used for the descriptive and comparative analysis for each outcome, separately.

Please note that during stepwise exclusions from the cohorts post data extraction (Primary outcome cohort), some characteristics were absent as they were either one of the exclusion criteria or characteristics associated with the exclusion criteria. Offspring with epilepsy fathers exposed to other AEDs than those of interest, and mothers exposed to AEDs or with a history of epilepsy are examples of these characteristics. Although these populations are described in this report, they are not part of the comparative analysis.

The study population of the Primary outcome cohort is depicted in Figure 16.

From all the 10586 pregnancies identified, the following were excluded: offspring from a mother without a continuous enrolment in database of at least 12 months prior to the childbirth (N=288), offspring from parents with a history of NDD or CM (N=2,179), offspring paternally unexposed to AEDs in the 3 months lookback period from LMP2 (N=1,934). Thus, the Primary outcome cohort consisted of 6,664 offspring. Briefly, there were 2,451 offspring included in the Primary outcome cohort for descriptive analyses, and 2,355 offspring in the Primary outcome cohort for comparative analyses.



AED: antiepileptic drug; LMP2: last menstrual period + 2 weeks
* LMP2: last menstrual period + 2 weeks. Note Swedish data holders requested to narrow down the population as much as possible for the extraction.
** The same child can be counted in different exclusion categories, explaining why numbers do not necessarily add up

CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 16: Study population of the Primary outcome cohort in Sweden

10.4.1 Neurodevelopmental disorders including autism spectrum disorder

10.4.1.1 Description of the offspring, maternal and paternal characteristics by paternal exposure group

This section presents demographic and clinical characteristics of offspring, mothers, and fathers according to paternal exposure in monotherapy to valproate, lamotrigine or levetiracetam, and the comparator group of composite lamotrigine/levetiracetam monotherapy. This analysis was performed in the Primary outcome cohort for descriptive analyses, which is described in Figure 16.

Table 59 shows offspring demographic characteristics of the Primary outcome cohort for descriptive analyses by paternal exposure group. A total of 968 offspring paternally exposed to valproate and 1483 offspring paternally exposed to lamotrigine / levetiracetal were included. Overall, the majority of offspring were male (51.2%) (50.1% in those paternally exposed to valproate and 52.0% in those paternally exposed to lamotrigine/levetiracetam) , born at term between 37-41 weeks of gestational age (88.5%, similar in both exposure groups) and weighing ≥2500 g (96.3%, similar in both exposure groups). The total offspring-years of follow-up was 13975.9, (6483.2 for valproate and 7492.6 for lamotrigine/levetiracetam group) and the mean follow-up in years per offspring was 6.7 for the valproate group and 5.1 for the lamotrigine/levetiracetam group (Table 59). The high proportions of offspring paternally exposed to valproate were conceived in the earlier years (from 2007-2015) of the study follow-up, in contrast to the lamotrigine and levetiracetam group where the highest proportions were observed in the more recent years of study follow-up (from 2014-2019).

Regarding clinical characteristics of offspring by paternal exposure to valproate and lamotrigine/levetiracetam groups, 2.1% of offspring paternally exposed to valproate and 1.4% paternally exposed to lamotrigine/levetiracetam were diagnosed with epilepsy. Exposure to AEDs between index and exit date was 2.2% among offspring paternally exposed to valproate and 1.3% among offspring paternally exposed to lamotrigine/levetiracetam.

The diagnosis of NDD including ASD, occurred in 5.4% of offspring paternally exposed to valproate and in 3.5% of offspring paternally exposed to lamotrigine/levetiracetam. The median (IQR) age in years at the first diagnosis of NDD including ASD was 6.2 (4.1, 8.7) for the valproate and 5.2 (3.4, 8.2) for the lamotrigine/levetiracetam group (Table 60).

ASD as the first NDD diagnosis, during all the study period, was observed in 1.7% of offspring paternally exposed to valproate and in 0.6% of offspring paternally exposed to lamotrigine/levetiracetam. All ASD diagnoses, this is, ever and not only as a first diagnosis, were observed in 2.2% of offspring paternally exposed to valproate and in 0.9% of offspring paternally exposed to lamotrigine/levetiracetam. The

median (IQR) age in years at the first diagnosis of ASD was 6.3 (5.1, 9.9) for offspring paternally exposed to valproate and 4.5 (3.6, 5.8) for offspring paternally exposed to lamotrigine/levetiracetam.

Table 59 Offspring demographic characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Sweden (N=2,451)

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=968**		**N=1483**		**N=1262**		**N=221**		**N=2451**	
	N	%	N	%	N	%	N	%	N	%
Gestational age (weeks)										
<28 (extremely preterm)	3	0.31	1	0.07	1	0.08	0	0.00	4	0.16
28-31 (very preterm)	6	0.62	11	0.74	9	0.71	2	0.90	17	0.69
32-36 (moderate to late preterm)	39	4.03	61	4.11	49	3.88	12	5.43	100	4.08
37-41 (at term)	858	88.64	1310	88.33	1120	88.75	190	85.97	2168	88.45
≥42 (post-term)	62	6.40	100	6.74	83	6.58	17	7.69	162	6.61
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	2	0.21	0	0.00	0	0.00	0	0.00	2	0.08
1000-1499 (very low)	6	0.62	7	0.47	4	0.32	3	1.36	13	0.53
1500-2499 (low)	33	3.41	41	2.76	33	2.61	8	3.62	74	3.02
≥2500	927	95.76	1433	96.63	1223	96.91	210	95.02	2360	96.29
Missing	0	0.00	2	0.13	2	0.16	0	0.00	2	0.08
Gender[a]										
Male	485	50.10	771	51.99	668	52.93	103	46.61	1256	51.24
Female	483	49.90	712	48.01	594	47.07	118	53.39	1195	48.76
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of birth										
2007	91	9.40	42	2.83	39	3.09	3	1.36	133	5.43
2008	82	8.47	58	3.91	52	4.12	6	2.71	140	5.71
2009	87	8.99	69	4.65	65	5.15	4	1.81	156	6.36
2010	75	7.75%	85	5.73	82	6.50	3	1.36	160	6.53
2011	74	7.64	105	7.08	94	7.45	11	4.98	179	7.30

	Paternal exposure group									
NDD Number of offspring	Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
2012	80	8.26	107	7.22	99	7.84	8	3.62	187	7.63
2013	77	7.95	107	7.22	94	7.45	13	5.88	184	7.51
2014	93	9.61	124	8.36	106	8.40	18	8.14	217	8.85
2015	77	7.95	148	9.98	120	9.51	28	12.67	225	9.18
2016	68	7.02	140	9.44	114	9.03	26	11.76	208	8.49
2017	67	6.92	166	11.19	136	10.78	30	13.57	233	9.51
2018	49	5.06	153	10.32	119	9.43	34	15.38	202	8.24
2019	48	4.96	179	12.07	142	11.25	37	16.74	227	9.26
Total number of years of follow-up	6483.28		7492.64		6655.62		837.02		13975.92	
Mean follow-up year	6.7		5.05		5.27		3.79		5.7	

NDD: neurodevelopmental disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth).

Table 60 Offspring clinical characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Sweden (N=2451)

	Paternal exposure group									
NDD Number of offspring	Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
Comorbidities[a]										
Congenital CMV	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04
Congenital rubella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Epilepsy	20	2.07	21	1.42	20	1.58	1	0.45	41	1.67

NDD Number of offspring	Paternal exposure group									
	Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
Foetal alcohol syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fragile X syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lejeune/cri du chat syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tuberous sclerosis	2	0.21	2	0.13	2	0.16	0	0.00	4	0.16
Medication use										
Exposure to AEDs[a]	21	2.17	19	1.28	18	1.43	1	0.45	40	1.63
Outcomes										
ASD (ever, not only as first diagnosis)	21	2.17	13	0.88	12	0.95	1	0.45	34	1.39
ASD (as first diagnosis)	16	1.65	9	0.61	8	0.63	1	0.45	25	1.02
NDD including ASD	52	5.37	52	3.51	44	3.49	8	3.62	104	4.24
Outcomes (ICD-10 codes, ever)[b]										
Intellectual Disability - Mild	3	0.31	4	0.27	3	0.24	1	0.45	7	0.29
Intellectual Disability - Moderate	4	0.41	1	0.07	1	0.08	0	0.00	5	0.20
Intellectual Disability -Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Intellectual Disability -Profound	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04
Other Intellectual Disability	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04
Unspecified Intellectual Disability	2	0.21	5	0.34	5	0.40	0	0.00	7	0.29
Specific developmental disorders of speech and language	11	1.14	9	0.61	6	0.48	3	1.36	20	0.82
Specific developmental disorders of scholastic skills	1	0.10	0	0.00	0	0.00	0	0.00	1	0.04
Mixed specific developmental delays	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

NDD Number of offspring	Paternal exposure group									
	Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
Pervasive developmental disorders	21	2.17	13	0.88	12	0.95	1	0.45	34	1.39
Other disorders of psychological development	1	0.10	0	0.00	0	0.00	0	0.00	1	0.04
Unspecified disorder of psychological development	1	0.10	4	0.27	3	0.24	1	0.45	5	0.20
Mental disorder, not otherwise specified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dyslexia and other symbolic dysfunctions, not elsewhere classified	1	0.10	3	0.20	2	0.16	1	0.45	4	0.16
Hyperkinetic disorders	26	2.69	25	1.69	22	1.74	3	1.36	51	2.08
Other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tic disorders	2	0.21	8	0.54	8	0.63	0	0.00	10	0.41
Specific developmental disorder of motor function	4	0.41	5	0.34	4	0.32	1	0.45	9	0.37
Stereotyped movement disorders	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Essential tremor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other specified forms of tremor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Myoclonus	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04
Other chorea	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other specified extrapyramidal and movement disorders	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Extrapyramidal and	1	0.10	0	0.00	0	0.00	0	0.00	1	0.04

NDD Number of offspring	Paternal exposure group									
	Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
movement disorder, unspecified										
Idiopathic nonfamilial dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Spasmodic torticollis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Idiopathic orofacial dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blepharospasm	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dystonia, unspecified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Extrapyramidal and movement disorders in diseases classified elsewhere	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Age at the first diagnosis (years)										
ASD (ever, not only as first diagnosis) [c,d]										
0-1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2-3	3	0.31	5	0.34	4	0.32	1	0.45	8	0.33
4-5	7	0.72	5	0.34	5	0.40	0	0.00	12	0.49
6-7	2	0.21	2	0.13	2	0.16	0	0.00	4	0.16
8-9	5	0.52	1	0.07	1	0.08	0	0.00	6	0.24
10-11	4	0.41	0	0.00	0	0.00	0	0.00	4	0.16
Total (offspring with the outcome)	21	2.17	13	0.88	12	0.96	1	0.45	34	1.38
Offspring without a diagnosis	947	97.83	1470	99.12	1250	99.05	220	99.55	2417	98.61
Mean (SD)	7.10 (2.80)		4.77 (1.73)		4.94 (1.69)		2.79 (-)		6.21 (2.68)	
Median (25^{th} - 75^{th} percentile)	6.31 (5.13, 9.90)		4.53 (3.64, 5.78)		4.78 (3.75, 5.95)		2.79 (2.79, 2.79)		5.66 (4.05, 8.55)	

NDD Number of offspring	Paternal exposure group: Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
Min, max	2.97, 11.84		2.27, 8.63		2.27, 8.63		2.79, 2.79		2.27, 11.84	
NDD including ASD[c,d]										
0-1	5	0.52	6	0.40	5	0.40	1	0.45	11	0.45
2-3	8	0.83	10	0.67	8	0.63	2	0.90	18	0.73
4-5	11	1.14	11	0.74	9	0.71	2	0.90	22	0.90
6-7	11	1.14	10	0.67	10	0.79	0	0.00	21	0.86
8-9	10	1.03	12	0.81	9	0.71	3	1.36	22	0.90
10-11	7	0.72	3	0.20	3	0.24	0	0.00	10	0.41
Total (offspring with the outcome)	52	5.38	52	3.49	44	3.48	8	3.61	104	4.25
Offspring without a diagnosis	916	94.63 %	1431	96.49%	1218	96.51%	213	96.38%	2347	95.76 %
Mean (SD)	6.44 (2.99)		5.67 (3.08)		5.73 (2.95)		5.38 (3.49)		6.06 (3.01)	
Median (25^{th} - 75^{th} percentile)	6.23 (4.12, 8.74)		5.16 (3.41, 8.24)		5.62 (3.57, 8.21)		4.71 (2.45, 9.00)		6.06 (3.72, 8.58)	
Min, max	0.71, 11.90		0.03, 11.30		0.03, 11.30		0.88, 9.87		0.03, 11.90	

AED: antiepileptic drug; ASD: autism spectrum disorders; CMV: cytomegalovirus; NDD: neurodevelopmental disorders; SD: standard deviation

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between index (childbirth) and exit date; b) ICD-10 codes refer to all records of NDD including ASD during the entire follow-up. Since offspring might have more than one distinct ICD-10 code, the sum of the distinct ICD-10 codes might not coincide with the total number of offspring with the composite outcome; c) categories may be adapted according to the data; d) denominator for the percentage was the number of offspring with the outcome.

Overall, the median (IQR) age of mothers from the Primary outcome cohort for descriptive analyses at childbirth was 31 (27, 35) years, similar for both exposure groups (Table 61). The most prevalent maternal clinical characteristics prior to childbirth were neurotic disorder observed in 9.8% and 13.1% of mothers of offspring paternally exposed to valproate and lamotrigine/levetiracetam, affective disorder observed in 9.0% and in 10.5% of mothers, and gestational diabetes observed in 2.7% and 3.2%, respectively (Table 62).

Regarding maternal characteristics of 2,451 offspring in the Primary outcome cohort for descriptive analyses, 14.1% had a record of smoking 3 months before LMP2 (16.3% in the valproate group, and 12.7% in the lamotrigine/levetiracetam group) and 6.4% of smoking during pregnancy (7.9% in the valproate group, and 5.5% in the lamotrigine/levetiracetam group). Maternal exposure to AEDs was uncommon, and the proportion of use of each AED was <1% for most of individual AED both before LMP2 and during pregnancy. Similar results were observed in the valproate and lamotrigine/levetiracetam group exposure groups, except for lamotrigine exposure (1.4% of mothers were exposed to lamotigine prior to LMP2 in the lamotrigine/levetiracetam group vs. 0.6% in the valproate group prior to LMP2, and these numbers were 1.2% vs. 0.5% during pregnancy, respectively) (Table 62). Regarding the concomitant medications associated with neuropsychiatric adverse events during pregnancy, this was similar among the exposed groups: 42.8% of mothers of offspring paternally exposed to valproate, and 46.7% of mothers of offspring paternally exposed to lamotrigine/levetiracetam had at least one prescription (Table 62).

Regarding paternal demographic characteristics, the overall median (IQR) age of fathers at childbirth was 34 (30-38) years, similar in both exposure groups. The highest proportion of offspring paternally exposed to valproate was conceived in 2014, during the earlier years of the study inclusion (2006-2015), in contrast to the lamotrigine/levetiracetam group where the highest proportions were observed in the more recent years of study inclusion (2011-2019) (Table 63).

Among fathers exposed to valproate, 13.5% presented neurotic disorder, 12.9% presented bipolar affective disorder and 11.1% affective disorder excluding bipolar and mania. Among fathers exposed to lamotrigine/levetiracetam, proportions were generally higher with 30.3% presenting affective disorder excluding bipolar disorder and mania, 29.5% presenting bipolar affective disorder and 27.4% neurotic disorder (Table 64). The most frequent indication[15] for AED treatment was epilepsy (70.7% in the valproate group compared to 46.1% in the lamotrigine/levetiracetam group) (Table 64).

In this study, clusters of fathers with homogenous trajectories of drug intake during the assessment period were identified, using the number of DDDs in every 14 days interval and grouping fathers with similar trajectories of this metric over time. Since it was assumed that treated fathers were exposed to 1 WHO DDD per day, the number of DDDs in each 14-days interval also coincided with the number of days

[15] Since indications for medications are not available in all the data sources used for this study, the indication for AEDs was estimated based on medical history. The following indications were considered for the three AEDs of interest (valproate, lamotrigine, levetiracetam): epilepsy, bipolar disorder and mania, other/unknown. The entire medical history for each father will be considered up to LMP2 (exclusive) to identify diagnosis records of epilepsy and bipolar disorder/mania. In case more than one diagnosis was found (e.g. epilepsy and bipolar disorder), only one indication was selected, with priority given to epilepsy, followed by bipolar disorder. In case none of these diagnoses are found in the medical history, the indication was considered "other/unknown".

covered in the same period (e.g. 10 DDDs=10 days covered in a specific 14-days interval). The longitudinal K-means clustering algorithm was applied to create K-means clusters with homogenous trajectories, as empirically driven by the data. No assumption about the number of clusters was made prior to running the algorithm.

The K-means algorithm, analysing DDD trajectories in fathers exposed to AEDs 3 months prior to conception (i.e. prior to LMP2) identified 3 different clusters A, B, and C (Figure 17), one constant high exposure (A), low-to-high exposure (B), and high-to-low exposure (C). In the valproate group, 41.3% were in cluster A, 30.9% were in cluster B, and 27.8% were cluster C. In the lamotrigine/levetiracetam group, 43.0% were in cluster A, 33.3% were in cluster B, and 23.7% were in cluster C (Table 64).

Table 61 Maternal demographic characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Sweden (N=2451)

	Paternal exposure group									
NDD	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=968		N=1483		N=1262		N=221		N=2451	
	N	%	N	%	N	%	N	%	N	%
Mother's age[a]										
≤20 years	20	2.07	24	1.62	21	1.66	3	1.36	44	1.80
21-25	150	15.50	177	11.94	154	12.20	23	10.41	327	13.34
26-30	301	31.10	442	29.80	376	29.79	66	29.86	743	30.31
31-35	298	30.79	489	32.97	413	32.73	76	34.39	787	32.11
36-40	168	17.36	305	20.57	259	20.52	46	20.81	473	19.30
>40	31	3.20	46	3.10	39	3.09	7	3.17	77	3.14
Mean (SD)	30.72 (5.29)		31.40 (5.24)		31.38 (5.23)		31.54 (5.25)		31.13 (5.27)	
Median (25th - 75th percentile)	31 (27.00, 35.00)		31 (28.00, 35.00)		31(28.00, 35.00)		32 (28.00, 35.00)		31 (27.00, 35.00)	
Min, max	18.00, 45.00		16.00, 53.00		16.00, 53.00		19.00, 48.00		16.00, 53.00	
Missing	-		-		-		-		-	

NDD: neurodevelopmental disorders; SD: standard deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. a) at index (childbirth).

Table 62 Maternal clinical characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Sweden (N=2451)

	Paternal exposure group									
NDD	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=968		N=1483		N=1262		N=221		N=2451	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										

NDD Number of offspring	Paternal exposure group Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/ levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
Affective disorder[a]	87	8.99	156	10.52	138	10.94	18	8.14	243	9.91
Diabetes[a]	11	1.14	18	1.21	17	1.35	1	0.45	29	1.18
Epilepsy[a]	8	0.83	11	0.74	11	0.87	0	0.00	19	0.78
Neurotic disorder[a]	95	9.81	194	13.08	167	13.23	27	12.22	289	11.79
Schizophrenia, schizotypal and delusional disorders[a]	4	0.41	5	0.34	4	0.32	1	0.45	9	0.37
Obesity[b]	11	1.14	16	1.08	15	1.19	1	0.45	27	1.10
CMV[c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gestational diabetes[c]	26	2.69	47	3.17	40	3.17	7	3.17	73	2.98
Rubella[c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lifestyle characteristics										
Alcohol abuse prior to LMP2[b]	9	0.93	2	0.13	2	0.16	0	0.00	11	0.45
Alcohol abuse during pregnancy[c]	1	0.10	2	0.13	1	0.08	1	0.45	3	0.12
Substance abuse prior to LMP2[b]	5	0.52	4	0.27	2	0.16	2	0.90	9	0.37
Substance abuse during pregnancy[c]	2	0.21	2	0.13	1	0.08	1	0.45	4	0.16
Smoking prior to LMP2[d]										
Yes	158	16.32	188	12.68	156	12.36	32	14.48	346	14.12
No	768	79.34	1211	81.66	1034	81.93	177	80.09	1979	80.74
Missing	42	4.34	84	5.66	72	5.71	12	5.43	126	5.14
Smoking during pregnancy[c]										
Yes	76	7.85	81	5.46	69	5.47	12	5.43	157	6.41
No	864	89.26	1357	91.50	1155	91.52	202	91.40	2221	90.62
Missing	28	2.89	45	3.03	38	3.01	7	3.17	73	2.98
Medication use										
Exposure to AEDs prior to LMP2[d]										
Valproic Acid	1	0.10	3	0.20	3	0.24	0	0.00	4	0.16

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=968		N=1483		N=1262		N=221		N=2451	
	N	%	N	%	N	%	N	%	N	%
Lamotrigine	6	0.62	21	1.42	20	1.58	1	0.45	27	1.10
Levetiracetam	1	0.10	0	0.00	0	0.00	0	0.00	1	0.04
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives[e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	2	0.13	2	0.16	0	0.00	2	0.08
Carboxamide derivatives	1	0.10	2	0.13	2	0.16	0	0.00	3	0.12
Fatty acid derivatives	1	0.10	3	0.20	3	0.24	0	0.00	4	0.16
Other antiepileptics	10	1.03	24	1.62	23	1.82	1	0.45	34	1.39
Exposure to AED during pregnancy[c]										
Valproic Acid	2	0.21	3	0.20	3	0.24	0	0.00	5	0.20
Lamotrigine	5	0.52	18	1.21	18	1.43	0	0.00	23	0.94
Levetiracetam	1	0.10	0	0.00	0	0.00	0	0.00	1	0.04
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives[e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04
Carboxamide derivatives	0	0.00	2	0.13	2	0.16	0	0.00	2	0.08
Fatty acid derivatives	2	0.21	3	0.20	3	0.24	0	0.00	5	0.20
Other antiepileptics	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
K-means cluster prior to LMP2[d]										
unexposed	956	98.76	1455	98.11	1235	97.86	220	99.55	2411	98.37
Cluster A[1]	6	0.62	20	1.35	20	1.58	0	0.00	26	1.06

NDD Number of offspring	Paternal exposure group Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/ levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
Cluster B[1]	6	0.62	8	0.54	7	0.55	1	0.45	14	0.57
K-means cluster during pregnancy[c]										
unexposed	959	99.07	1458	98.31	1237	98.02	221	100.00	2417	98.61
Cluster A[2]	7	0.72	17	1.15	17	1.35	0	0.00	24	0.98
Cluster B[2]	2	0.21	8	0.54	8	0.63	0	0.00	10	0.41
Maternal polypharmacy index prior to LMP2[d]										
0	644	66.53	995	67.09	843	66.80	152	68.78	1639	66.87
1-4	302	31.20	453	30.55	386	30.59	67	30.32	755	30.80
5-10	22	2.27	34	2.29	32	2.54	2	0.90	56	2.28
>10	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04
Mean (SD)	0.67 (1.25)		0.66 (1.24)		0.68 (1.28)		0.53 (0.99)		0.66 (1.25)	
Median (25th - 75th percentile)	0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)	
Min, max	0.00, 9.00		0.00, 11.00		0.00, 11.00		0.00, 6.00		0.00, 11.00	
Maternal polypharmacy index during pregnancy[c]										
0	505	52.17	717	48.35	603	47.78	114	51.58	1222	49.86
1-4	439	45.35	714	48.15	610	48.34	104	47.06	1153	47.04
5-10	24	2.48	50	3.37	47	3.72	3	1.36	74	3.02
>10	0	0.00	2	0.13	2	0.16	0	0.00	2	0.08
Mean (SD)	0.93 (1.34)		1.05 (1.48)		1.09 (1.53)		0.82 (1.14)		1.01 (1.43)	
Median (25th - 75th percentile)	0 (0.00, 1.00)		1 (0.00, 2.00)		1 (0.00, 2.00)		0 (0.00, 1.00)		1 (0.00, 2.00)	
Min, max	0.00, 9.00		0.00, 13.00		0.00, 13.00		0.00, 7.00		0.00, 13.00	

	Paternal exposure group									
NDD Number of offspring	Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/ levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
Concomitant medications associated with valproate-indicated psychiatric conditions prior toLMP2[b]- mothers with at least one prescription	111	11.47	219	14.77	198	15.69	21	9.50	330	13.46
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy[c]- mothers with at least 1 prescription	62	6.40	125	8.43	115	9.11	10	4.52	187	7.63
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2[b]-mothers with at least one prescription	598	61.78	909	61.29	780	61.81	129	58.37	1507	61.49
Concomitant medications associated with neuropsychiatric adverse events during pregnancy[c]-mothers with at least one prescription	414	42.77	693	46.73	594	47.07	99	44.80	1107	45.17

AED: antiepileptic drug; CMV: cytomegalovirus; NDD: neurodevelopmental disorders; SD: standard deviation; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth); b) 12 months lookback from LMP2; c) during pregnancy (from LMP2 until index date); d) 3 months lookback from LMP2; e) Oxazolidine derivatives were not marketed in Sweden.
Cluster A^1: constant high exposure, Cluster B^1: constant low exposure
Cluster A^2: constant low exposure, Cluster B^2: constant high exposure

Table 63 Paternal demographic characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Sweden (N=2451)

	Paternal exposure group

NDD	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=968		N=1483		N=1262		N=221		N=2451	
	N	%	N	%	N	%	N	%	N	%
Father's age[a]										
≤20 years	6	0.62	9	0.61	9	0.71	0	0.00	15	0.61
21-25	72	7.44	80	5.39	63	4.99	17	7.69	152	6.20
26-30	217	22.42	298	20.09	257	20.36	41	18.55	515	21.01
31-35	324	33.47	521	35.13	452	35.82	69	31.22	845	34.48
36-40	233	24.07	368	24.81	313	24.80	55	24.89	601	24.52
>40	116	11.98	207	13.96	168	13.31	39	17.65	323	13.18
Mean (SD)	33.61 (6.04)		34.31 (6.19)		34.19 (5.94)		35.00 (7.42)		34.03 (6.14)	
Median (25th - 75th percentile)	33(29.00, 38.00)		34(30.00, 38.00)		34(30.00, 38.00)		34(30.00, 39.00)		34(30.00, 38.00)	
Min, max	17.00, 63.00		16.00, 77.00		16.00, 70.00		21.00, 77.00		16.00, 77.00	
Year of offspring conception[b]										
2006	67	6.92	32	2.16	30	2.38	2	0.90	99	4.04
2007	83	8.57	56	3.78	49	3.88	7	3.17	139	5.67
2008	89	9.19	60	4.05	56	4.44	4	1.81	149	6.08
2009	77	7.95	88	5.93	85	6.74	3	1.36	165	6.73
2010	73	7.54	99	6.68	89	7.05	10	4.52	172	7.02
2011	72	7.44	104	7.01	97	7.69	7	3.17	176	7.18
2012	85	8.78	102	6.88	94	7.45	8	3.62	187	7.63
2013	85	8.78	132	8.90	111	8.80	21	9.50	217	8.85
2014	90	9.30	120	8.09	98	7.77	22	9.95	210	8.57
2015	61	6.30	160	10.79	131	10.38	29	13.12	221	9.02
2016	73	7.54	158	10.65	129	10.22	29	13.12	231	9.42
2017	47	4.86	162	10.92	127	10.06	35	15.84	209	8.53
2018	56	5.79	161	10.86	123	9.75	38	17.19	217	8.85
2019	10	1.03	49	3.30	43	3.41	6	2.71	59	2.41

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=968		N=1483		N=1262		N=221		N=2451	
	N	%	N	%	N	%	N	%	N	%

NDD: neurodevelopmental disorders; SD: standard deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth); b) at mother's LMP2.

Table 64 Paternal clinical characteristics by paternal exposure group; Primary outcome cohort for descriptive analyses in Sweden (N=2451)

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=968		N=1483		N=1262		N=221		N=2451	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Affective disorder excl. bipolar disorder and mania[a]	107	11.05	450	30.34	441	34.94	9	4.07	557	22.73
Bipolar affective disorder[a]	125	12.91	437	29.47	437	34.63	0	0.00	562	22.93
Mania[a]	14	1.45	20	1.35	20	1.58	0	0.00	34	1.39
Neurotic disorder[a]	131	13.53	407	27.44	390	30.90	17	7.69	538	21.95
Schizophrenia, schizotypal and delusional disorders[a]	39	4.0	52	3.51	48	3.80	4	1.81	91	3.71
Lifestyle characteristics										
Substance abuse[b]	13	1.34	10	0.67	7	0.55	3	1.36	23	0.94
Medication use										
AED indication [d]										
Epilepsy	684	70.66	683	46.06	493	39.06	190	85.97	1367	55.77
Bipolar affective disorder and mania	124	12.81	429	28.93	429	33.99	0	0.00	553	22.56
Other/unknown	160	16.53	371	25.02	340	26.94	31	14.03	531	21.66
K-means cluster[c]										
Cluster A	400	41.32	637	42.95	528	41.84	109	49.32	1037	42.31
Cluster B	299	30.89	494	33.31	427	33.84	67	30.32	793	32.35

NDD Number of offspring	Paternal exposure group Valproate N=968		Lamotrigine/levetiracetam N=1483		Lamotrigine N=1262		Levetiracetam N=221		Total (valproate + lamotrigine/ levetiracetam) N=2451	
	N	%	N	%	N	%	N	%	N	%
Cluster C	269	27.79	352	23.74	307	24.33	45	20.36	621	25.34
Paternal polypharmacy index[c]										
0	642	66.32	712	48.01	559	44.29	153	69.23	1354	55.24
1-4	295	30.48	707	47.67	644	51.03	63	28.51	1002	40.88
5-10	28	2.89	61	4.11	56	4.44	5	2.26	89	3.63
>10	3	0.31	3	0.20	3	0.24	0	0.00	6	0.24
Mean (SD)	0.75 (1.49)		1.13 (1.59)		1.24 (1.64)		0.55 (1.11)		0.98 (1.56)	
Median (25^{th} - 75^{th} percentile)	0 (0.00, 1.00)		1 (0.00, 2.00)		1 (0.00, 2.00)		0 (0.00, 1.0)		0 (0.00, 1.00)	
Min, max	0.00, 13.00		0.00, 12.00		0.00, 12.00		0.00, 7.00		0.00, 13.00	
Concomitant medications associated with valproate-indicated psychiatric conditions[b]- fathers with at least one prescription	233	24.07	652	43.96	621	49.21	31	14.03	885	36.11
Concomitant medications associated with neuropsychiatric adverse events[b]- fathers with at least one prescription	469	48.45	950	64.06	852	67.51	98	44.34	1419	57.89

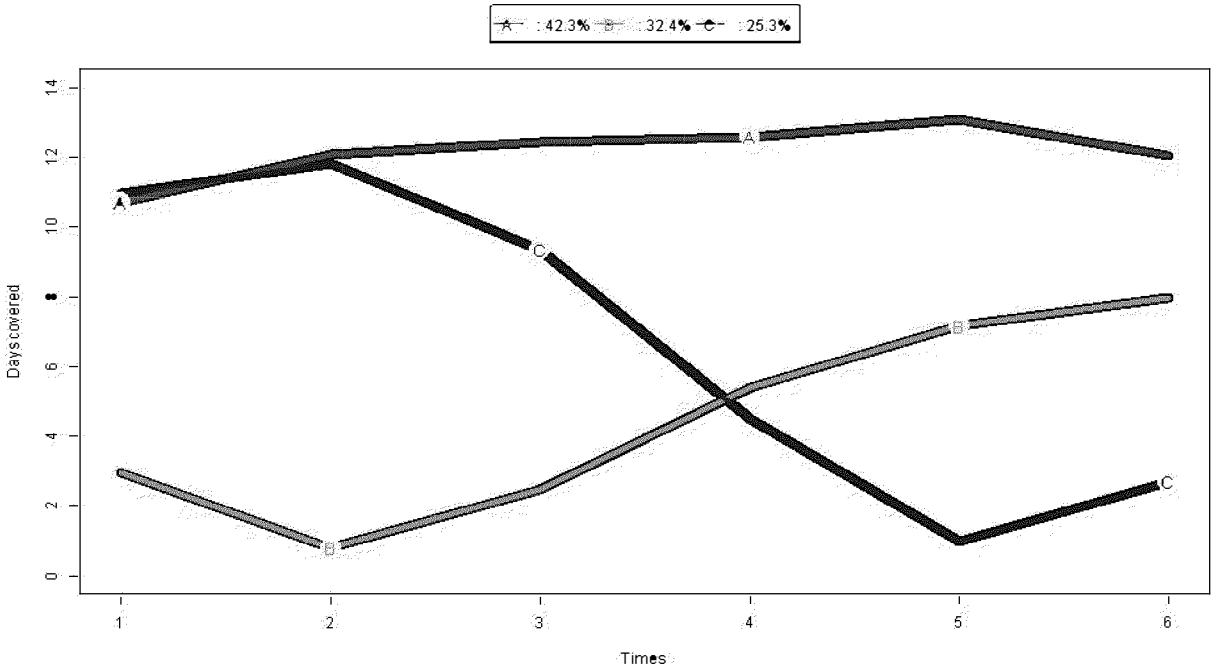
AED: antiepileptic drug; NDD: neurodevelopmental disorders; SD: standard deviation

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

Cluster A: constant high exposure; Cluster B: low-to-high exposure and Cluster C: high-to-low exposure

Comorbidities and AED indication: the same data were used for these 2 sets of categories (ICD-10 codes anytime before index, i.e. child birthdate for the primary outcome). However, for "comorbidities" all records were considered and a patient with a record of mania and a record of bipolar affective disorder was counted in both categories, whereas for "AED indication", categories were mutually exclusive, based on the following priority order: 1) epilepsy 2) bipolar affective disorder and mania 3) other/unknown, meaning a patient with a record of epilepsy and a record of mania were counted in the epilepsy category only.

a) all available data prior to index date (childbirth); b) at mother's LMP2; b) 12 months lookback from LMP2; c) 3 months lookback from LMP2; d) d) Since indications for medications are not available in all the data sources used for this study, the indication for AEDs was estimated based on medical history. The entire medical history for each father were considered up to LMP2 (exclusive) to identify diagnosis records of epilepsy and bipolar disorder/mania. In case more than one diagnosis was found (e.g. epilepsy and bipolar disorder), only one indication was selected, with priority given to epilepsy, followed by bipolar disorder. In case none of these diagnoses are found in the medical history, the indication was considered "other/unknown".



Legend: Time refers to the 14-days interval during which exposure was assessed (in this case 6 14 days interval (i.e.3 months). Days covered: days covered in each interval. Defined Daily Dose (DDD) trajectories: Cluster A: constant high exposure; Cluster B: low-to-high exposure and Cluster C: high-to-low exposure. The percentage shows the proportion of fathers exposed to valproate and lamotrigine/levetiracetam in each cluster.

Figure 17 Mean defined daily dose (DDD) trajectories for K exposed means clusters prior to last menstrual period date plus 2 weeks (LMP2) (paternal) in Sweden

10.4.1.2 Cumulative incidence proportion

Cumulative incidence proportions (risk) of NDD including ASD by paternal exposure group are presented overall in Table 65, and stratified by gender in Table 184 and Table 185 (see Appendix). The cumulative incidence proportions of NDD including ASD for 0-12 years of follow-up appeared to be higher in offspring paternally exposed to valproate (5.4%, 95% CI: 4.0, 6.8) than for offspring paternally exposed to lamotrigine/levetiracetam (3.5%, 95% CI: 2.6, 4.4), although the 95% CI overlapped (Table 65).

The cumulative incidence proportion for 0-12 years of follow-up also appeared to be higher in male offspring (5.8%, 95% CI: 4.5, 7.1) than female offspring (2.6%, 95% CI: 1.7, 3.5). However these proportions should be interpreted with caution since these are crude estimates, and no adjustments were made. In addition, offspring diagnosed with epilepsy and/treated with AEDs and/or exposed to AED in utero were not excluded in the descriptive cohort (Table 184 and Table 185, see Appendix).

Table 65 Cumulative incidence proportion (risk) of neurodevelopmental disorders (NDD) by paternal exposure group; Primary outcome cohort for descriptive analyses in Sweden (N=2451)

		Paternal exposure group				
NDD		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Follow-up period						
	N	968	1483	1262	221	2451
0-1 years	N	1	4	3	1	5
	n/N*100	0.10 (0.00, 0.31)	0.27 (0.01, 0.53)	0.24 (0.00, 0.51)	0.45 (0.00, 1.34)	0.20 (0.03, 0.38)
	N	917	1295	1114	181	2212
1-2 years	n	4	2	2	0	6
	n/N*100	0.44 (0.01, 0.86)	0.15 (0.00, 0.37)	0.18 (0.00, 0.43)	0.00 (0.00, 0.00)	0.27 (0.05, 0.49)
	N	861	1139	992	147	2000
2-3 years	n	2	6	4	2	8
	n/N*100	0.23 (0.00, 0.55)	0.53 (0.11, 0.95)	0.40 (0.01, 0.80)	1.36 (0.00, 3.23)	0.40 (0.12, 0.68)
	N	790	971	856	115	1761
3-4 years	n	6	4	4	0	10
	n/N*100	0.76 (0.15, 1.36)	0.41 (0.01, 0.81)	0.47 (0.01, 0.92)	0.00 (0.00, 0.00)	0.57 (0.22, 0.92)
	N	713	831	741	90	1544
4-5 years	n	3	6	5	1	9
	n/N*100	0.42 (0.00, 0.90)	0.72 (0.15, 1.30)	0.67 (0.09, 1.26)	1.11 (0.00, 3.28)	0.58 (0.20, 0.96)
	N	631	677	616	61	1308
5-6 years	n	8	5	4	1	13

	n/N*100	1.27 (0.39, 2.14)	0.74 (0.09, 1.38)	0.65 (0.02, 1.28)	1.64 (0.00, 4.83)	0.99 (0.46, 1.53)
	N	535	551	508	43	1086
6-7 years	n	4	7	7	0	11
	n/N*100	0.75 (0.02, 1.48)	1.27 (0.34, 2.21)	1.38 (0.36, 2.39)	0.00 (0.00, 0.00)	1.01 (0.42, 1.61)
	N	456	445	413	32	901
7-8 years	n	7	3	3	0	10
	n/N*100	1.54 (0.41, 2.66)	0.67 (0.00, 1.43)	0.73 (0.00, 1.55)	0.00 (0.00, 0.00)	1.11 (0.43, 1.79)
	N	374	338	314	24	712
8-9 years	n	5	7	6	1	12
	n/N*100	1.34 (0.17, 2.50)	2.07 (0.55, 3.59)	1.91 (0.40, 3.43)	4.17 (0.00, 12.16)	1.69 (0.74, 2.63)
	N	306	235	222	13	541
9-10 years	n	5	5	3	2	10
	n/N*100	1.63 (0.21, 3.05)	2.13 (0.28, 3.97)	1.35 (0.00, 2.87)	15.38 (0.00, 35.00)	1.85 (0.71, 2.98)
	N	231	155	145	10	386
10-11 years	n	4	1	1	0	5
	n/N*100	1.73 (0.05, 3.41)	0.65 (0.00, 1.91)	0.69 (0.00, 2.04)	0.00 (0.00, 0.00)	1.30 (0.17, 2.42)
	N	152	89	83	6	241
11-12 years	n	3	2	2	0	5
	n/N*100	1.97 (0.00, 4.18)	2.25 (0.00, 5.33)	2.41 (0.00, 5.71)	0.00 (0.00, 0.00)	2.07 (0.28, 3.87)
	N	**968**	**1483**	**1262**	**221**	**2451**
Overall (0-12 years)	**n**	52	52	44	8	104
	n/N*100	5.37 (3.95, 6.79)	3.51 (2.57, 4.44)	3.49 (2.47, 4.50)	3.62 (1.16, 6.08)	4.24 (3.45, 5.04)

NDD: neurodevelopmental disorders
Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) were presented.

10.4.1.3 Cumulative incidence rate and time to NDD diagnosis

Cumulative incidence rates of NDD including ASD by paternal exposure group are presented in Table 66, Table 186 and Table 187 (see Appendix), overall and stratified by gender, respectively. Considering the overall study follow-up, a higher incidence rate of NDD including ASD was observed among offspring paternally exposed to valproate (8.0, [95% CI: 6.0, 10.5] per 1000 PY) than among those exposed to lamotrigine/levetiracetam (6.9, [95% CI: 5.2, 9.1] per 1000 PY), although the 95% CIs for the 2 groups were overlapping. When stratifying by gender, the same pattern was observed in both male offspring and female offspring. When considering the overall period of follow-up, the cumulative incidence rate in male offspring was higher than in female offspring, in both paternal exposure groups.

Regarding the time to first diagnosis of NDD including ASD, the crude estimate for both exposure groups are presented as Kaplan-Meier curves in Figure 18. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI. The 5th percentile of the time to NDD including ASD was (91.7, [95% CI: 64.6, 136.0]) months for the valproate and (96.4, [95% CI: 62.23, 126.3]) months for the lamotrigine/levetiracetam paternal exposure groups.

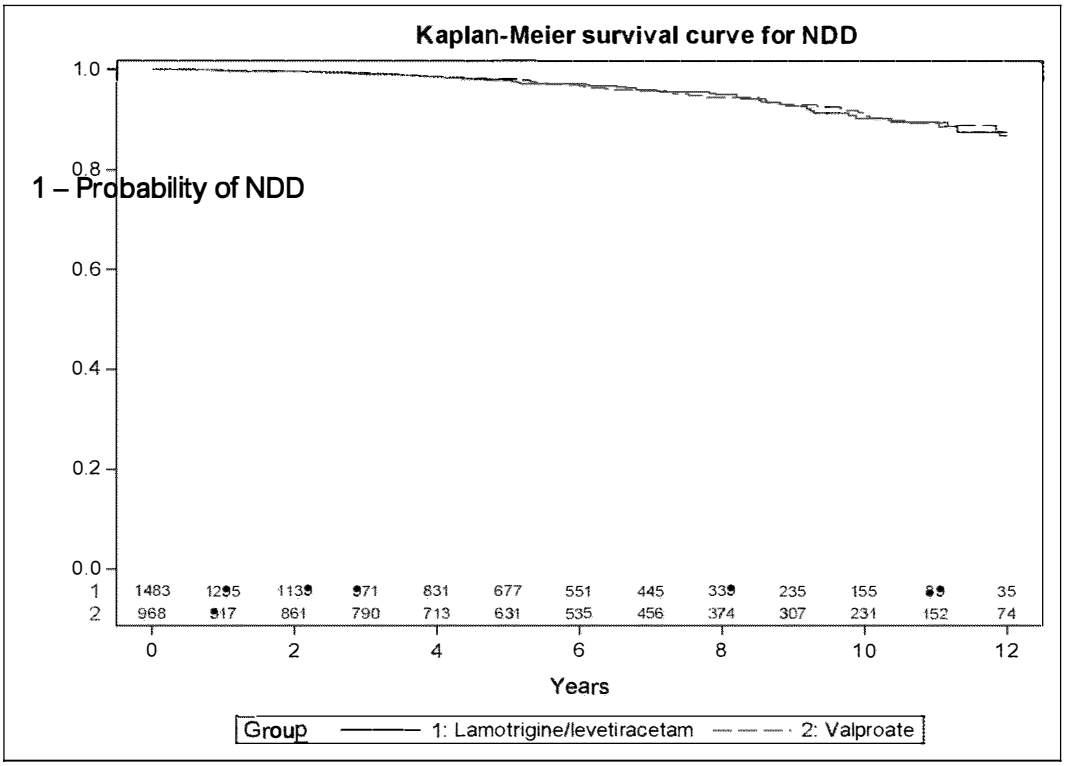
In the valproate paternal exposure group, for male offspring the 5th percentile of the time to NDD including ASD was 73.7 (95% CI: 52.6, 122.5) months and for female offspring was 136.0 (95% CI: 74.3, -) months (Table 188). In lamotrigine/levetiracetam paternal exposure group the corresponding 5th percentile values for male and female were 79.2 (95% CI: 46.3, 134.4) months and 112.5 (95% CI: 95.3, -) months, respectively. The crude estimate suggested that in both exposure groups time to diagnosis was shorter for males than females.

Table 66 Cumulative incidence rate of neurodevelopmental disorders (NDD) by paternal exposure group; Primary outcome cohort for descriptive analysis cohort in Sweden (N=2451)

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
0-1 years	PY	944.24	1388.88	1186.67	202.21	2333.12
	n	1	4	3	1	5
	n/PY*1000	1.06 (0.03, 5.90)	2.88 (0.78, 7.37)	2.53 (0.52, 7.39)	4.95 (0.13, 27.55)	2.14 (0.70, 5.00)
0-2 years	PY	1828.47	2607.69	2240.95	366.74	4436.16
	n	5	6	5	1	11
	n/PY*1000	2.73 (0.89, 6.38)	2.3 (0.84, 5.01)	2.23 (0.72, 5.21)	2.73 (0.07, 15.19)	2.48 (1.24, 4.44)
0-3 years	PY	2654.3	3666.84	3168.84	498	6321.14
	n	7	12	9	3	19
	n/PY*1000	2.64 (1.06, 5.43)	3.27 (1.69, 5.72)	2.84 (1.30, 5.39)	6.02 (1.24, 17.60)	3.01 (1.81, 4.69)
0-4 years	PY	3400.77	4570.22	3968.54	601.68	7970.99
	n	13	16	13	3	29
	n/PY*1000	3.82 (2.04, 6.54)	3.5 (2.00, 5.69)	3.28 (1.74, 5.60)	4.99 (1.03, 14.57)	3.64 (2.44, 5.23)
0-5 years	PY	4075.59	5321.11	4646.01	675.1	9396.70
	n	16	22	18	4	38
	n/PY*1000	3.93 (2.24, 6.38)	4.13 (2.59, 6.26)	3.87 (2.30, 6.12)	5.93 (1.61, 15.17)	4.04 (2.86, 5.55)
0-6 years	PY	4659.12	5935.83	5207.39	728.44	10594.95
	n	24	27	22	5	51
	n/PY*1000	5.15 (3.30, 7.66)	4.55 (3.00, 6.62)	4.22 (2.65, 6.40)	6.86 (2.23, 16.02)	4.81 (3.58, 6.33)
0-7 years	PY	5152.05	6432.76	5668.72	764.04	11584.81
	n	28	34	29	5	62
	n/PY*1000	5.43 (3.61, 7.85)	5.29 (3.66, 7.39)	5.12 (3.43, 7.35)	6.54 (2.12, 15.27)	5.35 (4.10, 6.86)
0-8 years	PY	5563.64	6826.42	6034.04	792.38	12390.06
	n	35	37	32	5	72
	n/PY*1000	6.29 (4.38, 8.75)	5.42 (3.82, 7.47)	5.3 (3.63, 7.49)	6.31 (2.05, 14.73)	5.81 (4.55, 7.32)
0-9 years	PY	5905.12	7113.21	6300.33	812.89	13018.33
	n	40	44	38	6	84
	n/PY*1000	6.77 (4.84, 9.22)	6.19 (4.49, 8.30)	6.03 (4.27, 8.28)	7.38 (2.71, 16.07)	6.45 (5.15, 7.99)
0-10 years	PY	6173.70	7309.35	6485.1	824.25	13483.05
	n	45	49	41	8	94
	n/PY*1000	7.29 (5.32, 9.75)	6.7 (4.96, 8.86)	6.32 (4.54, 8.58)	9.71 (4.19, 19.12)	6.97 (5.63, 8.53)
0-11 years	PY	6366.44	7429.99	6597.48	832.51	13796.42
	n	49	50	42	8	99

	n/PY*1000	7.7 (5.69, 10.18)	6.73 (4.99, 8.87)	6.37 (4.59, 8.61)	9.61 (4.15, 18.93)	7.18 (5.83, 8.74)
	PY	6483.28	7492.64	6655.62	837.02	13975.92
0-12 years	n	52	52	44	8	104
	n/PY*1000	8.02 (5.99, 10.52)	6.94 (5.18, 9.10)	6.61 (4.80, 8.87)	9.56 (4.13, 18.83)	7.44 (6.08, 9.02)

NDD: neurodevelopmental disorders
Legend: Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) were presented.



NDD	Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Number of events	52	52	44	8	104
Number of censor	916	1431	1218	213	2347
Survival time					
	91.70	96.37	96.37		94.90
5th percentile	(64.63, 136.00)	(62.23, 126.27)	(62.23, 134.43)	107.37 (53.27, -)	(67.40, 118.97)
10th percentile	125.87 (105.30, -)	126.27 (107.37, -)	134.43 (105.07, -)	107.37 (53.27, -)	125.87 (111.87, -)
25th percentile	-(-,-)	-(-,-)	-(-,-)	120.2 (107.37,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)

NDD: neurodevelopmental disorders

Legend: Due to low number of events the median time-to-event could not be calculated. Over the study period, the frequency of events were lower than 10% in the cohort, therefore only the 5th and 10th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event.

Figure 18 Kaplan-Meier survival curve for Neurodevelopmental Disorders (NDD) and distribution of time to NDD in Sweden

10.4.1.4 Association between potential risk factors/confounders for NDD including ASD and paternal exposure group

Association between potential covariates (risk factors and counfounders) for NDD including ASD and paternal exposure group was assessed in the Primary outcome cohort for descriptive analyses. Results of the crude associations are shown in in Table 67 to Table 69.

Offspring exposed to AEDs and/or diagnosed with epilepsy after birth are included in the primary outcome for descriptive analysis but excluded from the Primary outcome for comparative analysis, hence the absence of a summary for epilepsy in Table 67. Epilepsy was an exclusion criterion for selecting the population used for the comparative analyses because it is a strong risk factor for NDD including ASD (see Study Protocol v6.0, section 9.3.3.1) and offspring with epilepsy or receiving AEDs were already at risk of NDD including ASD regardless of paternal exposure.

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

For the offspring, none of the characteristics considered were associated with paternal exposure (Table 67).

Maternal characteristics identified as risk factors or confounders (see Table 4, Table 68), that were statistically significantly associated with paternal exposure in the offspring were:

- Age (p=0.0014), lower mean maternal age in the valproate paternal exposure group
- Neurotic disorder (p=0.0199), lower percentage in the valproate paternal exposure group
- Alcohol abuse prior to LMP2 (p=0.0002), higher percentage in the valproate paternal exposure group
- Smoking prior to LMP2 (p=0.0118) and during pregnancy (p=0.0156), higher percentage in the valproate paternal exposure group
- Maternal polypharmacy index during pregnancy (p=0.0419), lower mean index in the valproate paternal exposure group
- Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 (p=0.0302), lower percentage in the valproate paternal exposure group

Paternal characteristics identified as risk factors or confounders (see Table 4, Table 6, Table 69) that were statistically significantly associated with paternal exposure were:

- Affective disorder (excluding bipolar affective disorder and mania) (p<0.0001), bipolar affective disorder (p<0.0001), neurotic disorder (p<0.0001), all less frequent in the valproate exposure group
- Paternal polypharmacy index (p <0.0001), lower mean index in the valproate exposure group
- Concomitant medications associated with valproate-indicated psychiatric conditions (p<0.0001), lower percentage in the valproate exposure group
- Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 (p<0.0001), lower percentage in the valproate exposure group
- Age (p=0.0118), younger fathers in the valproate group
- Year of conception (p<.0001), earlier years in the valproate group and more recent years in the lamotrigine/levetiracetam group.

Table 67 Association between potential offspring risk factors for neurodevelopmental disorders (NDD) and paternal exposure group; Primary outcome cohort for comparative analysis in Sweden (N=2355)

	Paternal exposure group						
NDD **Number of offspring**	**Valproate** **N=930**		**Lamotrigine/levetiracetam** **N=1425**		**Total (valproate + lamotrigine/levetiracetam)** **N=2355**		**Comparison**
	N	**%**	**N**	**%**	**N**	**%**	**Valproate vs Lamotrigine /levetiracetam**
Offspring risk factors/confounders							
Gender [a]							
Male	464	49.89	741	52.00	1205	51.17	-
Female	466	50.11	684	48.00	1150	48.83	-
Missing	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	1.00 (0.3172)
Congenital CMV [b]	0	0.00	1	0.07	1	0.04	1.00 (1.0000) *
Congenital rubella [b]	0	0.00	0	0.00	0	0.00	-
Foetal alcohol syndrome [b]	0	0.00	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	0	0.00	-
Tuberous sclerosis [b]	1	0.11	0	0.00	1	0.04	0.39 (0.3949)*

CMV: cytomegalovirus; NDD: neurodevelopmental disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Differences between categorical variables are tested using Chi-square independence test; however, if the frequency of any of the categories analysed is <5, Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not Normal.
a) at index (childbirth); b) between index and exit date; * A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 68 Association between potential maternal risk factors for neurodevelopmental disorders (NDD) and paternal exposure group; Primary outcome cohort for comparative analysis in Sweden (N=2355)

Paternal exposure group

NDD Number of offspring	Valproate N=930		Lamotrigine/levetiracetam N=1425		Lamotrigine N=1207		Levetiracetam N=218		Total (valproate + lamotrigine/levetiracetam) N=2355		Comparison Valproate vs Lamotrigine /levetiracetam
	N	%	N	%	N	%	N	%	N	%	
Maternal risk factors/confounders											
Mother's age [a] (categorical)											
≤20 years	18	1.94	23	1.61	20	1.66	3	1.38	41	1.74	-
21-25	140	15.05	169	11.86	146	12.10	23	10.55	309	13.12	-
26-30	293	31.51	419	29.40	355	29.41	64	29.36	712	30.23	-
31-35	288	30.97	470	32.98	395	32.73	75	34.40	758	32.19	-
36-40	160	17.20	298	20.91	252	20.88	46	21.10	458	19.45	-
>40	31	3.33	46	3.23	39	3.23	7	3.21	77	3.27	-
Test statistics	-	-	-	-	-	-	-	-	-	-	10.24 (0.0687)
Mother's age [a] (continuous)											
Mean (SD)	30.76 (5.27)	-	31.46 (5.26)	-	31.44 (5.26)	-	31.57 (5.27)	-	31.18 (5.27)	-	1044028.50 (0.0014)*
Median (25^{th} - 75^{th} percentile)	31 (27.00, 35.00)	-	32 (28.00, 35.00)	-	31 (28.00, 35.00)	-	32 (28.00, 35.00)	-	31 (27.00, 35.00)	-	-
Min, max	18.00, 45.00	-	16.00, 53.00	-	16.00, 53.00	-	19.00, 48.00	-	16.00, 53.00	-	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Affective disorder [b]	78	8.39	134	9.40	117	9.69	17	7.80	212	9.00	0.71 (0.3995)
Diabetes [b]	8	0.86	18	1.26	17	1.41	1	0.46	26	1.10	0.84 (0.3603)
Gestational diabetes [c]	23	2.47	47	3.30	40	3.31	7	3.21	70	2.97	1.33 (0.2491)
Neurotic disorder [b]	85	9.14	174	12.21	148	12.26	26	11.93	259	11.00	5.42 (0.0199)
Schizophrenia, schizotypal and delusional disorders [b]	4	0.43	3	0.21	2	0.17	1	0.46	7	0.30	0.44 (0.4447)*
Obesity [d]	11	1.18	16	1.12	15	1.24	1	0.46	27	1.15	0.02 (0.8937)

NDD Number of offspring	Paternal exposure group Valproate N=930		Lamotrigine/levetiracetam N=1425		Lamotrigine N=1207		Levetiracetam N=218		Total (valproate + lamotrigine/levetiracetam) N=2355		Comparison Valproate vs Lamotrigine /levetiracetam
	N	%	N	%	N	%	N	%	N	%	
CMV [c]	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04	1.00 (1.0000)*
Rubella [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [d]	9	0.97	0	0.00	0	0.00	0	0.00	9	0.38	0.00 (0.0002)*
Alcohol abuse during pregnancy [c]	1	0.11	1	0.07	0	0.00	1	0.46	2	0.08	1.00 (1.0000)*
Substance abuse prior to LMP2 [d]	4	0.43	4	0.28	2	0.17	2	0.92	8	0.34	0.71 (0.7198)*
Substance abuse during pregnancy [c]	2	0.22	2	0.14	1	0.08	1	0.46	4	0.17	0.64 (0.6499)*
Smoking prior to LMP2 [d]											
No	739	79.46	1172	82.25	997	82.60	175	80.28	1911	81.15	-
Yes	151	16.24	177	12.42	145	12.01	32	14.68	328	13.93	-
Missing	40	4.30	76	5.33	65	5.39	11	5.05	116	4.93	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	6.34 (0.0118)
Smoking during pregnancy [c]											
No	832	89.46	1311	92.00	1111	92.05	200	91.74	2143	91.00	-
Yes	71	7.63	74	5.19	62	5.14	12	5.50	145	6.16	-
Missing	27	2.90	40	2.81	34	2.82	6	2.75	67	2.85	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	5.85 (0.0156)
Maternal polypharmacy index prior to LMP2 [e](categorical)											
0	623	66.99	966	67.79	816	67.61	150	68.81	1589	67.47	-
1-4	288	30.97	428	30.04	362	29.99	66	30.28	716	30.40	-
5-10	19	2.04	30	2.11	28	2.32	2	0.92	49	2.08	-
>10	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04	-

NDD Number of offspring	Paternal exposure group Valproate N=930		Lamotrigine/levetiracetam N=1425		Lamotrigine N=1207		Levetiracetam N=218		Total (valproate + lamotrigine/levetiracetam) N=2355		Comparison Valproate vs Lamotrigine /levetiracetam
	N	%	N	%	N	%	N	%	N	%	
Test statistics	-	-	-	-	-	-	-	-	-	-	0.88 (0.8308)
Maternal polypharmacy index prior to LMP2 [e] (continuous)											
Mean (SD)	0.65 (1.21)	-	0.64 (1.22)	-	0.66 (1.26)	-	0.53 (1.00)	-	0.64 (1.22)	-	1100052.00 (0.7358)*
Median (25th - 75th percentile)	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	-
Min, max	0.00, 8.00	-	0.00, 11.00	-	0.00, 11.00	-	0.00, 6.00	-	0.00, 11.00	-	-
Maternal polypharmacy index during pregnancy [c](categorical)											
0	492	52.90	694	48.70	583	48.30	111	50.92	1186	50.36	-
1-4	419	45.05	687	48.21	583	48.30	104	47.71	1106	46.96	-
5-10	19	2.04	42	2.95	39	3.23	3	1.38	61	2.59	-
>10	0	0.00	2	0.14	2	0.17	0	0.00	2	0.08	-
Test statistics	-	-	-	-	-	-	-	-	-	-	6.25 (0.1001)
Maternal polypharmacy index during pregnancy[c] (continuous)											
Mean (SD)	0.90 (1.28)	-	1.02 (1.44)	-	1.06 (1.48)	-	0.83 (1.14)	-	0.97 (1.38)	-	1065203.00 (0.0419)*
Median (25th - 75th percentile)	0 (0.00, 1.00)	-	1 (0.00, 2.00)	-	1 (0.00, 2.00)	-	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	-
Min, max	0.00, 9.00	-	0.00, 13.00	-	0.00, 13.00	-	0.00, 7.00	-	0.00, 13.00	-	-

NDD Number of offspring	Paternal exposure group Valproate N=930		Lamotrigine/levetiracetam N=1425		Lamotrigine N=1207		Levetiracetam N=218		Total (valproate + lamotrigine/levetiracetam) N=2355		Comparison Valproate vs Lamotrigine /levetiracetam
	N	%	N	%	N	%	N	%	N	%	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	98	10.54	193	13.54	173	14.33	20	9.17	291	12.36	4.70 (0.0302)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	53	5.70	109	7.65	99	8.20	10	4.59	162	6.88	3.34 (0.0676)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] -mothers with at least one prescription	571	61.40	863	60.56	737	61.06	126	57.80	1434	60.89	0.17 (0.6843)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	392	42.15	659	46.25	560	46.40	99	45.41	1051	44.63	3.82 (0.0507)

NDD: neurodevelopmental disorders; SD- Standard Deviation; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father appeared more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Differences between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2

e) 3 months lookback from LMP2
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 69 Association between potential paternal risk factors/confounders for NDD and paternal exposure group; Primary outcome cohort for comparative analysis in Sweden (N=2355)

	Paternal exposure group						
NDD **Number of offspring**	**Valproate** **N=930**		**Lamotrigine/levetiracetam** **N=1425**		**Total (valproate + lamotrigine/levetiracetam)** **N=2355**		**Comparison**
	N	**%**	**N**	**%**	**N**	**%**	**Valproate vs Lamotrigine /levetiracetam**
Paternal risk factors/confounders							-
Affective disorder excluding bipolar affective disorder and mania [a]	104	11.18	426	29.89	530	22.51	112.98 (<.0001)
Bipolar affective disorder [a]	122	13.12	418	29.33	540	22.93	83.72 (<.0001)
Mania [a]	13	1.40	20	1.40	33	1.40	0.00 (0.9909)
Neurotic disorder [a]	127	13.66	388	27.23	515	21.87	60.67 (<.0001)
Schizophrenia, schizotypal and delusional disorders [a]	38	4.09	52	3.65	90	3.82	0.29 (0.5888)
Substance abuse [c]	12	1.29	10	0.70	22	0.93	2.11 (0.1467)
Paternal polypharmacy index [d] (categorical)							
0	612	65.81	684	48.00	1296	55.03	-
1-4	288	30.97	680	47.72	968	41.10	-
5-10	27	2.90	58	4.07	85	3.61	-
>10	3	0.32	3	0.21	6	0.25	-
Test statistics	-	-	-	-	-	-	73.24 (<.0001)
Paternal polypharmacy index [d] (continuous)							
Mean (SD)	0.77 (1.51)		1.13 (1.58)		0.99 (1.56)		977885.50 (<.0001)*

	Paternal exposure group						
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**		**Comparison**
Number of offspring	**N=930**		**N=1425**		**N=2355**		
	N	**%**	**N**	**%**	**N**	**%**	**Valproate vs Lamotrigine /levetiracetam**
							-
Median (25th - 75th percentile)	0 (0.00, 1.00)		1 (0.00, 2.00)		0 (0.00, 1.00)		-
Min, max	0.00, 13.00		0.00, 12.00		0.00, 13.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] – fathers with at least one prescription	225	24.19	623	43.72	848	36.01	93.11 (<.0001)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription	449	48.28	909	63.79	1358	57.66	55.45 (<.0001)
Father's age [e] (categorical)							-
≤20 years	5	0.54	8	0.56	13	0.55	-
21-25	65	6.99	75	5.26	140	5.94	-
26-30	207	22.26	284	19.93	491	20.85	-
31-35	314	33.76	503	35.30	817	34.69	-
36-40	224	24.09	354	24.84	578	24.54	-
>40	115	12.37	201	14.11	316	13.42	-
Test statistics	-	-	-	-	-	-	6.07 (0.2993)
Father's age [e] (continuous)							
Mean (SD)	33.71 (6.04)		34.37 (6.19)		34.11 (6.14)		1054984.50 (0.0118)*
Median (25th - 75th percentile)	33 (29.00, 38.00)		34 (30.00, 38.00)		34 (30.00, 38.00)		-
Min, max	17.00, 63.00		16.00, 77.00		16.00, 77.00		-

	Paternal exposure group						
NDD **Number of offspring**	**Valproate** **N=930**		**Lamotrigine/levetiracetam** **N=1425**		**Total (valproate + lamotrigine/levetiracetam)** **N=2355**		**Comparison**
	N	**%**	**N**	**%**	**N**	**%**	**Valproate vs Lamotrigine /levetiracetam** -
Year of offspring conception [f,g]							
2006-2010	370	39.78	311	21.82	681	28.92	-
2011-2015	378	40.65	593	41.61	971	41.23	-
2016-2019	182	19.57	521	36.56	703	29.85	-
Test statistics	-	-	-	-	-	-	117.33 (<.0001)

NDD: neurodevelopmental disorders; SD- Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Differences between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed is <5, Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) all available data prior to index date (childbirth); c) 12 months lookback from LMP2; d) 3 months lookback from LMP2; e) at index (childbirth); f) at mother's LMP2; g) calendar years are grouped in each country according to the length of the study period.

10.4.1.5 Association between potential risk factors/confounders and NDD including ASD

Association between covariates (potential risk factors / confounders) and occurrence of NDD was assessed in the Primary outcome cohort for comparative analyses. Results of the crude associations are shown in Table 70 to Table 72.

These variables were initially selected based on literature review and clinical expert opinion, see section 9.4.4 Potential confounders/risk factors for an overview.

For offspring characteristics, only gender (OR: 0.41, 95% CI: 0.26, 0.66; p=0.0002) was associated with occurrence of NDD (Table 70); the proportion of events among females was lower than the proportion of events among males.

From maternal characteristics identified as risk factors (see Table 4), affective disorder (OR: 1.92, 95% CI: 1.07, 3.46; p=0.0294) was associated with the risk of NDD including ASD (Table 71).

For paternal characteristics identified as risk factors or confounders (see Table 4, Table 6, and Table 72), the following variables were significantly associated with offspring having a NDD including ASD event:

- Year of offspring conception (p<0.0001), offspring conceived after 2011 had a lower probability of having a NDD including ASD event compared to the reference category of 2006-2010 (years 2011-2015 OR: 0.27, 95% CI: 0.17, 0.43; 2016-2019 OR: 0.06, 95% CI: 0.02, 0.16).
- Paternal polypharmacy index (p=0.0445), offspring from fathers with the polypharmacy index between 1 to 4 had a lower risk of having a NDD including ASD event compared with the reference category of 0 (OR: 0.77, 95% CI: 0.48, 1.21), and the risk was higher among those from fathers with the polypharmacy index higher than 5 (OR: 2.49, 95% CI: 1.14, 5.42).

Table 70 Association between potential offspring risk factors/confounders and neurodevelopmental disorders (NDD); Primary outcome cohort for comparative analysis in Sweden (N=2355)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Offspring risk factors/confounders								
Gender [a]								
Male	1205	51.17	64	5.31	1141	94.69	Reference	-
Female	1150	48.83	26	2.26	1124	97.74	0.41 (0.26,0.66)	-
Missing	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	14.05 (0.0002)
Congenital CMV [b]								
No	2354	99.96	90	3.82	2264	96.18	Reference	-
Yes	1	0.04	0	0.00	1	100.00	0.00 (0.00,I)	0.00 (0.9895)
Congenital rubella [b]								
No	2355	100.00	90	3.82	2265	96.18	Reference	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Foetal alcohol syndrome [b]								
No	2355	100.00	90	3.82	2265	96.18	Reference	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Fragile X syndrome [b]								
No	2355	100.00	90	3.82	2265	96.18	Reference	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Lejeune/cri du chat syndrome [b]								
No	2355	100.00	90	3.82	2265	96.18	Reference	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Tuberous sclerosis [b]								
No	2354	99.96	90	3.82	2264	96.18	Reference	-
Yes	1	0.04	0	0.00	1	100.00	0.00 (0.00,I)	0.00 (0.9895)

CMV: cytomegalovirus; NDD: neurodevelopmental disorders
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of offspring diagnosed with having a NDD event and offspring without a diagnosis ('non-event') according to the characteristic of interest (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristic and the outcome was examined by fitting a logistic regression model; the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported. The largest group (most frequent) in each of the age variables was used as a reference in order to increase quality of OR estimation. a) at index (childbirth); b) between index and exit date.

Table 71 Association between potential maternal risk factors/confounders and NDD; Primary outcome cohort for comparative analysis in Sweden (N=2355)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Maternal risk factors/confounders								
Mother's age [a] **(categorical)**								
≤20 years	41	1.74	5	12.20	36	87.80	3.52 (1.28, 9.69)	-
21-25	309	13.12	11	3.56	298	96.44	0.94 (0.46, 1.91)	-
26-30	712	30.23	27	3.79	685	96.21	Reference	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
31-35	758	32.19	25	3.30	733	96.70	0.87 (0.50, 1.51)	-
36-40	458	19.45	19	4.15	439	95.85	1.10 (0.60, 2.00)	-
>40	77	3.27	3	3.90	74	96.10	1.03 (0.30, 3.47)	-
Wald test	-	-	-	-	-	-	-	7.57 (0.1818)
Affective disorder [b]								
No	2143	91.00	76	3.55	2067	96.45	Reference	-
Yes	212	9.00	14	6.60	198	93.40	1.92 (1.07, 3.46)	4.75 (0.0294)
Diabetes [b]								
No	2329	98.90	88	3.78	2241	96.22	Reference	-
Yes	26	1.10	2	7.69	24	92.31	2.12 (0.49, 9.12)	1.02 (0.3114)
Gestational diabetes [c]								
No	2285	97.03	87	3.81	2198	96.19	Reference	-
Yes	70	2.97	3	4.29	67	95.71	1.13 (0.35, 3.67)	0.04 (0.8372)
Neurotic disorder [b]								
No	2096	89.00	79	3.77	2017	96.23	Reference	-
Yes	259	11.00	11	4.25	248	95.75	1.13 (0.59, 2.16)	0.14 (0.7052)
Schizophrenia, schizotypal and delusional disorders [b]								
No	2348	99.70	89	3.79	2259	96.21	Reference	-
Yes	7	0.30	1	14.29	6	85.71	4.23 (0.50, 35.51)	1.77 (0.1840)
Obesity [d]								
No	2328	98.85	88	3.78	2240	96.22	Reference	-
Yes	27	1.15	2	7.41	25	92.59	2.04 (0.48-8.73)	0.92 (0.3381)
CMV [c]								
No	2354	99.96	90	3.82	2264	96.18	Reference	-
Yes	1	0.04	0	0.00	1	100.00	0.00(0.00,I)	0.00 (0.9895)
Rubella [c]								
No	2355	100.00	90	3.82	2265	96.18	Reference	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse prior to LMP2 [d]								
No	2346	99.62	90	3.84	2256	96.16	Reference	-
Yes	9	0.38	0	0.00	9	100.00	0.00 (0.00,I)	0.00 (0.9862)
Alcohol abuse during pregnancy [c]								
No	2353	99.92	90	3.82	2263	96.18	Reference	-
Yes	2	0.08	0	0.00	2	100.00	0.00 (0.00,I)	0.00 (0.9852)
Substance abuse prior to LMP2 [d]								
No	2347	99.66	90	3.83	2257	96.17	Reference	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Yes	8	0.34	0	0.00	8	100.00	0.00 (0.00,I)	0.00 (0.9870)
Substance abuse during pregnancy [c]								
No	2351	99.83	90	3.83	2261	96.17	Reference	-
Yes	4	0.17	0	0.00	4	100.00	0.00 (0.00,I)	0.00 (0.9861)
Smoking prior to LMP2 [e]								
No	1911	81.15	69	3.61	1842	96.39	Reference	-
Yes	328	13.93	16	4.88	312	95.12	1.37 (0.78, 2.39)	-
Missing	116	4.93	5	4.31	111	95.69	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	1.22(0.2690)
Smoking during pregnancy [c]								
No	2143	91.00	76	3.55	2067	96.45	Reference	-
Yes	145	6.16	9	6.21	136	93.79	1.80 (0.88, 3.67)	-
Missing	67	2.85	5	7.46	62	92.54	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	2.61(0.1059)
Maternal polypharmacy index prior to LMP2 [e](categorical)								
0	1589	67.47	58	3.65	1531	96.35	Reference	-
1-4	716	30.40	30	4.19	686	95.81	1.15 (0.74, 1.81)	-
5-10	49	2.08	2	4.08	47	95.92	1.12 (0.27, 4.74)	-
>10	1	0.04	0	0.00	1	100.00	0.00(0.00,I)	-
Wald test	-	-	-	-	-	-	-	0.40 (0.9403)
Maternal polypharmacy index during pregnancy [c](categorical)								
0	1186	50.36	44	3.71	1142	96.29	Reference	-
1-4	1106	46.96	44	3.98	1062	96.02	1.08 (0.70, 1.65)	-
5-10	61	2.59	2	3.28	59	96.72	0.88 (0.21, 3.72)	-
>10	2	0.08	0	0.00	2	100.00	0.00 (0.00,I)	-
Wald test	-	-	-	-	-	-	-	0.16 (0.9833)
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription								
No	2064	87.64	76	3.68	1988	96.32	Reference	-
Yes	291	12.36	14	4.81	277	95.19	1.32 (0.74, 2.37)	0.88 (0.3478)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription								

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
No	2193	93.12	80	3.65	2113	96.35	Reference	-
Yes	162	6.88	10	6.17	152	93.83	1.74 (0.88, 3.42)	2.55 (0.1100)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription								
No	921	39.11	36	3.91	885	96.09	Reference	-
Yes	1434	60.89	54	3.77	1380	96.23	0.96 (0.63, 1.48)	0.03 (0.8592)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription								
No	1304	55.37	44	3.37	1260	96.63	Reference	-
Yes	1051	44.63	46	4.38	1005	95.62	1.31 (0.86, 2.00)	1.58 (0.2083)

CMV: cytomegalovirus; LMP2: last menstrual period + 2 weeks; NDD: neurodevelopmental disorders
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of offspring diagnosed with having a NDD event and offspring without a diagnosis ('non-event') according to the characteristic of interest (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristic and the outcome was examined by fitting a logistic regression model; the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported. The largest group (most frequent) in each of the age variables was used as a reference in order to increase quality of OR estimation.
a) at index (childbirth); b) all available data prior to index date; c) during pregnancy (from LMP2 until index date); d) 12 months lookback from LMP2.

Table 72 Association between potential paternal risk factors/confounders and neurodevelopmental disorders (NDD); Primary outcome cohort for comparative analysis in Sweden (N=2355)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Paternal risk factors/confounders								
Affective disorder excluding bipolar affective disorder and mania [a]								
No	1825	77.49	75	4.11	1750	95.89	Reference	-
Yes	530	22.51	15	2.83	515	97.17	0.68 (0.39, 1.19)	1.81 (0.1788)
Bipolar affective disorder [a]								
No	1815	77.07	72	3.97	1743	96.03	Reference	-
Yes	540	22.93	18	3.33	522	96.67	0.83 (0.49, 1.41)	0.45 (0.5008)
Mania [a]								
No	2322	98.60	89	3.83	2233	96.17	Reference	-
Yes	33	1.40	1	3.03	32	96.97	0.78 (0.11, 5.80)	0.06 (0.8119)
Neurotic								

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
disorder [a]								
No	1840	78.13	72	3.91	1768	96.09	Reference	-
Yes	515	21.87	18	3.50	497	96.50	0.89 (0.53, 1.50)	0.19 (0.6621)
Schizophrenia, schizotypal and delusional disorders [a]								
No	2265	96.18	84	3.71	2181	96.29	Reference	-
Yes	90	3.82	6	6.67	84	93.33	1.85 (0.79, 4.37)	2.00 (0.1574)
Substance abuse [c]								
No	2333	99.07	89	3.81	2244	96.19	Reference	-
Yes	22	0.93	1	4.55	21	95.45	1.20 (0.16, 9.03)	0.03 (0.8589)
Paternal polypharmacy index [d] (categorical)								
0	1296	55.03	52	4.01	1244	95.99	Reference	-
1-4	968	41.10	30	3.10	938	96.90	0.77 (0.48, 1.21)	-
5-10	85	3.61	8	9.41	77	90.59	2.49 (1.14, 5.42)	-
>10	6	0.25	0	0.00	6	100.00	0.00(0.00,I)	-
Wald test	-	-	-	-	-	-	-	8.08 (0.0445)
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription								
No	1507	63.99	57	3.78	1450	96.22	Reference	-
Yes	848	36.01	33	3.89	815	96.11	1.03 (0.67, 1.60)	0.02 (0.8941)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription								
No	997	42.34	36	3.61	961	96.39	Reference	-
Yes	1358	57.66	54	3.98	1304	96.02	1.11 (0.72, 1.70)	0.21 (0.6476)
Father's age [e] (categorical)								
≤20 years	13	0.55	1	7.69	12	92.31	2.11 (0.27, 16.77)	-
21-25	140	5.94	6	4.29	134	95.71	1.14 (0.46, 2.77)	-
26-30	491	20.85	21	4.28	470	95.72	1.13 (0.64, 1.99)	-
31-35	817	34.69	31	3.79	786	96.21	Reference	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
36-40	578	24.54	22	3.81	556	96.19	1.00 (0.57, 1.75)	-
>40	316	13.42	9	2.85	307	97.15	0.74 (0.35, 1.58)	-
Wald test	-	-	-	-	-	-	-	1.67 (0.8927)
Year of offspring conception [f,g]								
2006-2010	681	28.92	61	8.96	620	91.04	Reference	-
2011-2015	971	41.23	25	2.57	946	97.43	0.27 (0.17, 0.43)	-
2016-2019	703	29.85	4	0.57	699	99.43	0.06 (0.02, 0.16)	-
Wald test	-	-	-	-	-	-		51.88 (<.0001)

NDD: neurodevelopmental disorders
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of offspring diagnosed with having a NDD event and offspring without a diagnosis ('non-event') according to the characteristic of interest (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristic and the outcome was examined by fitting a logistic regression model; the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported. The largest group (most frequent) in each of the age variables was used as a reference in order to increase quality of OR estimation.
a) all available data prior to index date (childbirth); c) 12 months lookback from LMP2; d) 3 months lookback from LMP2; e) at index (date of childbirth); f) at mother's LMP2; g) calendar years are grouped in each country according to the length of the study period

10.4.1.6 Variable estimates from propensity score

Variables found to be associated with the outcome were included in the PS models for the analyses of the Primary outcome cohort for comparative analyses. This means all specified confounders for which an association with both the outcome and the exposure was observed and all specified risk factors (associated with the outcome but not the exposure) were included in the PS models. Notably some maternal characteristics appeared to be associated with the exposure as well as the outcome; further evaluation of the impact of these variables were undertaken to minimise introduction of bias. If any of these above mentioned variables remained unbalance after performing PS weighting, they were included in the final Cox regression model.

In the PS model estimated from logistic regression (Table 73), gender of the offspring was not associated with the paternal exposure to valproate or lamotrigine/levetiracetam (OR: 1.06, 95% CI: 0.88, 1.28, p=0.5121). Offspring with mothers with gestational diabetes (OR: 0.26, 95% CI: 0.12, 0.56, p<0.0007) had lower probability of being in the valproate exposure group. Offspring with fathers with affective disorders (OR: 0.40, 95% CI: 0.29, 0.56, p <0.0001), bipolar affective disorder (OR: 0.54, 95% CI: 0.41, 0.73, p<0.0001), paternal polypharmacy 1-4 (OR: 0.70, 95% CI: 0.54, 0.91, p=0.0064), and years of offspring conception 2011-2015 (OR: 0.57, 95% CI: 0.46, 0.71, p<0.0001) and 2016-2019 (OR: 0.29, 95% CI: 0.22, 0.37, p<0.0001), had a lower probability of being in the valproate exposure group, whereas those with fathers with paternal schizophrenia, schizotypal and delusional disorders (OR: 2.31, 95% CI: 1.34, 4.00, p<0.0026), had a higher probability of being in the valproate exposure group.

Variables or interactions associated with NDD including ASD in the PS model from logistic regression informed by random forest were maternal concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 (OR: 0.64, 95% CI: 0.46, 0.90, p=0.0109), and paternal affective disorder (OR: 0.23, 95% CI: 0.16 - 0.33, p<0.0001), bipolar affective disorder (OR: 0.34 95% CI: 0.25, 0.47, p<0.0001), concomitant medications associated with neuropsychiatric adverse events (OR: 0.70, 95% CI: 0.57, 0.86, p=0.0005), categories of calendar year of offspring conception 2011-2015 (OR: 0.59, 95% CI: 0.47, 0.73, p<0.0001) and 2016-2019 (OR: 0.26, 95% CI: 0.20, 0.34, p<0.0001) (Table 189).

Plots of each PS model are depicted in Figure 19, Figure 34, Figure 35. The PS model that best achieved a balance in the weighted exposure groups after using inverse probability of treatment weights was the PS model estimated from logistic regression, as shown in Figure 19 and

Table 191. Thus, the logistic regression model was used to apply inverse probability of treatment weights in the effect estimation analysis (presented in Section 10.4.1.6.1).

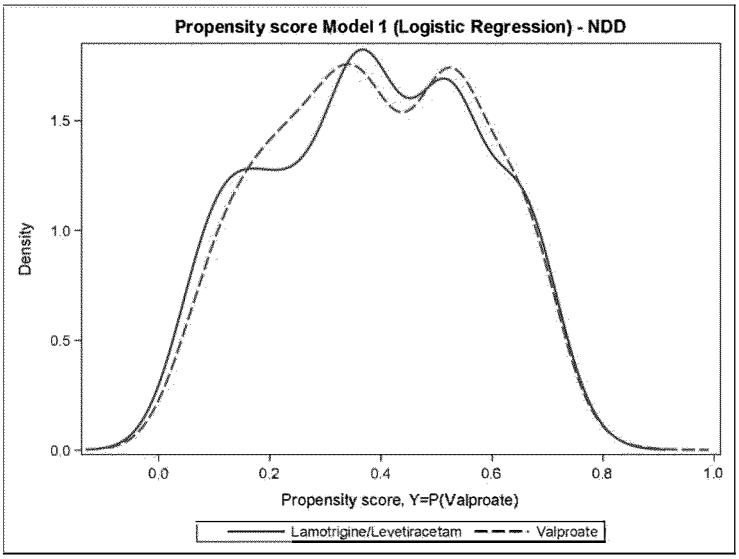
Table 73 Variable estimates from logistic regression propensity score model; Primary outcome cohort in Sweden (N=2355)

Exposure group (valproate vs lamotrigine/levetiracetam)	Estimate		
Variable (or interaction)[a]	OR	95% CI	P-value
Offspring risk factors/confounders			
Gender [b]			
Male	Reference	-	-
Female	1.06	(0.88, 1.28)	0.5121
Maternal risk factors/confounders			
Affective disorder [d]	1.21	(0.80, 1.84)	0.3644
Gestational diabetes [e]	0.26	0.12, 0.56	0.0007
Neurotic disorder [d]	0.90	0.62, 1.31	0.5851
Obesity [f]	0.50	0.15, 1.60	0.2398
Smoking prior to LMP2 [f]			
No	Reference	-	-
Yes	0.95	0.68, 1.33	0.7778
Smoking during pregnancy [e]			
No	Reference	-	-
Yes	1.53	0.93, 2.51	0.0926
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.69	0.45, 1.04	0.0728
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	1.08	0.62, 1.87	0.7837
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.90	0.74, 1.10	0.2911
Paternal risk factors/confounders			
Affective disorder [d,g]	0.40	0.29, 0.56	<.0001
Bipolar affective disorder [d]	0.54	0.41, 0.73	<.0001
Mania [d]	0.88	0.31, 2.49	0.8126
Neurotic disorder [d]	0.83	0.62, 1.13	0.2402
Schizophrenia, schizotypal and delusional disorders [d]	2.31	1.34, 4.00	0.0026
Substance abuse [f]	5.82	0.92, 36.91	0.0615
Paternal polypharmacy index [h] **(categorical)**			
0	Reference	-	-
1-4	0.70	0.54, 0.91	0.0064
5-10	0.61	0.32, 1.15	0.1246
>10	0.55	(0.05, 6.21)	0.6281
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with atleast one prescription	0.84	(0.66, 1.07)	0.1673
Year of offspring conception [I,J]			
2006-2010	Reference	-	-
2011-2015	0.57	(0.46, 0.71)	<.0001
2016-2019	0.29	(0.22, 0.37)	<.0001

Legend: LMP2: Last Menstrual Period Date Plus 2 weeks; Odds ratios (OR), 95% confidence intervals (CI) and p-values were represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model were listed here, however some of the variables might not be included in the final set of variables.
a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.
b) at index (childbirth)
c) between index and exit date
d) all available data prior to index date
e) during pregnancy (from LMP2 until index date)
f) 12 months lookback from LMP2
g) excluding bipolar affective disorder and mania

Exposure group (valproate vs lamotrigine/levetiracetam)	Estimate		
Variable (or interaction)[a]	OR	95% CI	P-value

h) 3 months lookback from LMP2
i) at mother's LMP2
j) calendar years were grouped in each country according to the length of the study period



NDD: neurodevelopmental disorders

Figure 19 Balance of PS Model 1- Logistic Regression; Primary outcome cohort in Sweden.

10.4.1.6.1 Effect estimation for NDD including ASD

The effect estimation for NDD including ASD was assessed by using crude Cox regression model as presented in Table 74. In this model were included 2,355 offspring, among whom 930 were from fathers exposed to valproate and 1,425 from fathers exposed to lamotrigine/levetiracetam; no influential subjects were identified. Respectively, 5.3% (N=49) of offspring of the valproate group and 2.9% (N=41) of the lamotrigine/levetiracetam group presented a NDD including ASD event. In the crude analysis, no increased risk for NDD including ASD was observed comparing offspring of fathers exposed to valproate to offspring of fathers exposed to lamotrigine/levetiracetam group (HR: 1.16, 95% CI: 0.76, 1.76).

The effect estimate for NDD including ASD using PS-weighted Cox regression model was assessed in a total of 2,175 offspring, 841 offspring from the valproate group and 1,334 offspring from the lamotrigine/levetiracetam group. Respectively, 5.6% (N=47) of offspring of the valproate group and 2.5% (N=34) of the lamotrigine/levetiracetam group presented a NDD including ASD event. In the PS-weighted Cox regression model, no increased risk for NDD including ASD was observed comparing offspring of fathers exposed to valproate to offspring of fathers exposed to lamotrigine/levetiracetam group (HR: 1.54, 95% CI: 0.95, 2.51) (Table 75).

Table 76 presents the effect estimation for NDD including ASD using PS-weighted Cox regression model adjusted for the K-means exposure cluster (Cluster A: constant high exposure; Cluster B: low-to-high exposure and Cluster C: high-to-low exposure, for further details on the K-means cluster in the main analyses please check Figure 17 and Table 64). In order to obtain estimates of the effect of valproate vs lamotrigine/levetiracetam in each cluster identified by the K-means algorithm, an interaction term between the K-means clusters variable and the main exposure variable was included in the model. The effect estimation was assessed in a total of 2,175 offspring, and no increased risk for NDD including ASD was

observed in offspring of fathers exposed to valproate compared to offspring of fathers exposed to lamotrigine/levetiracetam, in the different cluster of exposure. Likewise, no interaction between exposure and paternal K-means cluster was observed.

In the analysis of effect estimate in cluster A (i.e. trajectories with constant higher exposure), 355 offspring from the valproate group, of which 6.5% (N=23) presented a NDD including ASD event and 577 from lamotrigine/levetiracetam group, of which 2.6% (N=15) presented a NDD including ASD event, were considered. No increased risk for NDD including ASD of offspring from fathers exposed to the valproate in cluster A was observed comparing to offspring from fathers exposed to lamotrigine/levetiracetam in cluster A (HR: 1.63, 95% CI: 0.83, 3.20) (Table 76). The effect estimated in cluster B (i.e. trajectories with low-to-high exposure) considered 258 offspring from the valproate group, of which 4.3% (N=11) presented a NDD including ASD event and 445 from lamotrigine/levetiracetam, of which 2.5% (N=11) presented a NDD including ASD event. No increased risk for NDD including ASD of offspring from fathers exposed to the valproate in cluster B was observed comparing to offspring from fathers exposed to lamotrigine/levetiracetam in cluster B (HR: 1.40, 95% CI: 0.54, 3.62) (Table 76). For cluster C (i.e. trajectories with high-to-low exposure), 228 offspring from the valproate group, of which 5.7% (N=13) presented a NDD including ASD event and 312 from lamotrigine/levetiracetam, of which 2.6% (N=8) presented a NDD including ASD event, were considered. No increased risk for NDD including ASD in offspring from fathers exposed to the valproate in cluster C was observed comparing to offspring from fathers exposed to lamotrigine/levetiracetam in cluster C (1.54, 95% CI: 0.58, 4.13) (Table 76).

Table 74 Effect estimation for neurodevelopmental disorders (NDD) using crude Cox regression model; Primary outcome cohort for comparative analysis in Sweden (N=2355)

Variable	Total	Number of events	Number of subjects included in the model (after excluding influential subjects) [a]		Model estimates		
	N	N	N	%	HR	95% CI	P-value
Valproate	930	49					
Lamotrigine/levetiracetam	1425	41					
Paternal exposure: valproate vs lamotrigine/levetiracetam	2355		2355	100.00	1.16	(0.76, 1.76)	0.4843

HR: hazard ratio; CI: confidence interval
Legend a) Influential subjects were identified using the dfbetas for the main exposure coefficient.

Table 75 Effect estimation for neurodevelopmental disorders (NDD) using Propensity Score weighted Cox regression model; Primary outcome cohort for comparative analysis in Sweden (N=2175)

Variable	Total N	Number of events	Model estimates[1]		
			HR	95% CI	P-value
Valproate	841	47			
Lamotrigine/levetiracetam	1334	34			
Paternal exposure: valproate vs lamotrigine/levetiracetam	2175		1.54	(0.95, 2.51)	0.0814

Legend: CI: confidence interval; HR: hazard ratio; NDD: neurodevelopmental disorders
[1] **The logistic regression PS model includes all variables from Table 73, following described: Offspring risk factors/confounders:** "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications

associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of: "concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "year of offspring conception at mother's LMP2"

Table 76 Effect estimation for neurodevelopmental disorders (NDD) using Propensity Score weighted Cox regression model adjusted for K-means exposure cluster; Primary outcome cohort for comparative analysis in Sweden (N=2175)

Variable	Total N	Number of events	Model estimates[1]		
			HR	95% CI	P-value
Valproate – cluster A	355	23			
Lamotrigine/Levetiracetam – cluster A	577	15			
Valproate – cluster B	258	11			
Lamotrigine/Levetiracetam – cluster B	445	11			
Valproate – cluster C	228	13			
Lamotrigine/Levetiracetam – cluster C	312	8			
Paternal exposure: valproate *vs* lamotrigine/levetiracetam	2175		-	-	0.1595
K-means exposure cluster:					
K-means exposure cluster B	-		-	-	0.8895
K-means exposure cluster C	-		-	-	0.9006
Paternal exposure * cluster:					
Valproate * cluster B	-		-	-	0.8025
Valproate * cluster C	-		-	-	0.9289
Effect of exposure across K-means cluster:					
Valproate vs lamotrigine/levetiracetam in cluster A	-		1.63	(0.83, 3.20)	-
Valproate vs lamotrigine/levetiracetam in cluster B	-		1.40	(0.54, 3.62)	-
Valproate vs lamotrigine/levetiracetam in cluster C	-		1.54	(0.58, 4.13)	-

Legend: HR: hazard ratio; CI: confidence interval

[1] **The logistic regression PS model includes all variables from Table 73, following described: Offspring risk factors/confounders:** "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of: "concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "year of offspring conception at mother's LMP2"
Cluster A: constant high exposure; Cluster B: low-to-high exposure and Cluster C: high-to-low exposure

10.4.1.7 Case assessment

Overall, considering all the groups of paternal exposure, cases of NDD including ASD were identified in 4.2% of the offspring, of which the majority (73.1%) were considered in the case assessment as a probable case (meeting the criteria of multiple diagnosis for NDD including ASD recorded during the follow-up). The same was observed considering valproate and lamotrigine/levetiracetam group, with a higher percentage of NDD including ASD being observed in the valproate group. Considering the valproate group, cases of NDD including ASD were identified in 5.4% of the offspring, of which 82.7% were classified in the case assessment as probable cases. Considering the lamotrigine/levetiracetam group, cases of NDD including ASD were identified in 3.5% of the offspring, of which 63.5% were classified in the case assessment as probable cases (Table 77).

Table 77. Case assessment in Sweden

	Paternal exposure group									
NDD Number of offspring	**Valproate N=968**		**Lamotrigine/ levetiracetam N=1483**		**Lamotrigine N=1262**		**Levetiracetam N=221**		**Total (valproate +lamotrigine/ levetiracetam) N=2451**	
N of offspring identified as cases of NDD	52	5.37%	52	3.51%	44	3.49%	8	3.62%	104	4.24%

including ASD *										
Case assessment										
Possible **	9	17.31%	19	36.54%	17	38.64%	2	25.00%	28	26.92%
Probable **	43	82.69%	33	63.46%	27	61.36%	6	75.00%	76	73.08%

NDD: neurodevelopmental disorders; ASD: Autism Spectrum Disorders
* Percentages were calculated over the total pregnancies in each group
** percentages were calculated over the total number of offspring identified as cases of NDD including ASD in each group
Possible case: The offspring aged ≤12 years were considered a possible case if they satisfy the criteria that only one diagnosis record for NDD including ASD was recorded during follow-up.
Probable case: The offspring aged ≤12 years were considered a probable case if they satisfy the criteria that multiple diagnoses for NDD including ASD were recorded during follow-up, regardless of whether the same code was recorded multiple times or different codes are recorded

10.4.1.8 Exploratory analyses – NDD including ASD cohort

10.4.1.8.1 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Exploratory analysis 5)

Results from exploratory analysis 5 are presented in Table 192 to Table 203 (see Appendix) in Section 15.2.5 (see Appendix). The analysis was performed in the Primary outcome cohort to answer Exploratory Objective 5, which aimed to describe the risk factors and frequency of NDD including ASD in offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine/levetiracetam) and lamotrigine/levetiracetam (in combination with other AEDs excluding valproate) at the time of the conception. Findings were compared to results from the primary cohort for comparative analysis (main analysis).

For the exploratory analyses 5, the inclusion criterion was all offspring from the Primary outcome cohort (N=6,664). After additional exclusions, a total of 414 offspring were included in this analysis, with 92 in valproate and 322 in lamotrigine/levetiracetam group (Figure 36).

Extremely preterm born offspring (gestational age <28 weeks) were 2.2% (2 offspring) in the valproate polytherapy group, and 0.3% (one offspring) in the lamotrigine/levetiracetam polytherapy group. Extremely low (<1000g) birth weight was observed in 2.2% (2 offspring) and 0.9% (3 offspring) in the valproate and lamotrigine/levetiracetam polytherapy groups, respectively. Gestational age and birth weight were similarly distributed between the exposure groups. Compared with the valproate monotherapy in main analysis (Table 67), a similar proportion of girls was observed in the valproate polytherapy group (51.1% vs 50.1% female in the main analyses).

The proportions of offspring in lamotrigine/levetiracetam polytherapy group shows an increasing pattern with more recent birth year in this exploratory analysis, in line with the main analysis (Table 192).

The proportion of NDD including ASD was higher in the offspring paternally exposed to polytherapy (8.7% valproate and 7.5% lamotrigine/levetiracetam) (Table 193) compared with those in monotherapy in the main analysis (5.3% valproate and 2.9% lamotrigine/levetiracetam) (section 10.4.1.6.1).

Compared with the main analyses (Table 68), mothers of this exploratory analyses presented a slightly lower median(IQR) age (30 [27, 34] vs. IQR 31 [27, 35]), and lower proportion of comorbidities, such as neurotic disorders (valproate group: 5.4% vs. 9.1%, lamotrigine/levetiracetam group: 9.9% vs. 12.2%), affective disorders (valproate group: 5.4% vs. 8.4%, lamotrigine/levetiracetam group: 10.6% vs. 9.4%), and gestational diabetes (valproate group: 1.1% vs. 2.5%, lamotrigine/levetiracetam group: 3.4% vs. 3.3%) (Table 194 and Table 195).

Regarding paternal characteristics, fathers for this exploratory analyses compared with the ones included in the main analyses (Table 69) presented similar median age in the valproate and in the lamotrigine/levetiracetam groups.

Compared with the main analyses, in the exploratory analyses 5, a higher proportion was observed in the group of valproate users of neurotic disorder (21.7% vs. 13.7%), affective disorder excluding bipolar affective disorder and mania (14.1% vs. 11.2%), and lower proportion of bipolar affective disorder (8.7% vs. 13.1%). Compared with the main analyses, in exploratory analysis 5, in the group of lamotrigine/levetiracetam a lower proportion was observed for neurotic disorder (17.4% vs. 27.2%), affective disorder excluding bipolar affective disorder and mania (13.0% vs. 29.9%), and bipolar affective disorder (5.3 vs. 29.3%). The most frequent indication for AED treatment in exploratory analyses 5 was epilepsy, in valproate group with 73.9%, and in the lamotrigine/levetiracetam group with 86.6% (Table 69 and Table 197).

The distribution of potential risk factors and confounders for NDD including ASD by paternal exposure of polytherapy group were examined for the Primary outcome cohort for explorative objective 5. Results of univariable analyses are presented in Table 198-Table 200.

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

As observed in the main analyses (Table 67), none of the offspring characteristics were associated with paternal polytherapy exposure (Table 198).

When compared to the main analysis (Table 68), less maternal characteristics were associated to paternal exposure in the exploratory analyses 5 (Table 199). The characteristics were statistically associated with paternal polytherapy exposure:

- Age (continuous, p=0.0413), younger age in the paternal valproate polytherapy exposure group. Age was also identified as a risk factor in the main analysis.
- Concomitant medications associated with neuropsychiatric adverse events 12 months prior to LMP2 (p=0.0015), higher proportions of mothers in the paternal valproate polytherapy exposure group had at least one prescription compared with lamotrigine/levetiracetam polytherapy group. Concomitant medications were also identified as a risk factor in the main analysis.

Also, less paternal characteristics were associated to paternal exposure in the exploratory analyses 5 (Table 200), when compared to the main analyses (Table 69). The following characteristics were statistically associated with paternal polytherapy exposure:

- Schizophrenia, schizotypal and delusional disorders before childbirth (p=0.0463), was less frequent in the lamotrigine/levetiracetam polytherapy group, however this was not identified as a risk factor in the main analyses, and should be interpreted with caution since "schizophrenia, schizotypal and delusional disorders" were presented among 4 fathers from the valproate group and in 3 from the lamotrigine/levetiracetam.
- Year of conception (p=0.0103), more frequently distributed in earlier years of conception in the valproate polytherapy group, and in more recent years in the lamotrigine/levetiracetam polytherapy group. Year of conception was also identified as a risk factor in the main analyses.

The distribution of potential risk factors and confounders were examined by NDD including ASD group in the Primary outcome cohort for explorative objective 5. Results of univariable analyses are presented in Table 201-Table 203. All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

For the offspring characteristics, only gender (OR: 0.26, 95% CI: 0.11, 0.61; p=0.0020) was associated with NDD including ASD event (Table 201), with the proportion of events among males were significantly higher than the proportion of events among females, and the same was observed in the main analyses (Table 70).

For maternal characteristics (Table 202), smoking 3 months prior to LMP2 (OR: 2.58, 95% CI: 1.18, 5.65; p=0.0178) was associated with increased risk of NDD including ASD, however it was not associated in the main analyses (Table 71).

For paternal characteristics (Table 203), the following risk factors were statistically significantly associated with NDD including ASD event:

- Paternal substance abuse (OR: 13.07, 95% CI: 2.52-67.66; p=0.0022), was associated with increased risk of NDD including ASD diagnosis in offspring, however this association was not observed in the main analyses.
- Age (categorical, OR: 5.85, 95% CI: 1.97-17.38; p=0.0338), father's age>40 was associated with increased risk of NDD including ASD, however this association was not observed in the main analyses.
- Year of conception (OR: 0.34, 95% CI: 0.15-0.79; p=0.0416), offspring concepted in earlier years were associated with increased risk of NDD including ASD. Likewise, this association was observed in the main analyses.

10.4.1.8.2 Paternal exposure to valproate or lamotrigine/levetiracetam in discordant siblings (Exploratory analysis 6)

Results from exploratory analysis 6 are presented in Table 204 (see Appendix) in section 15.2.6. The analysis was performed in the Primary outcome cohort for explorative objective 6. This objective aimed to describe the risk factors and frequency of NDD including ASD, in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception. Findings were compared to results obtained from the primary cohort for comparative analysis (main analyses).

For the exploratory analyses 6, the inclusion criterion was all offspring from the Primary outcome cohort for comparative analyses (N=2355). The study population is depicted in Figure 37. A total of 29 matched siblings were included in this analysis, with 15 in valproate and 14 in lamotrigine/levetiracetam group.

Most of the matched siblings of the valproate and lamotrigine/levetiracetam groups were born at term (86.7% and 78.6%, respectively) and weighted ≥2500 g (100% and 78.6%, respectively). In this exploratory analyses a lower proportion of offspring born moderate to late preterm was observed in the valproate group when compared to those in the lamotrigine/levetiracetam group (6.7% vs. 14.3%, respectively), the same was observed for the female gender (46.7% vs. 78.6%, respectively). In the exploratory analysis 6, a higher mean of total years of follow-up was observed in the valproate group than in the lamotrigine/levetiracetam (8.6 vs. 6.2, respectively) Table 204. Highest proportions of offspring paternally exposed to valproate were conceived in the earlier years of the study follow-up, compared to those in the lamotrigine/levetiracetam group (Table 204).

Only 2 events of NDD including ASD were observed in the group of valproate and one in the group of lamotrigine/levetiracetam (Table 205).

Median age of mothers at childbirth was lower in the valproate than in the lamotrigine/levetiracetam group (32, IQR 29, 34 vs. 35, IQR 30, 36, respectively) (Table 206), although similar age was observed between groups in the main analyses (31, IQR 27, 35 vs. 32, IQR 28, 35, respectively) (Table 68). The most common maternal comorbities among valproate and lamotrigine/levetiracetam were the same, i.e. neurotic disorder (26.7% vs. 28.6%, respectively), affective disorder (13.3% vs. 14.3%), diabetes (6.7% vs. 7.1%), and gestational diabetes (6.7% vs. 7.1%). Median maternal polypharmacy index prior to LMP2 was 1.0 (IQR 0.0, 2.0) in valproate and 0.5 (IQR 0.0, 2.0) in lamotrigine/levetiracetam group (Table 207). Although proportions seemed to be higher than in main analyses, exploratory analyses population is comprised only of 29 offspring.

Mean age of fathers at childbirth was lower in the valproate than in the lamotrigine/levetiracetam group (35.2 SD: 3.4, vs. 37.3 SD: 5.0) (Table 208), similar results were observed in the main analyses (Table 69). As in the main analyses, the highest proportions of offspring paternally exposed to valproate were conceived in the earlier years of the study follow-up, compared to those in the lamotrigine/levetiracetam group (Table 208). The most common paternal comorbities among the groups of valproate and lamotrigine/levetiracetam were affective disorder excluding bipolar affective disorder and mania (26.7% and 35.7%, respectively) and bipolar affective (26.7% and 28.6%, respectively), and neurotic disorder (20.0% and 42.9%, respectively). Epilepsy was the most frequent indication for the use of valproate and lamotrigine/levetiracetam in this exploratory analyses 6 (66.7% and 57.1%, respectively) (Table 209). No associations were observed between offspring or maternal characteristics and paternal exposure to valproate or lamotrigine/levetiracetam (Table 210 and Table 211). For fathers, age (categorical) was the

only characteristic statistically associated parternal exposure to valproate or lamotrigine/levetiracetam (p=0.0124) (Table 212)

The associations between offspring, maternal, and paternal characteristics and NDD including ASD were not estimated since the number of events was below 10.

10.4.1.9 Sensitivity analyses for NDD including ASD

Multiple sensitivity analyses were performed to examine the robustness of the main analysis findings. Summary tables of the main results for each of the sensitivity analyses are presented in this section. All tables produced for each of the sensitivity analyses are presented in a separate document (Annex document).

Findings from extending the exposure window for the primary outcome to 6 months (sensitivity analysis 1), excluding offspring with low birth weight or born prior to 8th month for the primary cohort (sensitivity analysis 3), comparing PS-matched model with covariate adjusted model for the primary cohort (sensitivity analysis 6) and examining the effect of paternal exposure to valproate on NDD including ASD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy (sensitivity analysis 7) were consistent with results observed in the main analyses. However, when using a narrower definition of the outcome (sensitivity analysis 11), stronger associations were observed. See Table 78 for further details.

In sensitivity analysis 5, simple pairwise comparison between valproate and lamotrigine: the crude Cox regression model, PS-weighted Cox regression model showed no higher risk of NDD including ASD in the offspring paternally exposed to valproate when compared with offspring paternally exposed to lamotrigine, similarly with estimates from the main analyses. In the PS-weighted Cox regression model adjusted for K-means exposure for cluster A (i.e. constant high exposure), offspring whose fathers had constant higher exposure to valproate had higher risk of NDD including ASD when compared with those exposed to lamotrigine (HR: 2.27, 95% CI: 1.02-5.05). For this cluster (i.e. cluster A), the number of offspring with NDD including ASD events observed in the valproate and lamotrigine group were 22 and 10, respectively. For cluster B (from low-to-high exposure) and C (high-to-low exposure), no higher risk of NDD including ASD was observed in the offspring paternally exposed to valproate when compared with offspring paternally exposed to lamotrigine. See Table 78 for further details.

In sensitivity analysis 5, simple pairwise comparison between valproate and levetiracetam. In the crude Cox regression model, there were 49 offspring with NDD including ASD reported in the fathers exposed to valproate while zero events reported in the levetiracetam group resulting non-interpretable HR. The PS-weighted cox regression model reported no increased risk of NDD including ASD in the offspring paternally exposed to valproate (47 offspring with NDD including ASD events) when compared with levetiracetam (4 offspring with NDD including ASD events) (HR: 0.67, 95% CI: 0.20-2.24). In PS-weighted Cox regression model adjusted for K-means exposure clusters, fathers in the constant higher exposure (cluster A), no increased risk of NDD including ASD in the offspring paternally exposed to valproate (22 offspring with NDD including ASD events) when compared with levetiracetam (4 offspring with NDD including ASD events) (HR: 0.0, 95% CI: 0.12-1.32). No offspring with NDD including ASD event reported in the levetiracetam group for cluster B and cluster C while 11 and 13 NDD including ASD events reported in the valproate group for the earlier and the later cluster, respectively making the HR non-interpretable. See Table 78 for further details

In sensitivity analysis 11, a narrower definition of NDD was applied to the Primary outcome cohort for the descriptive analysis. No higher risk of NDD was observed in the crude Cox regression model (HR 1.26, 95% CI: 0.82-1.93), however, in the PS-weighted Cox regression model a significant higher risk of NDD including ASD was observed (HR 1.70, 95% CI: 1.02-3.96). In the PS-weighted Cox regression model

adjusted for K-means exposure similar results were observed when compared to the main analysis, although the magnitude of the estimates was stronger for cluster A and cluster C. See Table 78 for further details.

Table 78. Summary of main analysis and sensitivity analyses for Neurodevelopmental Disorders (NDD) including Autism Spectrum Disorders (ASD) in Sweden

Analyses	Population considered	HR (95% CI) estimates		HR (95% CI) estimates by cluster of exposure		
		Crude*	Adjusted**	Cluster A	Cluster B	Cluster C
Main analysis N sample = 2355	Please check Section 9.3	1.16 (0.76, 1.76)	1.54 (0.95, 2.51)	1.63 (0.83, 3.20)	1.40 (0.54, 3.62)	1.54 (0.58, 4.13)
Sensitivity analysis 1 N sample = 2504	Extended risk window of paternal valproate exposure (6 months)	1.13 (0.74, 1.71)	1.43 (0.89, 2.31)	1.93 (1.03, 3.64)	0.89 (0.43, 1.844)	-
Sensitivity analysis 3 N sample = 2335	Exclusion of offspring with low birth weight or born prior to 8th months	1.19 (0.78, 1.81)	1.48 (0.91, 2.42)	1.50 (0.74, 3.02)	1.42 (0.55, 3.69)	1.50 (0.58, 3.89)
Sensitivity analysis 5[A] N sample = 2137	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	1.31 (0.84, 2.04)	1.65 (0.98, 2.77)	2.27 (1.02, 5.05)	1.07 (0.41, 2.78)	1.58 (0.59, 4.27)
Sensitivity analysis 5[B] N sample = 1140	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	-	0.67 (0.20, 2.24)	0.40 (0.12, 1.32)	-	-
Sensitivity analysis 6 N sample = 2355	Comparison of PS-weighted model with covariate adjustment model		1.17 (0.77, 1.78)			
Sensitivity analysis 7 N sample = 2399	Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy	1.04 (0.70, 1.54)	1.34 (0.84, 2.11)	1.54 (0.79, 3.01)	1.36 (0.58, 3.15)	1.05 (0.43, 2.55)
Sensitivity analysis 11 N sample = 2355	Narrow definition of NDD	1.26 (0.82,1.93)	1.70 (1.02,2.81)	1.92 (0.93,3.96)	1.31 (0.49,3.49)	1.86 (0.67-5.15)

Cluster A: constant high exposure; Cluster B: low-to-high exposure; and Cluster C: high-to-low exposure
ASD: Autism Spectrum Disorders; CI: Confidence Interval; HR: Hazard ratio; NDD: neurodevelopmental disorders; SD: Standard Deviation; **5[A]** analysis comparing valproate and lamotrigine; **5[B]** analysis comparing valproate and levetiracetam; (-) HR not estimated because the number of events was lower than 10. *: for sensitivity analysis 7 the "crude" hazard ratio was adjusted for offspring epilepsy and offspring exposure AED; **** The logistic regression PS models used in sensitivity analysis include variables following described:**

Sensitivy analysis 1: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2" "Year of offspring conception"

Sensitivy analysis 3: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Gestational diabetes", "Neurotic disorder", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during Pregnancy", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", "Year of offspring conception"

Sensitivy analysis 5[A]: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", "Year of offspring conception LMP2"

Sensitivy analysis 5[B]: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Gestational diabetes", "Neurotic disorder", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Neurotic disorder" fathers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", Year of offspring conception"

Sensitivy analysis 6: no PS weighting performed

Sensitivy analysis 7: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders**: "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2, "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception"

Sensitivy analysis 11: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders**: "Affective disorder", "Gestational diabetes", "Obesity", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", "Polypharmacy index", fathers with at least one prescription of: "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception"

Validation of the assumption that individuals were exposed to one DDD per day (sensitivity analysis 8) was performed among fathers who had prescriptions of AED for epilepsy, the estimated treatment durations (estimated from the number of prescriptions as described in section 9.9.4.8) were similar for fathers treated with lamotrigine 90.00 (±73.60) days and those on levetiracetam 90.17 (±52.24) days, while those in the valproate group had relatively short expected treatment duration 76.86 (±45.57) days. The actual observed time between prescriptions was longer for fathers prescribed with lamotrigine 97.05 (±35.39) days followed by valproate 93.86 (±34.27) days and levetiracetam 90.86 (±33.53) days. The ratio (observed vs estimated) was higher for lamotrigine 1.69 followed by valproate 1.46 and levetiracetam 1.23 (Table 79). Under the assumption of perfect compliance of each father, ratios depart from the approximation range 0.8-1.20, which indicate the real daily dose prescribed diverge from the WHO DDD (see Table 79 for further details).

Sensitivity analysis 8 was also performed among fathers who had dispenses of AED without indication for epilepsy, the estimated treatment durations (expected) were similar for fathers treated with lamotrigine 74.33 (±55.06) days and those on valproate 72.87 (±41.31) days, while those in the levetiracetam group had shorter expected treatment duration 66.81 (±45.71) days. Time between prescriptions (observed) was also similar for fathers prescribed with valproate 94.88 (±37.74) days and lamotrigine 94.66 (±37.52) days, while fathers prescribed with levetiracetam had shorter observed time between prescriptions 77.94 (±35.54) days. The ratio (observed vs expected) was higher for lamotrigine 2.11 followed by valproate 1.69 and levetiracetam 1.56 (Table 79). Under the assumption of perfect compliance of each father, ratios depart from the approximation range 0.8-1.20 which indicate the real daily dose prescribed diverge from the WHO DDD (see Table 79 for further details).

Table 79. Distribution of estimated treatment durations and time between prescriptions for fathers with/without an indication for epilepsy; Primary outcome cohort in Sweden

	Distribution of estimated treatment durations and time between prescriptions for fathers with an indication for epilepsy			**Distribution of estimated treatment durations and time between prescriptions for fathers without an indication for epilepsy; primary outcome**		
	Paternal exposure group			**Paternal exposure group**		
NDD	**Valproate**	**Lamotrigine**	**Levetiracetam**	**Valproate**	**Lamotrigine**	**Levetiracetam**
Number of offspring	**N=684**	**N=493**	**N=190**	**N=284**	**N=769**	**N=31**
Estimated treatment durations (expected)	76.86 (45.57)	90.00 (73.60)	90.17 (52.24)	72.87 (41.31)	74.33 (55.06)	66.81 (45.71)
Time between prescriptions (observed)	93.86 (34.27)	97.05 (35.39)	90.86 (33.53)	94.88 (37.74)	94.66 (37.52)	77.94 (35.54)
Ratio (observed vs expected)	1.46	1.69	1.23	1.69	2.11	1.56

NDD: neurodevelopmental disorders

In sensitivity analysis 10, the mean paternal cumulative exposure to valproate was 50.3 (±22.9) days, while in the lamotrigine/levetiracetam group mean paternal cumulative exposure 49.6 (±24.6) days reported (see Table 80). Comparing paternal cumulative exposure to valproate with

lamotrigine/levetiracetam at specific cumulative exposure level (mean cumulative exposure 50.1) showed no increased risk NDD including ASD to the offspring (HR 1.17, 95% CI: 0.62, 2.18). At this particular mean cumulative exposure, the number of events reported in the valproate group and lamotrigine/levetiracetam group were 26 and 21, respectively. See Table 81 for further detail (NDD including ASD event data not shown).

Among fathers exposed to valproate, medium cumulative exposure to valproate showed lower risk of NDD including ASD in the offspring when compared with low cumulative exposure to valproate (HR: 0.11, 95% CI: 0.03- 0.46). However, only 2 NDD, including ASD, events were observed in the medium cumulative exposure while 17 events for the low cumulative exposure to valproate, which may have influenced the HR estimates. Comparison between high paternal exposure to valproate and low paternal exposure to valproate showed no difference in the risk of NDD including ASD in the offspring (HR: 1.01, 95% CI: 0.52-1.95). The number of NDD including ASD events reported to the high cumulative exposure to valproate group was 18.

Among fathers exposed to lamotrigine, no NDD including ASD event reported for both low cumulative exposure and medium cumulative exposure to lamotrigine, hence the HR for these comparisons were not relevant. In the high cumulative exposure to lamotrigine, 10 NDD including ASD events were reported, but comparing with low cumulative exposure to lamotrigine (0 event), resulted quasi-separation and hence infinite HR was observed. See Table 82 (NDD including ASD events, data not shown).

Table 80. Paternal cumulative exposure to AEDs by paternal exposure group; Primary outcome cohort in Sweden

Paternal exposure group										
NDD **Number of offspring**	**Valproate** **N=930**		**Lamotrigine/levetiracetam** **N=1425**		**Lamotrigine** **N=1207**		**Levetiracetam** **N=218**		**Total (valproate + lamotrigine/levetiracetam)** **N=2355**	
Cumulative exposure to AEDs	N	%	N	%	N	%	N	%	N	%
Low	300	32.26	477	33.47	404	33.47	72	33.03	773	32.82
Medium	322	34.62	468	32.84	402	33.31	72	33.03	806	34.23
High	308	33.12	480	33.68	401	33.22	74	33.94	776	32.95
Mean (SD)	50.25 (22.85)		49.64 (24.93)		48.61 (24.98)		55.35 (23.90)		49.88 (24.12)	
Median (25th - 75th percentile)	50 (34.00, 68.00)		51 (30.00, 71.00)		50 (29.00, 70.00)		57 (34.00, 81.00)		51 (32.00, 70.00)	
Min, max	1.00, 84.00		1.00, 84.00		1.00, 84.00		5.00, 84.00		1.00, 84.00	

AED: antiepileptic drugs; NDD: neurodevelopmental disorders; SD: Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father appeared more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

Table 81. Effect estimation for neurodevelopmental disorders (NDD) using Cox regression model adjusted for covariates; Primary outcome cohort in Sweden

NDD	**Model estimates**		
Number of subjects included in analysis prior to exclusion influential subjects [a]	2355		
Number of subjects included in the model (after excluding influential subjects) [b]	2312 (98.17%)		
Variable **Effect of valproate at a specific cumulative exposure level:**	**HR**	**95% CI**	**P-value**
Valproate vs lamotrigine/levetiracetam at the mean cumulative exposure=50.11419	1.17	(0.62, 2.18)	-

Legend: Hazard ratios (HR), 95% confidence intervals (CI); NDD: neurodevelopmental disorders, and p-values were represented for risk factors and confounders included in the covariate adjustment model. All variables potentially included in the model were listed here, however some of the variables might not be included in the final set of variables.
a) Number of subjects included represents the total number of subjects in the cohort of interest minus those subjects who had at least one missing value for any of the variables included in each model.
b) Influential subjects were identified using the dfbetas for the exposure coefficient.

Table 82. Effect estimation for neurodevelopmental disorders (NDD) using Cox covariate adjustment model for valproate and lamotrigine treatment group; Primary outcome cohort in Sweden

	Valproate			Lamotrigine		
	N	HR (95% CI)	P-value	N	HR (95% CI)	P-value
Number of subjects included in analysis prior to exclusion influential subjects [a]	930			1207		
Number of subjects included in the model (after excluding influential subjects) [b]	918 (98.71%)			1184 (98.09%)		
Paternal cumulative exposure						
Low		Reference			Reference	Reference
Medium		0.11 (0.03, 0.46)	0.0025		1.00	0.9854
High		1.01 (0.52, 1.95)	0.9813		*	

Legend: Hazard ratios (HR), 95% confidence intervals (CI) and p-values were represented for risk factors and confounders included in the covariate adjustment model. All variables potentially included in the model are listed here, however some of the variables might not be included in the final set of variables.
a) Number of subjects included represents the total number of subjects in the cohort of interest minus those subjects who had at least one missing value for any of the variables included in each model.
b) Influential subjects were identified using the dfbetas for the exposure coefficient.
* no event in Lamotrigine group was recorded resulted in quasi-separation, hence the computed HR was not interpretable

10.4.2 Congenital Malformations

10.4.2.1 Risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment at the time of conception (Exploratory analysis 7)

Results from exploratory analysis 7 are presented in Table 213 to Table 226 (see Appendix) in section 15, and in Table 83 to Table 85 (effect estimation, below). The analyses were performed in order to answer the Exploratory Objective 7, which aimed to investigate the risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam (monotherapy composite) treatment at the time of conception. Assessing the risk of CM in Sweden was only performed as an Exploratory analysis, as the Swedish population for analysis is comprised of live births only.

For the exploratory analysis 7, the inclusion criterion was all offspring from the Secondary outcome cohort for exploratory analyses in Sweden (N=6664).The study population flowchart is depicted in Figure 38. For the comparative analyses were included 888 offspring, with 418 from the valproate and 470 from lamotrigine/levetiracetam group.

Results for demographic and clinical characteristics were obtained from the Secondary outcome cohort for explorative objective 7 (descriptive analyses). The majority of the offspring was born at term (valproate

group 88.6% and lamotrigine/levetiracetam group 88.3%), weighted ≥2,500 g (valproate group 95.8%, lamotrigine/levetiracetam 96.6%), and there was a similar gender distribution (males 50.1% in valproate group and 52.0% in lamotrigine/levetiracetam) (Table 213). Clinical characteristics of offspring were similar in terms of congenital malformation for the valproate (10.4%, with 5.6% major and 5.9% minor) and lamotrigine/levetiracetam (10.5%, with 5.5% major and 5.7% minor) (Table 214).

Regarding maternal demographic characteristics, mean (SD) age in years was 30.7 (5.3) in the group of valproate and 31.4 (5.2) in lamotrigine/levetiracetam group (Table 215). The most frequent maternal clinical characteristics for valproate and lamotrigine/levetiracetam were gestational diabetes (2.7% and 3.2%, respectively), diabetes (1.1% and 1.2%, respectively), and obesity (1.1% and 1.1%, respectively). The proportion of mothers that reported smoking prior to LMP2 was 16.3% in the valproate and 12.7% in the lamotrigine/levetiracetam group. The proportion of mothers with at least one prescription of drugs with teratogenic activity/foetal toxicity prior to LMP2 was 26.0% in the valproate and 27.4% in the lamotrigine/levetiracetam group. The proportion of mothers with at least one prescription of drugs with teratogenic activity/foetal toxicity during pregnancy was 29.2% in the valproate and 33.3% in the lamotrigine/levetiracetam group. Nevertheless, these exposures were considered as risk factors for CM and excluded for the comparative analysis (Table 216).

Regarding paternal demographic characteristics, mean (SD) age in years was 33.6 (6.0) in the group of valproate and 34.3 (6.2) in lamotrigine/levetiracetam group. A higher proportion of offspring in the valproate group were conceived in the earlier study years, whereas for the group lamotrigine/levetiracetam a higher proportion of offspring were conceived in more recent years (Table 217).

The most frequent AED indication was epilepsy for both valproate (70.7%) and lamotrigine/levetiracetam (46.1%) groups, followed by other/unknown in the valproate (16.5%) and bipolar affective disorders and mania in lamotrigine/levetiracetam (28.9%). The proportion of paternal exposure to teratogenic activity/foetal toxicity prior to LMP2 was 28.1% in the valproate and 45.1% in the lamotrigine/levetiracetam group, nevertheless this exposure was considered as risk factor for CM and excluded for the comparative analysis (Table 218).

The K-means algorithm analysing DDD trajectories in fathers exposed to AEDs 3 months before LMP2 was performed in the Secondary outcome cohort for explorative objective 7 (descriptive analyses), and identified 3 different clusters A, B, and C: Cluster A: constant high exposure; Cluster B: low-to-high exposure and Cluster C: high-to-low exposure (Figure 39). In the valproate group, 41.3% were in cluster A, 30.9% were in cluster B, and 27.8% in cluster C. In the lamotrigine/levetiracetam polytherapy group, 43% were in cluster A, 33.3% were in cluster B, and 23.7% were in the cluster C (Table 218).

The observed cumulative incidence of CM was assessed in the Secondary outcome cohort for explorative objective 7 (descriptive analyses). Results were fairly similar between the group of valproate in overall study follow-up (0-12+ years) (10.4%, 95% CI: 8.5%, 12.4%) and lamotrigine/levetiracetam (10.5, 95% CI: 9.0%, 12.1%), and in each of the strata of years of follow-up, with proportions with overlapping CIs (Table 219).

Results for associations between potential risk factors/confounders for CM with study exposure (valproate vs. lamotrigine/levetiracetam) and CM were obtained from the Secondary outcome cohort for explorative objective 7 (comparative analyses). No characteristics of offspring were significantly associated to paternal exposure (Table 220). Age (continuous) (p=0.0506) and alcohol abuse prior to LMP2 (p=0.0487) were the maternal characteristics associated to the paternal exposure (Table 221). For paternal characteristics only the categories of calendar year of offspring conception was associated with the paternal exposure (p<0.0001) (Table 222).
No association was observed between offspring and paternal characteristics and the CM occurrence (Table 223 and

Table 225).

Gestational diabetes (OR: 7.11, 95% CI: 2.13,-23.76, p=0.0014) was the maternal characteristic associated with CM (Table 224).

The variable estimates from logistic regression propensity score models presented in Table 226 show that maternal smoking prior to LMP2 (OR: 1.86, 95% CI: 1.10, 3.13, p=0.0198) and smoking during pregnancy (OR: 0.46, 95% CI: 0.22, 0.99, p=0.0483) were associated with CM. The PS models for random forest and logistic regression informed by random forest were not performed for the present exploratory analysis 7, since all offspring presented a value of zero for the selected risk factors. Figure 40 depicts the balanced weighting score plot of PS logistic regression model. The logistic regression model was used to apply inverse probability of treatment weights in the effect estimation analysis.

The effect estimation for CM was assessed by using crude logistic regression model as presented in Table 83, and included 888 subjects from the Secondary outcome cohort for explorative objective 7 (comparative analyses). The OR of CM in offspring of fathers exposed to valproate when compared to those with fathers exposed to lamotrigine/levetiracetam was (OR: 1.01, 95% CI: 0.66, 1.55).

The effect estimation for CM using PS-weighted logistic regression model was assessed in a total of 838 offspring of fathers exposed to either valproate or lamotrigine/levetiracetam and the OR was (OR: 0.92, 95% CI: 0.59, 1.44) (Table 84).

Table 85 presents the effect estimation for CM using PS-weighted logistic regression model adjusted for the K-means exposure cluster. The estimation was assessed in a total of 838 offspring, and no significant differences on the effect across K-means cluster of valproate compared with lamotrigine/levetiracetam group were observed for cluster A (OR: 1.36, 95% CI: 0.65, 2.82), B (OR: 0.56, 95% CI: 0.22, 1.38), or C (OR: 0.86, 95% CI: 0.42, 1.78). Likewise, no interaction between exposure and paternal K-means cluster was observed.

Table 83 Effect estimation for Congenital Malformations (CM) using crude logistic model; Secondary outcome cohort in Sweden

Variable	Total N	Model estimates		
	N	OR	95% CI	P-value

Paternal exposure: valproate vs lamotrigine/levetiracetam	888	1.01	(0.66, 1.55)	0.9456

OR: Odds ratio; CI: Confidence Interval

Table 84 Effect estimation for Congenital Malformations (CM) using Propensity Score weighted logistic model; Secondary outcome cohort in Sweden

Variable	Total N	Model estimates [1]		
	N	OR	95% CI	P-value
Paternal exposure: valproate vs lamotrigine/levetiracetam	838	0.92	(0.59, 1.44)	0.7174

OR: Odds ratio; CI: Confidence Interval

[1] **The logistic regression PS model includes variables following described: Maternal risk factors/confounders:** "Smoking prior to LMP2", "Smoking during pregnancy"

Table 85 Effect estimation for Congenital Malformations (CM) using Propensity Score weighted logistic regression model on offspring with concordant K-means exposure cluster; Secondary outcome cohort in Sweden

Variable	Total N	Model estimates [1]		
		OR	95% CI	P-value
Paternal exposure: valproate vs lamotrigine/levetiracetam	838	-	-	0.6875
K-means exposure cluster:				
K-means exposure cluster B	-	-	-	0.7497
K-means exposure cluster C	-	-	-	0.6819
Paternal exposure * cluster:				
Valproate * cluster B	-	-	-	0.3909
Valproate * cluster C	-	-	-	0.4599
Effect of valproate across K-means cluster:				
Valproate vs lamotrigine/levetiracetam in cluster A	-	1.36	(0.65, 2.82)	-
Valproate vs lamotrigine/levetiracetam in cluster B	-	0.56	(0.22, 1.38)	-
Valproate vs lamotrigine/levetiracetam in cluster C	-	0.86	(0.42, 1.78)	-

OR: Odds ratio; CI: Confidence Interval
Cluster A: constant high exposure; Cluster B: low-to-high exposure; and Cluster C: high-to-low exposure.
[1] **The logistic regression PS model includes variables following described: Maternal risk factors/confounders:** "Smoking prior to LMP2", "Smoking during pregnancy"

10.5Results for Norway

After applying all the inclusion and exclusion criteria, a total of 40,220 pregnancies were identified in databases in Norway. Subsequently additional exclusion criteria, not mutually exclusive, were applied to obtain the populations used for the descriptive and comparative analysis for each outcome, separately.

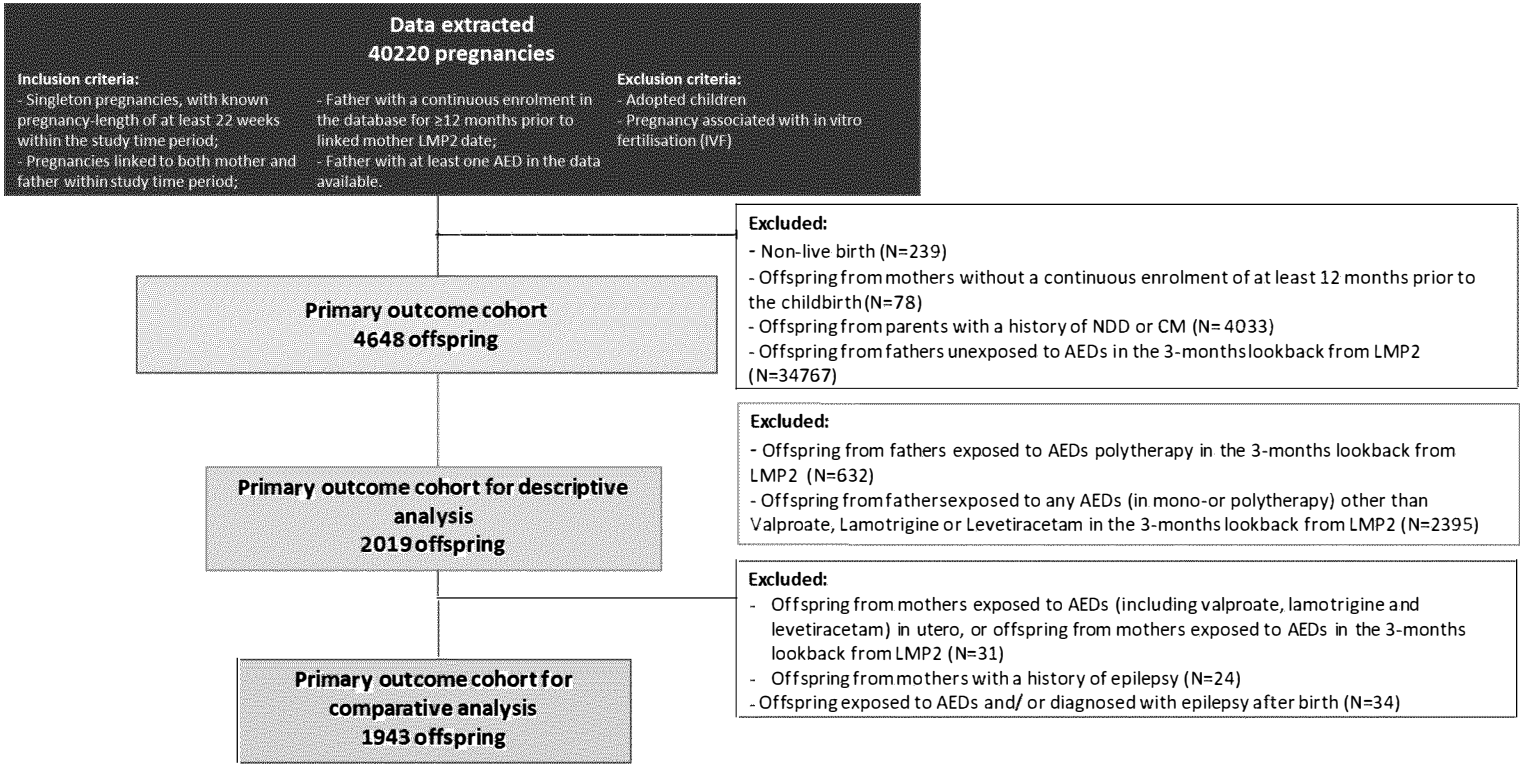
Please note that during stepwise exclusions from the cohorts post data extraction (Primary outcome cohort and Secondary outcome cohort), some characteristics were absent as they were either one of the exclusion criteria or characteristics associated with the exclusion criteria. Offspring with epilepsy, fathers exposed to other AEDs than those of interest, and mothers exposed to AEDs or with a history of epilepsy are examples of excluded characteristics. Although these populations are described in this report, they are not part of the comparative analysis.

The selection of the Primary outcome cohort is presented in Figure 20.

From all the 40,220 pregnancies identified, the following were excluded: non-live births (N=239), offspring from a mother without a continuous enrolment in database of at least 12 months prior to the childbirth (N=78), offspring from parents with a history of NDD including ASD or CM (N=4033), offspring from paternally unexposed to AEDs in the 3 months lookback period from LMP2 (N=34767). Thus, the Primary outcome cohort consisted of 4,648 offspring. Briefly, there were 2,019 offspring included in the Primary

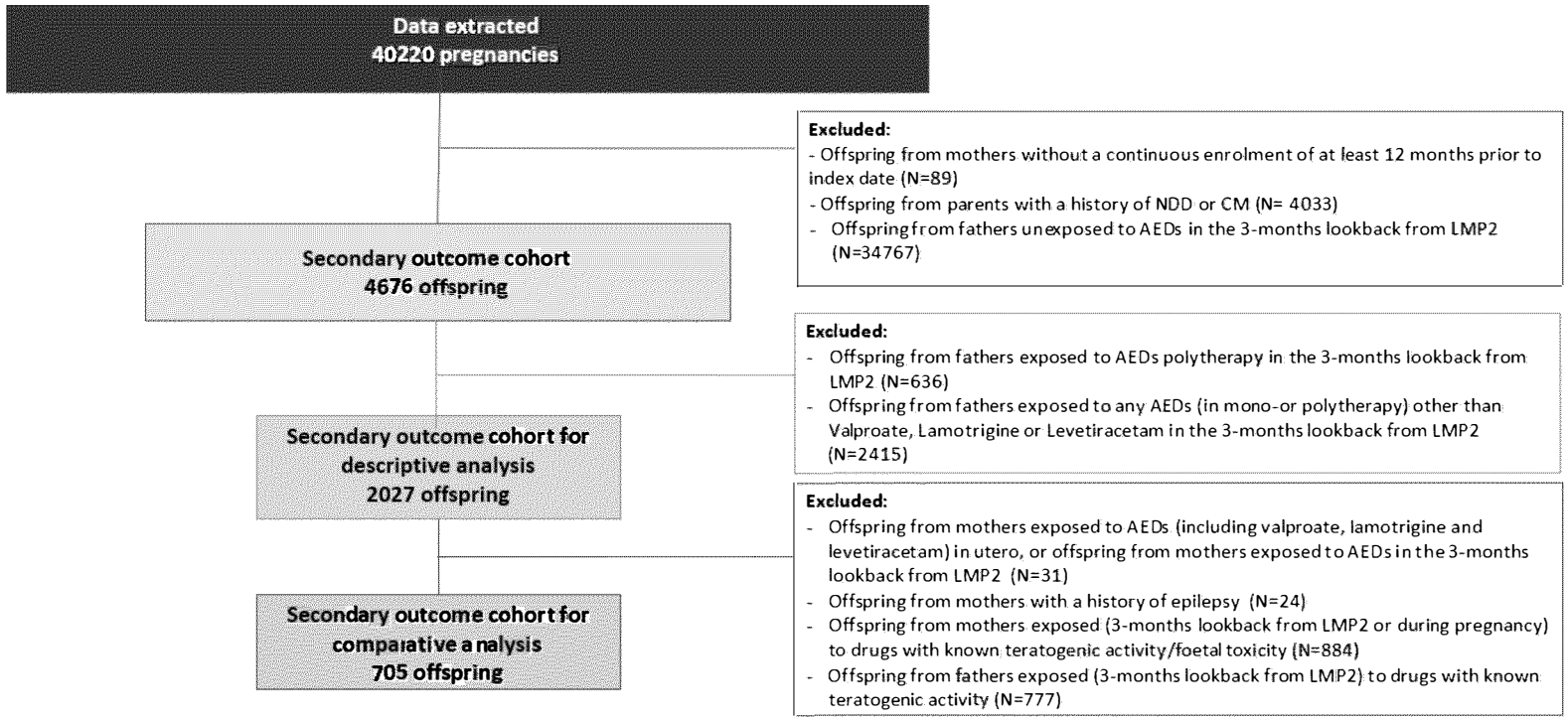
outcome cohort for descriptive analyses, and 1943 offspring in the Primary outcome cohort for comparative analyses.

The selection of the Secondary outcome cohort, used to assess risk of CM is depicted in Figure 21. The Secondary outcome cohort for descriptive analyses consisted of 2027 offspring, the Secondary outcome cohort for comparative analyses consisted of 705 offspring.



AED: antiepileptic drug; LMP2: last menstrual period + 2 weeks; CM: Congenital Malformation; NDD: neurodevelopmental disorders
LMP2: last menstrual period + 2 weeks.
The same child could be counted in different exclusion categories, explaining why numbers do not necessarily add up

Figure 20 Study population of the Primary outcome cohort in Norway



AED: antiepileptic drug; CM: Congenital Malformation; NDD: neurodevelopmental disorders;
LMP2: last menstrual period + 2 weeks.
The same child could be counted in different exclusion categories, explaining why numbers do not necessarily add up

Figure 21 Study population of the Secondary outcome cohort in Norway

10.5.1 Neurodevelopmental disorders including autism spectrum disorder

10.5.1.1 Description of the offspring, maternal and paternal characteristics by paternal exposure group

This section presents demographic and clinical characteristics of offspring, mothers, and fathers according to paternal exposure in monotherapy to valproate, lamotrigine or levetiracetam and the comparator group of composite lamotrigine/levetiracetam monotherapy. This analysis was performed in the Primary outcome cohort for descriptive analyses, which was described in Figure 20.

Table 86 shows offspring demographic characteristics of the Primary outcome cohort for descriptive analyses by paternal exposure group. A total of 640 offspring paternally exposed to valproate and 1379 offspring paternally exposed to lamotrigine / levetiracetal were included. The majority of offspring were male (52.2%) (50.3% in those paternally exposed to valproate and 53.1% in those paternally exposed to lamotrigine/levetiracetam), born at term between 37-41 weeks of gestational age (overall 89.5%; (87.8% in those paternally exposed to valproate and 90.3% in those paternally exposed to lamotrigine/levetiracetam), and weighing ≥2500 g (96.6%, similar in both exposure groups). A higher proportion of offspring in the lamotrigine/levetiracetam group were conceived in the later years of the study time period (2010-2019) compared to those in the valproate group, leading to a higher follow-up period among offspring paternally exposed to valproate. The total offspring-years of follow-up was 13072.4 (4491.0 for valproate and 8581.4 for lamotrigine/levetiracetam group), and the mean follow-up in years per offspring was 7.0 for the valproate group and 6.2 for the lamotrigine/levetiracetam group (Table 86).

Regarding clinical characteristics of offspring by paternal exposure to valproate and lamotrigine/levetiracetam groups, 2.5% offspring paternally exposed to valproate and 1.2% paternally exposed to lamotrigine/levetiracetam were diagnosed with epilepsy, and 1.4% of offspring paternally exposed to valproate and 0.7% of offspring paternally exposed to lamotrigine/levetiracetam were exposed to AEDs between birth and exit date.

In the descriptive cohort, 6.7% of offspring paternally exposed to valproate and 4.0% of offspring paternally exposed to lamotrigine/levetiracetam was diagnosed having a NDD including ASD during the follow-up. The median age in years at the first diagnosis of NDD including ASD was 6.6 (4.7- 7.9) for the valproate and 6.1 (3.9- 8.3) for the lamotrigine/levetiracetam group (Table 87)

ASD as the first NDD diagnosis, during all the study period, was observed in 0.63% of offspring paternally exposed to valproate and in 0.58% of offspring paternally exposed to lamotrigine/levetiracetam. All ASD diagnoses, ever and not only as a first diagnosis, were observed in 1.6% of offspring paternally exposed to valproate and in 0.7% of offspring paternally exposed to lamotrigine/levetiracetam. The median (IQR)

age in years at the first diagnosis of ASD was 4.9 (3.6, 9.6) for offspring paternally exposed to valproate and 4.8 (4.0, 7.2) for offspring paternally exposed to lamotrigine/levetiracetam.

Table 86 Offspring demographic characteristics by paternal exposure group; Primary outcome cohort in Norway (N=2019)

	Paternal exposure group									
NDD Number of offspring	Valproate N=640		Lamotrigine/levetiracetam N=1379		Lamotrigine N=1185		Levetiracetam N=194		Total (valproate + lamotrigine/levetiracetam) N=2019	
	N	%	N	%	N	%	N	%	N	%
Gestational age (weeks)										
<28 (extremely preterm)	2	0.31	4	0.29	4	0.34	0	0.00	6	0.30
28-31 (very preterm)	3	0.47	7	0.51	6	0.51	1	0.52	10	0.50
32-36 (moderate to late preterm)	35	5.47	55	3.99	47	3.97	8	4.12	90	4.46
37-41 (at term)	562	87.81	1245	90.28	1068	90.13	177	91.24	1807	89.50
≥42 (post-term)	38	5.94	68	4.93	60	5.06	8	4.12	106	5.25
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	3	0.47	7	0.51	6	0.51	1	0.52	10	0.50
1000-1499 (very low)	2	0.31	4	0.29	4	0.34	0	0.00	6	0.30
1500-2499 (low)	17	2.66	35	2.54	29	2.45	6	3.09	52	2.58
≥2500	618	96.56	1333	96.66	1146	96.71	187	96.39	1951	96.63
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gender [a]										
Male	322	50.31	732	53.08	618	52.15	114	58.76	1054	52.20
Female	318	49.69	647	46.92	567	47.85	80	41.24	965	47.80
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of birth										
2006	52	8.13	65	4.71	60	5.06	5	2.58	117	5.79
2007	62	9.69	51	3.70	49	4.14	2	1.03	113	5.60
2008	56	8.75	95	6.89	83	7.00	12	6.19	151	7.48
2009	57	8.91	110	7.98	97	8.19	13	6.70	167	8.27
2010	33	5.16	90	6.53	82	6.92	8	4.12	123	6.09
2011	48	7.50	117	8.48	107	9.03	10	5.15	165	8.17
2012	45	7.03	85	6.16	76	6.41	9	4.64	130	6.44
2013	47	7.34	105	7.61	88	7.43	17	8.76	152	7.53

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=640**		**N=1379**		**N=1185**		**N=194**		**N=2019**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
2014	43	6.72	120	8.70	99	8.35	21	10.82	163	8.07
2015	43	6.72	105	7.61	87	7.34	18	9.28	148	7.33
2016	44	6.88	122	8.85	96	8.10	26	13.40	166	8.22
2017	45	7.03	109	7.90	94	7.93	15	7.73	154	7.63
2018	37	5.78	97	7.03	81	6.84	16	8.25	134	6.64
2019	28	4.38	108	7.83	86	7.26	22	11.34	136	6.74
Total number of years of follow-up	4490.96		8581.42		7546.97		1034.45		13072.38	
Mean follow-up year	7.02		6.22		6.37		5.33		6.47	

NDD: neurodevelopmental disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 87 Offspring clinical characteristics by paternal exposure group; Primary outcome cohort in Norway (N=2019)

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=640**		**N=1379**		**N=1185**		**N=194**		**N=2019**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Comorbidities [a]										
Congenital CMV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Epilepsy	16	2.50	16	1.16	12	1.01	4	2.06	32	1.58
Foetal alcohol syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fragile X syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lejeune/cri du chat syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tuberous sclerosis	0	0.00	1	0.07	1	0.08	0	0.00	1	0.05
Medication use										
Exposure to AEDs [a]	9	1.41	9	0.65	7	0.59	2	1.03	18	0.89
Outcomes										
ASD (ever, not only as 1st diagnosis)	10	1.56	10	0.73	10	0.84	0	0.00	20	0.99
ASD (as 1st diagnosis)	4	0.63	8	0.58	8	0.68	0	0.00	12	0.59
NDD including ASD	43	6.72	55	3.99	48	4.05	7	3.61	98	4.85
Outcomes (ICD-10 codes, ever) [b]										
Intellectual Disability - Mild	1	0.16	1	0.07	1	0.08	0	0.00	2	0.10
Intellectual Disability - Moderate	2	0.31	1	0.07	1	0.08	0	0.00	3	0.15
Intellectual Disability -Severe	0	0.00	1	0.07	1	0.08	0	0.00	1	0.05
Intellectual Disability -Profound	0	0.00	1	0.07	1	0.08	0	0.00	1	0.05
Other Intellectual Disability	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Unspecified Intellectual Disability	1	0.16	4	0.29	4	0.34	0	0.00	5	0.25
Specific developmental disorders of speech and language	14	2.19	13	0.94	12	1.01	1	0.52	27	1.34
Specific developmental disorders of scholastic skills	5	0.78	8	0.58	8	0.68	0	0.00	13	0.64
Mixed specific developmental delays	7	1.09	4	0.29	2	0.17	2	1.03	11	0.54
Pervasive developmental disorders	10	1.56	11	0.80	11	0.93	0	0.00	21	1.04
Other disorders of psychological development	0	0.00	1	0.07	1	0.08	0	0.00	1	0.05
Unspecified disorder of psychological development	1	0.16	1	0.07	1	0.08	0	0.00	2	0.10
Mental disorder, not otherwise specified	1	0.16	0	0.00	0	0.00	0	0.00	1	0.05
Dyslexia and other symbolic dysfunctions,	2	0.31	1	0.07	1	0.08	0	0.00	3	0.15

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=640		N=1379		N=1185		N=194		N=2019	
	N	%	N	%	N	%	N	%	N	%
not elsewhere classified										
Hyperkinetic disorders	24	3.75	26	1.89	24	2.03	2	1.03	50	2.48
Other specified behavioral and emotional disorders with onset usually occurring in childhood and adolescence	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tic disorders	3	0.47	6	0.44	5	0.42	1	0.52	9	0.45
Specific developmental disorder of motor function	3	0.47	4	0.29	4	0.34	0	0.00	7	0.35
Stereotyped movement disorders	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Essential tremor	0	0.00	1	0.07	0	0.00	1	0.52	1	0.05
Other specified forms of tremor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Myoclonus	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other chorea	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other specified extrapyramidal and movement disorders	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Extrapyramidal and movement disorder, unspecified	0	0.00	1	0.07	1	0.08	0	0.00	1	0.05
Idiopathic nonfamilial dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Spasmodic torticollis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Idiopathic orofacial dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blepharospasm	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dystonia, unspecified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Extrapyramidal and movement disorders in diseases classified elsewhere	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Age at the first diagnosis (years)										
ASD (ever, not only as 1st diagnosis) [c,d]										
0-1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2-3	3	0.47	2	0.15	2	0.17	0	0.00	5	0.25
4-5	3	0.47	4	0.29	4	0.34	0	0.00	7	0.35
6-7	1	0.16	3	0.22	3	0.25	0	0.00	4	0.20
8-9	2	0.31	1	0.07	1	0.08	0	0.00	3	0.15
10-11	1	0.16	0	0.00	0	0.00	0	0.00	1	0.05
Total (offspring with the outcome)	10	1.57	10	0.73	10	0.84	0	0	20	1.00

	Paternal exposure group									
NDD **Number of offspring**	**Valproate** **N=640**		**Lamotrigine/levetiracetam** **N=1379**		**Lamotrigine** **N=1185**		**Levetiracetam** **N=194**		**Total (valproate + lamotrigine/levetiracetam)** **N=2019**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Offspring without a diagnosis	630	99.44	1369	99.27	1175	99.16	194	100.00	1999	99.01
Mean (SD)	6.21 (2.97)		5.50 (1.88)		5.50 (1.88)		-		5.86 (2.44)	
Median (25th - 75th percentile)	4.94 (3.63, 9.63)		4.8 (4.01, 7.24)		4.8 (4.01, 7.24)		.()		4.94 (3.97, 7.70)	
Min, max	3.02, 10.79		3.16, 8.14		3.16, 8.14		-		3.02, 10.79	
NDD including ASD [c,d]										
0-1	3	0.47	2	0.15	2	0.17	0	0.00	5	0.25
2-3	4	0.63	13	0.94	12	1.01	1	0.52	17	0.84
4-5	12	1.88	12	0.87	9	0.76	3	1.55	24	1.19
6-7	14	2.19	10	0.73	10	0.84	0	0.00	24	1.19
8-9	7	1.09	13	0.94	11	0.93	2	1.03	20	0.99
10-11	3	0.47	5	0.36	4	0.34	1	0.52	8	0.40
Total (offspring with the outcome)	43	6.73	55	3.99	48	4.05	7	3.62	98	4.86
Offspring without a diagnosis	597	93.28	1324	96.01	1137	95.95	187	96.39	1921	95.15
Mean (SD)	6.36 (2.68)		6.17 (2.75)		6.08 (2.74)		6.78 (2.92)		6.25 (2.71)	
Median (25th - 75th percentile)	6.58 (4.68, 7.94)		6.08 (3.93, 8.26)		6.22 (3.82, 8.11)		5.3 (4.34, 9.87)		6.42 (4.11, 8.14)	
Min, max	0.60, 11.70		1.08, 11.66		1.08, 11.66		3.55, 10.03		0.60, 11.70	

AED: antiepileptic drugs; ASD: Autism Spectrum Disorders; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; NDD: neurodevelopmental disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between index (childbirth) and exit date
b) ICD-10 codes refer to all records of NDD including ASD during the entire follow-up. Since offspring might have more than one distinct ICD-10 code, the sum of the distinct ICD-10 codes might not coincide with the total number of offspring with the composite outcome
c) Categories may be adapted according to the data.
d) 3 months lookback from LMP2

Overall, the median (IQR) age of mothers from the Primary outcome cohort for descriptive analyses at childbirth was 30 (27-34) years, similar for both exposure groups (Table 88). The most prevalent clinical characteristics recorded in mothers prior to childbirth were: neurotic disorder which was observed in 10.0% of mothers of offspring paternally exposed to valproate and in 11.3% of mothers of offspring paternally exposed to lamotrigine/levetiracetam; affective disorder which was observed in 4.2% of mothers of offspring paternally exposed to valproate and in 9.0% of mothers of offspring paternally exposed to lamotrigine/levetiracetam; and gestational diabetes which was observed in 4.5% of mothers of offspring paternally exposed to valproate and in 5.7% of mothers of offspring paternally exposed to lamotrigine/levetiracetam (Table 89).

Regarding maternal characteristics of the 2019 offspring included in the Primary outcome cohort for descriptive analyses, 7.5% had a record of smoking during pregnancy (9.2% in valproate exposure group and 6.7% in lamotrigine/levetiracetam exposure group). Correspondingly, the proportion of mothers smoking prior to LMP2 pregnancy was 13.1% (14.2% and 12.6 in the valproate and lamotrigine/levetiracetam exposure groups, respectively), although a high proportion of missingness (22.9%) was observed (Table 89).

A polypharmacy index during pregnancy between 1 and 4 was observed in 44.5% of mothers of offspring paternally exposed to valproate group, and in 47.1% of mothers of offspring paternally exposed to lamotrigine/levetiracetam group. Regarding the use of concomitant medications associated with neuropsychiatric adverse events during pregnancy, 40.3% of mothers of offspring paternally exposed to valproate, and 43.6% of mothers of offspring paternally exposed to lamotrigine/levetiracetam had at least one prescription (Table 89).

Regarding paternal demographic characteristics, the overall median (IQR) age of fathers at childbirth was 33 (29-37) years (32 (29-36) years in the valproate group and 33 (29-38) years in the lamotrigine/levetiracetam group). Higher proportions of offspring paternally exposed to valproate were conceived in the earlier years of the study inclusion (2005-2009), in contrast to the lamotrigine/levetiracetam group where higher proportions were observed in the latest years of study inclusion (2010-2019) (Table 90).

Regarding clinical characteristics of the fathers from the Primary outcome cohort for descriptive analyses, in the group of offspring paternally exposed to valproate, 10.5% of fathers presented bipolar affective disorder, 5.5% presented affective disorder excluding bipolar and mania, and 5.0% presented neurotic disorder. Among offspring paternally exposed to lamotrigine/levetiracetam, proportions were generally higher with 22.2% of fathers presenting bipolar affective disorder, 17.9% of fathers presenting affective disorder excluding bipolar and mania, and 12.7% presenting neurotic disorder (Table 91).

The indication for AED treatment was unknown for 50.6% in the valproate group, and 44.4% in the lamotrigine/levetiracetam group (Table 91). This indication was followed by epilepsy (39.1% in the valproate and 33.6% in the lamotrigine/levetiracetam group), and bipolar affective disorder and mania (10.3% and 22.0% in the valproate and lamotrigine/levetiracetam exposure groups, respectively) [16]

[16] Since indications for medications are not available in all the data sources used for this study, the indication for AEDs was estimated based on medical history. The following indications were considered for the three AEDs of interest (valproate, lamotrigine, levetiracetam): epilepsy, bipolar disorder and mania, other/unknown. The entire medical history for each father will be considered up to LMP2

Regarding the use of concomitant medications associated with neuropsychiatric adverse events, 59.4% of fathers of offspring paternally exposed to valproate, and 65.8% of fathers of offspring paternally exposed to lamotrigine/levetiracetam had at least one prescription.

The K-means algorithm, analysing DDD trajectories in fathers exposed to AEDs 3 months prior to conception (i.e. prior to LMP2) identified 2 different clusters A and B (Figure 22), one with constant low exposure (i.e. a low quantity of DDDs of exposure in the 14 days intervals of the assessment period, cluster B) and one with constant high exposure to AEDs (cluster A). In the valproate group, a larger proportion of fathers were in cluster A (68.3%) than in cluster B (31.7%). In the lamotrigine/levetiracetam group, the same was observed (74.3% in cluster A and 25.7% in cluster B) (Table 91).

(exclusive) to identify diagnosis records of epilepsy and bipolar disorder/mania. In case more than one diagnosis was found (e.g. epilepsy and bipolar disorder), only one indication was selected, with priority given to epilepsy, followed by bipolar disorder. In case none of these diagnoses are found in the medical history, the indication was considered “other/unknown”.

Table 88 Maternal demographic characteristics by paternal exposure group; Primary outcome cohort in Norway (N=2019)

	Paternal exposure group									
NDD Number of offspring	Valproate N=640		Lamotrigine/levetiracetam N=1379		Lamotrigine N=1185		Levetiracetam N=194		Total (valproate + lamotrigine/levetiracetam) N=2019	
	N	%	N	%	N	%	N	%	N	%
Mother's age [a]										
≤20 years	20	3.13	29	2.10	26	2.19	3	1.55	49	2.43
21-25	105	16.4 1	202	14.65	172	14.5 1	30	15.4 6	307	15.21
26-30	218	34.0 6	444	32.20	369	31.1 4	75	38.6 6	662	32.79
31-35	212	33.1 3	452	32.78	396	33.4 2	56	28.8 7	664	32.89
36-40	73	11.4 1	207	15.01	190	16.0 3	17	8.76	280	13.87
>40	12	1.88	45	3.26	32	2.70	13	6.70	57	2.82
Mean (SD)	29.94 (5.07)		30.71 (5.21)		30.77 (5.18)		30.37 (5.37)		30.47 (5.18)	
Median (25^{th} - 75^{th} percentile)	30 (27.00, 34.00)		31 (27.00, 34.00)		31 (27.00, 35.00)		30 (27.00, 33.00)		30 (27.00, 34.00)	
Min, max	16.00, 47.00		17.00, 46.00		18.00, 46.00		17.00, 44.00		16.00, 47.00	
Missing	-		-		-		-		-	

NDD: neurodevelopmental disorders; SD- Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 89 Maternal clinical characteristics by paternal exposure group; Primary outcome cohort in Norway (N=2019)

Paternal exposure group

NDD Number of offspring	Valproate N=640		Lamotrigine/levetiracetam N=1379		Lamotrigine N=1185		Levetiracetam N=194		Total (valproate + lamotrigine/levetiracetam) N=2019	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Affective disorder [a]	27	4.22	124	8.99	118	9.96	6	3.09	151	7.48
Diabetes [a]	12	1.88	30	2.18	29	2.45	1	0.52	42	2.08
Epilepsy [a]	7	1.09	17	1.23	14	1.18	3	1.55	24	1.19
Neurotic disorder [a]	64	10.00	156	11.31	140	11.81	16	8.25	220	10.90
Schizophrenia, schizotypal and delusional disorders [a]	1	0.16	3	0.22	3	0.25	0	0.00	4	0.20
Obesity [b]	6	0.94	11	0.80	11	0.93	0	0.00	17	0.84
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gestational diabetes [c]	29	4.53	79	5.73	72	6.08	7	3.61	108	5.35
Rubella [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lifestyle characteristics										
Alcohol abuse prior to LMP2 [b]	1	0.16	2	0.15	2	0.17	0	0.00	3	0.15
Alcohol abuse during pregnancy [c]	1	0.16	1	0.07	1	0.08	0	0.00	2	0.10
Substance abuse prior to LMP2 [b]	2	0.31	4	0.29	4	0.34	0	0.00	6	0.30
Substance abuse during pregnancy [c]	2	0.31	3	0.22	3	0.25	0	0.00	5	0.25
Smoking prior to LMP2 [b]										
No	374	58.44	918	66.57	774	65.32	144	74.23	1292	63.99
Yes	91	14.22	174	12.62	158	13.33	16	8.25	265	13.13
Missing	175	27.34	287	20.81	253	21.35	34	17.53	462	22.88
Smoking during pregnancy [c]										
No	489	76.41	1130	81.94	959	80.93	171	88.14	1619	80.19
Yes	59	9.22	93	6.74	91	7.68	2	1.03	152	7.53
Missing	92	14.38	156	11.31	135	11.39	21	10.82	248	12.28

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=640		N=1379		N=1185		N=194		N=2019	
	N	%	N	%	N	%	N	%	N	%
Medication use										
Exposure to AEDs prior to LMP2 [d]										
Valproate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lamotrigine	0	0.00	19	1.38	19	1.60	0	0.00	19	0.94
Levetiracetam	0	0.00	2	0.15	2	0.17	0	0.00	2	0.10
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	1	0.16	1	0.07	1	0.08	0	0.00	2	0.10
Carboxamide derivatives	3	0.47	2	0.15	1	0.08	1	0.52	5	0.25
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	0	0.00	22	1.60	21	1.77	1	0.52	22	1.09
Exposure to AED during pregnancy [c]										
Valproate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lamotrigine	0	0.00	17	1.23	17	1.43	0	0.00	17	0.84
Levetiracetam	1	0.16	2	0.15	2	0.17	0	0.00	3	0.15
Barbiturates and derivatives	1	0.16	0	0.00	0	0.00	0	0.00	1	0.05
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	2	0.15	2	0.17	0	0.00	2	0.10

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=640		N=1379		N=1185		N=194		N=2019	
	N	%	N	%	N	%	N	%	N	%
Carboxamide derivatives	4	0.63	3	0.22	2	0.17	1	0.52	7	0.35
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	1	0.16	20	1.45	19	1.60	1	0.52	21	1.04
K-means cluster prior to LMP2 [d]										
Unexposed	637	99.53	1355	98.26	1163	98.14	192	98.97	1992	98.66
Cluster A[1]	2	0.31	17	1.23	15	1.27	2	1.03	19	0.94
Cluster B[1]	1	0.16	7	0.51	7	0.59	0	0.00	8	0.40
K-means cluster during pregnancy [c]										
Unexposed	636	99.38	1355	98.26	1163	98.14	192	98.97	1991	98.61
Cluster A[2]	2	0.31	15	1.09	13	1.10	2	1.03	17	0.84
Cluster B[2]	2	0.31	9	0.65	9	0.76	0	0.00	11	0.54
Maternal polypharmacy index prior to LMP2 [d]										
0	422	65.94	877	63.60	751	63.38	126	64.95	1299	64.34
1-4	205	32.03	478	34.66	413	34.85	65	33.51	683	33.83
5-10	11	1.72	24	1.74	21	1.77	3	1.55	35	1.73
>10	2	0.31	0	0.00	0	0.00	0	0.00	2	0.10
Mean (SD)	0.68 (1.31)		0.65 (1.12)		0.65 (1.12)		0.61 (1.08)		0.66 (1.18)	
Median (25th - 75th percentile)	0 (0.00, 1.00)		0(0.00, 1.00)		0(0.00, 1.00)		0(0.00, 1.00)		0(0.00, 1.00)	
Min, max	0.00, 12.00		0.00, 8.00		0.00, 8.00		0.00, 5.00		0.00, 12.00	
Maternal polypharmacy index during pregnancy [c]										

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=640		N=1379		N=1185		N=194		N=2019	
	N	%	N	%	N	%	N	%	N	%
0	341	53.28	695	50.40	594	50.13	101	52.06	1036	51.31
1-4	285	44.53	650	47.14	560	47.26	90	46.39	935	46.31
5-10	14	2.19	34	2.47	31	2.62	3	1.55	48	2.38
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mean (SD)	0.85 (1.27)		0.95 (1.32)		0.97 (1.34)		0.85 (1.14)		0.92 (1.30)	
Median (25th - 75th percentile)	0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)	
Min, max	0.00, 9.00		0.00, 10.00		0.00, 10.00		0.00, 5.00		0.00, 10.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	66	10.31	165	11.97	146	12.32	19	9.79	231	11.44
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	28	4.38	93	6.74	84	7.09	9	4.64	121	5.99
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] -mothers with at least one prescription	442	69.06	941	68.24	817	68.95	124	63.92	1383	68.50

	Paternal exposure group									
NDD	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=640		N=1379		N=1185		N=194		N=2019	
	N	%	N	%	N	%	N	%	N	%
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	258	40.31	602	43.65	522	44.05	80	41.24	860	42.60

AED: antiepileptic drugs; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; NDD: neurodevelopmental disorders; SD: Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until index date)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Norway during the study period
Cluster A[1]: Constant moderate exposure, Cluster B[1]: Constant low exposure
Cluster A[2]: Constant low exposure, Cluster B[2]: Constant moderate-low exposure

Table 90 Paternal demographic characteristics by paternal exposure group; Primary outcome cohort in Norway (N=2019)

	Paternal exposure group									
NDD	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=640		N=1379		N=1185		N=194		N=2019	
	N	%	N	%	N	%	N	%	N	%
Father's age [a]										
≤20 years	7	1.09	4	0.29	3	0.25	1	0.52	11	0.54
21-25	58	9.06	110	7.98	91	7.68	19	9.79	168	8.32
26-30	163	25.47	308	22.34	257	21.69	51	26.29	471	23.33
31-35	232	36.25	444	32.20	377	31.81	67	34.54	676	33.48

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=640**		**N=1379**		**N=1185**		**N=194**		**N=2019**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
36-40	128	20.00	319	23.13	284	23.97	35	18.04	447	22.14
>40	52	8.13	194	14.07	173	14.60	21	10.82	246	12.18
Mean (SD)	32.57 (5.74)		33.84 (6.32)		33.99 (6.37)		32.92 (5.97)		33.44 (6.17)	
Median (25th - 75th percentile)	32 (29.00, 36.00)		33 (29.00, 38.00)		34 (30.0, 38.00)		33 (29.00, 37.00)		33 (29.00, 37.00)	
Min, max	18.00, 53.00		18.00, 64.00		18.00, 64.00		20.00, 51.00		18.00, 64.00	
Year of offspring conception [b]										
2005	42	6.56	44	3.19	40	3.38	4	2.06	86	4.26
2006	46	7.19	63	4.57	60	5.06	3	1.55	109	5.40
2007	63	9.84	77	5.58	68	5.74	9	4.64	140	6.93
2008	55	8.59	109	7.90	96	8.10	13	6.70	164	8.12
2009	45	7.03	91	6.60	82	6.92	9	4.64	136	6.74
2010	44	6.88	118	8.56	109	9.20	9	4.64	162	8.02
2011	42	6.56	89	6.45	78	6.58	11	5.67	131	6.49
2012	51	7.97	108	7.83	94	7.93	14	7.22	159	7.88
2013	42	6.56	104	7.54	83	7.00	21	10.82	146	7.23
2014	47	7.34	114	8.27	96	8.10	18	9.28	161	7.97
2015	49	7.66	117	8.48	94	7.93	23	11.86	166	8.22
2016	40	6.25	111	8.05	96	8.10	15	7.73	151	7.48
2017	34	5.31	100	7.25	80	6.75	20	10.31	134	6.64
2018	32	5.00	109	7.90	89	7.51	20	10.31	141	6.98
2019	8	1.25	25	1.81	20	1.69	5	2.58	33	1.63

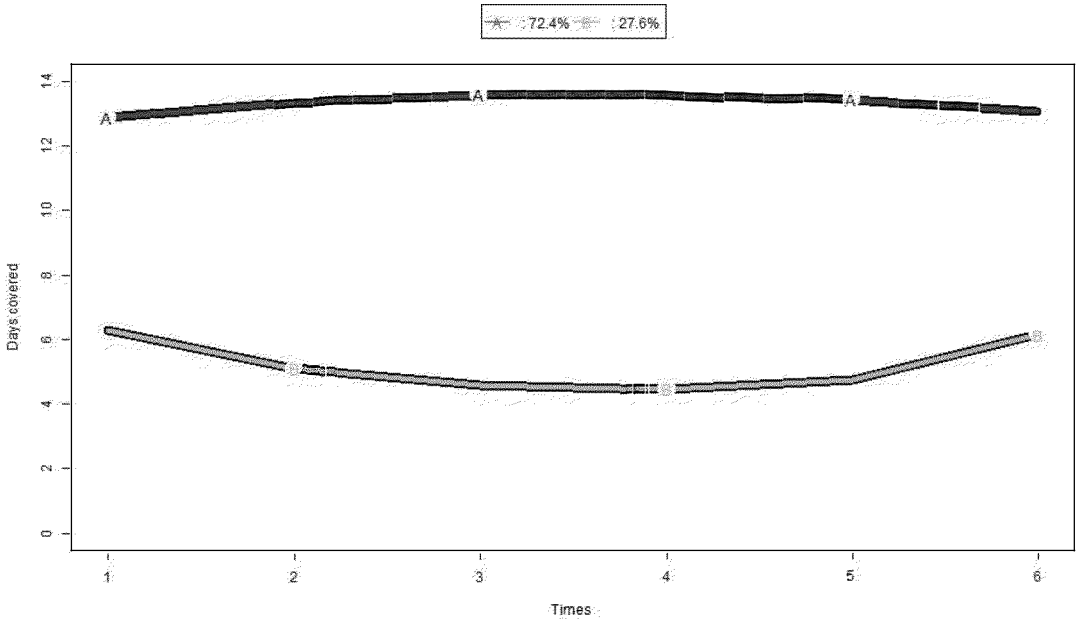
NDD: neurodevelopmental disorders; SD- Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) at mother's LMP2

Table 91 Paternal clinical characteristics by paternal exposure group; Primary outcome cohort in Norway (N=2019)

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=640		N=1379		N=1185		N=194		N=2019	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Bipolar affective disorder excl. bipolar disorder and mania [a]	35	5.47	247	17.91	245	20.68	2	1.03	282	13.97
Bipolar affective disorder [a]	67	10.47	306	22.19	306	25.82	0	0.00	373	18.47
Mania [a]	7	1.09	7	0.51	7	0.59	0	0.00	14	0.69
Neurotic disorder [a]	32	5.00	175	12.69	173	14.60	2	1.03	207	10.25
Schizophrenia, schizotypal and delusional disorders [a]	14	2.19	21	1.52	21	1.77	0	0.00	35	1.73
Lifestyle characteristics										
Substance abuse [b]	11	1.72	23	1.67	23	1.94	0	0.00	34	1.68
Medication use										
AED indication										
Epilepsy	250	39.06	463	33.58	308	25.99	155	79.90	713	35.31
Bipolar affective disorder and mania	66	10.31	303	21.97	303	25.57	0	0.00	369	18.28
Other/unknown	324	50.63	613	44.45	574	48.44	39	20.10	937	46.41
K-means cluster [c]										
Cluster A	437	68.28	1025	74.33	861	72.66	164	84.54	1462	72.41
Cluster B	203	31.72	354	25.67	324	27.34	30	15.46	557	27.59
Paternal polypharmacy index [c]										
0	386	60.31	690	50.04	562	47.43	128	65.98	1076	53.29
1-4	241	37.66	639	46.34	577	48.69	62	31.96	880	43.59
5-10	13	2.03	47	3.41	43	3.63	4	2.06	60	2.97
>10	0	0.00	3	0.22	3	0.25	0	0.00	3	0.15
Mean (SD)	0.73 (1.20)		1.06 (1.53)		1.13 (1.57)		0.63 (1.23)		0.95 (1.45)	
Median (25th - 75th percentile)	0 (0.00, 1.00)		0 (0.00, 2.00)		1 (0.00, 2.00)		0 (0.00, 1.00)		0 (0.00, 1.00)	
Min, max	0.00, 8.00		0.00, 13.00		0.00, 13.00		0.00, 8.00		0.00, 13.00	

NDD	Paternal exposure group									
	Valproate		Lamotrigine/levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of offspring	N=640		N=1379		N=1185		N=194		N=2019	
	N	%	N	%	N	%	N	%	N	%
Concomitant medications associated with valproate-indicated psychiatric conditions [b] - fathers with at least one prescription	159	24.84	534	38.72	516	43.54	18	9.28	693	34.32
Concomitant medications associated with neuropsychiatric adverse events [b] - fathers with atleast one prescription	380	59.38	907	65.77	813	68.61	94	48.45	1287	63.74

AED: antiepileptic drugs; NDD: neurodevelopmental disorders; SD: Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
Cluster A: constant high exposure; Cluster B: constant low exposure
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
b) 12 months lookback from LMP2
b) 12 months lookback from LMP2
c) 3 months lookback from LMP2



Legend: Times refers to the 14-days interval during which exposure was assessed (in this case, 6 14 days interval [i.e.3 months]); Days covered refers to days covered in each 14-day interval; Defined Daily Dose (DDD) trajectories: Cluster A: constant high exposure; Cluster B: constant low exposure. The percentage showed the proportion of fathers exposed to valproate and lamotrigine/levetiracetam in each cluster.

Figure 22 Mean defined daily dose (DDD) trajectories for fathers exposed to AEDs in the 3 months lookback prior to Last Menstrual Period Date Plus 2 weeks (LMP2) in Norway

10.5.1.2 Cumulative incidence proportion

Cumulative incidence proportions (risk) of NDD including ASD by paternal exposure group are presented overall in Table 92, and stratified by gender in Table 233 and Table 234 (please see Appendix section 15.3.2).

The cumulative incidence proportions (risk) of NDD including ASD for 0-12 years of follow-up appeared to be higher in offspring paternally exposed to valproate (6.7%, 95% CI: 4.8, 8.7) than in offspring paternally exposed to lamotrigine/levetiracetam (4.0%, 95% CI: 3.0, 5.2), although the 95% CI overlapped (Table 92).

The cumulative incidence proportion for 0-12 years of follow-up also appeared to be higher in male (6.4%, 95% CI: 4.9, 7.8) than female offspring (3.2%, 95% CI: 2.1, 4.3). However these proportions should be interpreted with caution since these are crude estimates, no adjustments were made. In addition,

offspring diagnosed with epilepsy and/treated with AEDs and/or exposed to AEDs in utero were not excluded in the descriptive cohort (Table 233 and Table 234, see Appendix).

Table 92 Cumulative incidence proportion (risk) of NDD by paternal exposure group; Primary outcome cohort in Norway

		Paternal exposure group				
NDD		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Follow-up period						
	N	640	1379	1185	194	2019
0-1 years	n	2	0	0	0	2
	n/N*10 0	0.31 (-0.12,0.74)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.00 (0.00,0.00)	0.10 (-0.04,0.24)
	N	607	1268	1096	172	1875
1-2 years	n	1	2	2	0	3
	n/N*10 0	0.16 (-0.16,0.49)	0.16 (-0.06,0.38)	0.18 (-0.07,0.44)	0.00 (0.00,0.00)	0.16 (-0.02,0.34)
	N	565	1167	1011	156	1732
2-3 years	n	2	6	6	0	8
	n/N*10 0	0.35 (-0.14,0.84)	0.51 (0.10,0.92)	0.59 (0.12,1.07)	0.00 (0.00,0.00)	0.46 (0.14,0.78)
	N	516	1048	909	139	1564
3-4 years	n	2	7	6	1	9
	n/N*10 0	0.39 (-0.15,0.92)	0.67 (0.17,1.16)	0.66 (0.13,1.19)	0.72 (-0.69,2.12)	0.58 (0.20,0.95)
	N	471	918	806	112	1389
4-5 years	n	7	8	6	2	15
	n/N*10 0	1.49 (0.39,2.58)	0.87 (0.27,1.47)	0.74 (0.15,1.34)	1.79 (-0.67,4.24)	1.08 (0.54,1.62)
	N	420	810	716	94	1230
5-6 years	n	5	4	3	1	9
	n/N*10 0	1.19 (0.15,2.23)	0.49 (0.01,0.98)	0.42 (-0.05,0.89)	1.06 (-1.01,3.14)	0.73 (0.26,1.21)
	N	374	688	615	73	1062
6-7 years	n	4	6	6	0	10
	n/N*10 0	1.07 (0.03,2.11)	0.87 (0.18,1.57)	0.98 (0.20,1.75)	0.00 (0.00,0.00)	0.94 (0.36,1.52)
	N	324	582	526	56	906
7-8 years	n	10	4	4	0	14
	n/N*10 0	3.09 (1.20,4.97)	0.69(0.02,1.36)	0.76 (0.02,1.50)	0.00 (0.00,0.00)	1.55 (0.74,2.35)
	N	273	497	450	47	770
8-9 years	n	3	8	8	0	11
	n/N*10 0	1.10 (-0.14,2.34)	1.61 (0.50,2.72)	1.78 (0.56,3.00)	0.00 (0.00,0.00)	1.43 (0.59,2.27)
	N	228	379	341	38	607
9-10 years	n	4	5	3	2	9
	n/N*10 0	1.75 (0.05,3.46)	1.32 (0.17,2.47)	0.88 (-0.11,1.87)	5.26 (-1.84, 12.36)	1.48 (0.52,2.44)
	N	194	291	262	29	485

		Paternal exposure group				
NDD		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Follow-up period						
10-11 years	n	1	3	2	1	4
	n/N*10 0	0.52 (-0.49,1.52)	1.03 (-0.13,2.19)	0.76 (-0.29,1.82)	3.45 (-3.19, 10.09)	0.82 (0.02,1.63)
	N	149	188	172	16	337
11-12 years	n	2	2	2	0	4
	n/N*10 0	1.34 (-0.51,3.19)	1.06 (-0.40,2.53)	1.16 (-0.44,2.76)	0.00 (0.00,0.00)	1.19 (0.03,2.34)
	N	640	1379	1185	194	2019
Overall (0-12 years)	n	43	55	48	7	98
	n/N*10 0	6.72 (4.78,8.66)	3.99 (2.96,5.02)	4.05(2.93,5.17)	3.61 (0.98,6.23)	4.85 (3.92,5.79)

NDD: neurodevelopmental disorders
Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) were presented.

10.5.1.3 Cumulative incidence rate and time to NDD diagnosis

Cumulative incidence rates of NDD including ASD by paternal exposure group are presented in Table 93, Table 235, and Table 236 (see Appendix), overall and stratified by gender, respectively. Considering the overall study follow-up, a higher incidence rate of NDD including ASD was observed among offspring paternally exposed to valproate (9.6, [95% CI: 6.9, 12.9] per 1000 PY) than among those paternally exposed to lamotrigine/levetiracetam (6.4, [95% CI: 4.8, 8.3] per 1000 PY), although the 95% CIs for the 2 groups were overlapping. When stratifying by gender, the same pattern was observed in both male and female offspring subgroups. When considering the overall period of follow-up, the cumulative incidence rate in male offspring was higher than in female offspring, in both paternal exposure groups.

Regarding the time to first diagnosis of NDD including ASD, the crude estimate for both exposure groups are presented as Kaplan-Meier curves. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event. The 5th percentile of the time to NDD including ASD was 83.1 (95% CI: 57.6, 124.9) months for the valproate and 98.4 (95% CI: 66.2, 137.7) months for the lamotrigine/levetiracetam paternal exposure groups.

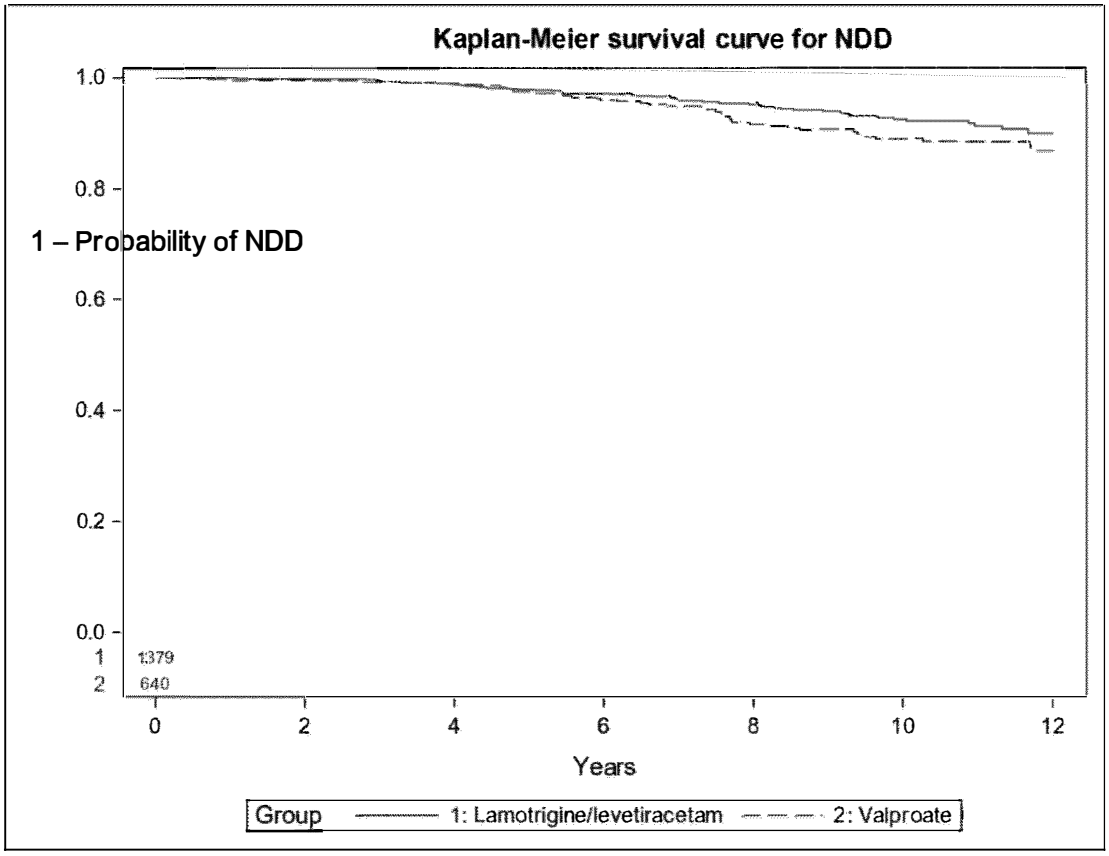
In the valproate paternal exposure group, for male offspring the 5th percentile of the time to NDD including ASD was 83.1 (95% CI: 56.1, -) months and for female offspring was 89.5 (95% CI: 57.6, -) months. In lamotrigine/levetiracetam paternal exposure group the corresponding 5th percentile values for male and female were 83.6 (95% CI: 48.2, 137.7) months and 132.3 (95% CI: 98.0, -) months, respectively.

Table 93 Cumulative incidence rate of NDD by paternal exposure group; Primary outcome cohort in Norway

NDD		Paternal exposure group: Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Follow-up period						
	PY	622.54	1322.18	1138.95	183.23	1944.72
0-1 years	n	2	0	0	0	2
	n/PY*1000	3.21 (0.39, 11.61)	0 (-, 2.79)	0 (-, 3.24)	0 (-, 20.13)	1.03 (0.12, 3.72)
	PY	1204.68	2538.89	2191.58	347.31	3743.57
0-2 years	n	3	2	2	0	5
	n/PY*1000	2.49 (0.51, 7.28)	0.79 (0.10, 2.85)	0.91 (0.11, 3.30)	0 (-, 10.62)	1.34 (0.43, 3.12)
	PY	1747.68	3650.75	3157.66	493.08	5398.42
0-3 years	n	5	8	8	0	13
	n/PY*1000	2.86 (0.93, 6.68)	2.19 (0.95, 4.32)	2.53 (1.09, 4.99)	0 (-, 7.48)	2.41 (1.28, 4.12)
	PY	2245.8	4636.14	4015.39	620.75	6881.95
0-4 years	n	7	15	14	1	22
	n/PY*1000	3.12 (1.25, 6.42)	3.24 (1.81, 5.34)	3.49 (1.91, 5.85)	1.61 (0.04, 8.98)	3.2 (2.00, 4.84)
	PY	2694.23	5500.3	4776.71	723.59	8194.53
0-5 years	n	14	23	20	3	37
	n/PY*1000	5.2 (2.84, 8.72)	4.18 (2.65, 6.27)	4.19 (2.56, 6.47)	4.15 (0.86, 12.12)	4.52 (3.18, 6.22)
	PY	3092.09	6244.23	5436.13	808.1	9336.32
0-6 years	n	19	27	23	4	46
	n/PY*1000	6.14 (3.70, 9.60)	4.32 (2.85, 6.29)	4.23 (2.68, 6.35)	4.95 (1.35, 12.67)	4.93 (3.61, 6.57)
	PY	3442.2	6883.26	6009.76	873.5	10325.46
0-7 years	n	23	33	29	4	56
	n/PY*1000	6.68 (4.24, 10.03)	4.79 (3.30, 6.73)	4.83 (3.23, 6.93)	4.58 (1.25, 11.72)	5.42 (4.10, 7.04)
	PY	3738.03	7423.38	6498.03	925.35	11161.42
0-8 years	n	33	37	33	4	70
	n/PY*1000	8.83 (6.08, 12.40)	4.98 (3.51, 6.87)	5.08 (3.50, 7.13)	4.32 (1.18, 11.07)	6.27 (4.89, 7.92)
	PY	3990.68	7863.73	6895.53	968.2	11854.41
0-9 years	n	36	45	41	4	81
	n/PY*1000	9.02 (6.32, 12.49)	5.72 (4.17, 7.66)	5.95 (4.27, 8.07)	4.13 (1.13, 10.58)	6.83 (5.43, 8.49)
	PY	4202.87	8198.95	7196.89	1002.06	12401.82

0-10 years	n	40	50	44	6	90
	n/PY*1000	9.52 (6.80, 12.96)	6.1 (4.53, 8.04)	6.11 (4.44, 8.21)	5.99 (2.20, 13.03)	7.26 (5.84, 8.92)
	PY	4371.21	8439.87	7416.08	1023.79	12811.08
0-11 years	n	41	53	46	7	94
	n/PY*1000	9.38 (6.73, 12.72)	6.28 (4.70, 8.21)	6.2 (4.54, 8.27)	6.84 (2.75, 14.09)	7.34 (5.93, 8.98)
	PY	4490.96	8581.42	7546.97	1034.45	13072.38
0-12 years	n	43	55	48	7	98
	n/PY*1000	9.57 (6.93, 12.90)	6.41 (4.83, 8.34)	6.36 (4.69, 8.43)	6.77 (2.72, 13.94)	7.5 (6.09, 9.14)

NDD: neurodevelopmental disorders; PY: Person-Years
Legend: Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) were presented.



Paternal exposure group					
NDD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**

Number of events	43	55	48	7	98
Number of censor	597	1324	1137	187	1921
Survival time					
5th percentile	83.10 (57.60, 124.87)	98.40 (66.23, 137.73)	98.40 (73.97, 141.97)	117.50 (52.83, -)	92.00 (71.93, 115.27)
10th percentile	114.23(92.27, -)	141.97(112.87, -)	122.17(117.50, -)	137.73(112.33, -)	-(-,-)
25th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)

NDD: neurodevelopmental disorders
Legend: some attrition figures below the curve were not provided for data privacy reasons. Due to low number of events the median time-to-event could not be calculated. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th and the 10th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event.

Figure 23 Kaplan-Meier survival curve for Neurodevelopmental Disorders (NDD) and distribution of time to NDD in in Norway

10.5.1.4 Association between potential risk factors/confounders for NDD including ASD and paternal exposure group

Association between potential covariates (risk factors and counfounders) for NDD including ASD and paternal exposure group was assessed in the Primary outcome cohort for comparative analyses. Results of the crude associations are shown in Table 94 to Table 96.

Offspring exposed to AEDs and/or diagnosed with epilepsy after birth were included in the primary outcome for descriptive analyses but excluded from the primary outcome for comparative analyses, hence the absence of a summary for epilepsy in Table 94. Epilepsy was an exclusion criterion for selecting the population for the comparative analyses because it was a strong risk factor for NDD including ASD (see Study Protocol v6.0, section 9.3.3.1) and offspring with epilepsy or receiving AEDs are already at risk of NDD including ASD regardless of paternal exposure.

All the variables examined were initially selected based on literature review and clinical expert opinion, see Section 9.4.4 for an overview.

For the offspring, gender was associated with paternal exposure (p=0.0031) (Table 94).

Maternal characteristics identified as risk factors or confounders (see Table 4, Table 95), that were statistically significantly associated with paternal exposure in the offspring were:

- Age (p=0.0063), younger age in the valproate paternal exposure group

- Affective disorder (p=0.0009), lower percentage in the valproate paternal exposure group.
- Smoking prior to LMP2 (p=0.0290) and during pregnancy (p=0.0158), higher percentage in the valproate paternal exposure group

Paternal characteristics identified as risk factors or confounders (see Table 4, Table 6, Table 96) that were statistically significantly associated with paternal exposure were:

- Affective disorder (excluding bipolar affective disorder and mania) (p<0.0001), bipolar affective disorder (p<0.0001), and neurotic disorder (p<0.0001) were all less frequent in the valproate exposure group
- Polypharmacy index (p<0.0001), lower in the valproate exposure group
- Concomitant medications associated with valproate-indicated psychiatric conditions (p<0.0001) a lower percentage in the valproate exposure group
- Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 a lower percentage in the valproate exposure group (p=0.0158)
- Age (p<0.0001), younger fathers in the valproate group
- Year of conception (p<0.0001), earlier years in the valproate group and more recent years in the lamotrigine/levetiracetam group

Table 94 Association between potential offspring risk factors/confounders for NDD by paternal exposure group; Primary outcome cohort in Norway

	Paternal exposure group										Comparison
NDD **Number of pregnancies**	**Valproate** **N=617**		**Lamotrigine/levetiracetam** **N=1326**		**Lamotrigine** **N=1140**		**Levetiracetam** **N=186**		**Total (valproate + lamotrigine/levetiracetam)** **N=1943**		**Valproate vs Lamotrigine /levetiracetam** -
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Offspring risk factors/confounders											
Gender [a]											
Male	309	50.08	703	53.02	592	51.93	111	59.68	1012	52.08	-
Female	308	49.92	623	46.98	548	48.07	75	40.32	931	47.92	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	1.45 (0.2279)
Congenital CMV [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Foetal alcohol syndrome [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-

Legend: Number of pregnancies represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was less than 5 Fischer's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) at index (childbirth)

b) between index and exit date

* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 95 Association between potential maternal risk factors/confounders for NDD by paternal exposure group; Primary outcome cohort in Norway

	Paternal exposure group										Comparison
NDD	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproatevs Lamotrigine /levetiracetam
Number of offspring	N=617		N=1326		N=1140		N=186		N=1943		-
	N	%	N	%	N	%	N	%	N	%	
Maternal risk factors/confounders											
Mother's age [a] (categorical)											
≤20 years	19	3.08	27	2.04	24	2.11	3	1.61	46	2.37	-
21-25	100	16.21	189	14.25	162	14.21	27	14.52	289	14.87	-
26-30	211	34.20	430	32.43	359	31.49	71	38.17	641	32.99	-
31-35	203	32.90	438	33.03	383	33.60	55	29.57	641	32.99	-
36-40	72	11.67	198	14.93	181	15.88	17	9.14	270	13.90	-
>40	12	1.94	44	3.32	31	2.72	13	6.99	56	2.88	-
Test statistics	-	-	-	-	-	-	-	-	-	-	9.40 (0.0941)
Mother's age [a] (continuous)											
Mean (SD)	29.98 (5.08)	-	30.74 (5.17)	-	30.77 (5.14)	-	30.51 (5.40)	-	30.49 (5.16)	-	568304.00 (0.0063)*
Median (25th - 75th percentile)	30 (27.00, 34.00)	-	31 (27.00, 34.00)	-	31 (27.00, 35.00)	-	30 (27.00, 33.00)	-	30 (27.00, 34.00)	-	-
Min, max	16.00, 47.00	-	17.00, 46.00	-	18.00, 46.00	-	17.00, 44.00	-	16.00, 47.00	-	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Affective disorder [b]	26	4.21	111	8.37	106	9.30	5	2.69	137	7.05	11.10 (0.0009)
Diabetes [b]	11	1.78	27	2.04	26	2.28	1	0.54	38	1.96	0.14 (0.7073)
Gestational diabetes [c]	28	4.54	75	5.66	68	5.96	7	3.76	103	5.30	1.05 (0.3059)

NDD	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproatevs Lamotrigine /levetiracetam
Number of offspring	N=617		N=1326		N=1140		N=186		N=1943		-
	N	%	N	%	N	%	N	%	N	%	
Neurotic disorder [b]	61	9.89	148	11.16	133	11.67	15	8.06	209	10.76	0.71 (0.3985)
Schizophrenia, schizotypal and delusional disorders [b]	1	0.16	3	0.23	3	0.26	0	0.00	4	0.21	1.00 (1.0000)*
Obesity [d]	6	0.97	10	0.75	10	0.88	0	0.00	16	0.82	0.25 (0.6201)
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Rubella [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [d]	1	0.16	2	0.15	2	0.18	0	0.00	3	0.15	1.00 (1.0000)*
Alcohol abuse during pregnancy [c]	1	0.16	1	0.08	1	0.09	0	0.00	2	0.10	0.53 (0.5344)*
Substance abuse prior to LMP2 [d]	2	0.32	4	0.30	4	0.35	0	0.00	6	0.31	1.00 (1.0000)*
Substance abuse during pregnancy [c]	2	0.32	3	0.23	3	0.26	0	0.00	5	0.26	0.65 (0.6554)*
Smoking prior to LMP2 [d]											
No	357	57.86	888	66.97	749	65.70	139	74.73	1245	64.08	-
Yes	89	14.42	161	12.14	146	12.81	15	8.06	250	12.87	-
Missing	171	27.71	277	20.89	245	21.49	32	17.20	448	23.06	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	4.77 (0.0290)
Smoking during pregnancy [c]											
No	468	75.85	1086	81.90	922	80.88	164	88.17	1554	79.98	-
Yes	57	9.24	86	6.49	84	7.37	2	1.08	143	7.36	-
Missing	92	14.91	154	11.61	134	11.75	20	10.75	246	12.66	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	5.82 (0.0158)

NDD	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproatevs Lamotrigine /levetiracetam
Number of offspring	N=617		N=1326		N=1140		N=186		N=1943		-
	N	%	N	%	N	%	N	%	N	%	
Maternal polypharmacy index prior to LMP2 [e](categorical)											
0	411	66.61	850	64.10	730	64.04	120	64.52	1261	64.90	-
1-4	194	31.44	454	34.24	391	34.30	63	33.87	648	33.35	-
5-10	10	1.62	22	1.66	19	1.67	3	1.61	32	1.65	-
>10	2	0.32	0	0.00	0	0.00	0	0.00	2	0.10	-
Test statistics	-	-	-	-	-	-	-	-	-	-	5.70 (0.1273)
Maternal polypharmacy index prior to LMP2 [e] (continuous)											
Mean (SD)	0.66 (1.29)	-	0.63 (1.10)	-	0.64 (1.10)	-	0.61 (1.07)	-	0.64 (1.16)	-	592480.00 (0.4578)[*]
Median (25^{th} - 75^{th} percentile)	0(0.00, 1.00)	-	0(0.00, 1.00)	-	0(0.00, 1.00)	-	0(0.00, 1.00)	-	0(0.00, 1.00)	-	-
Min, max	0.00, 12.00	-	0.00, 8.00	-	0.00, 8.00	-	0.00, 5.00	-	0.00, 12.00	-	-
Maternal polypharmacy index during pregnancy [c](categorical)											
0	327	53.00	675	50.90	577	50.61	98	52.69	1002	51.57	-
1-4	277	44.89	620	46.76	535	46.93	85	45.70	897	46.17	-
5-10	13	2.11	31	2.34	28	2.46	3	1.61	44	2.26	-
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	0.77 (0.6793)

	Paternal exposure group										Comparison
NDD Number of offspring	Valproate N=617		Lamotrigine/ levetiracetam N=1326		Lamotrigine N=1140		Levetiracetam N=186		Total (valproate + lamotrigine/ levetiracetam) N=1943		Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	N	%	N	%	N	%	
Maternal polypharmacy index during pregnancy[c] (continuous)											
Mean (SD)	0.84 (1.26)	-	0.93 (1.29)	-	0.95 (1.31)	-	0.81 (1.12)	-	0.90 (1.28)	-	584209.00 (0.1423)*
Median (25th - 75th percentile)	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	-
Min, max	0.00, 9.00	-	0.00, 9.00	-	0.00, 9.00	-	0.00, 5.00	-	0.00, 9.00	-	-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	57	9.24	149	11.24	132	11.58	17	9.14	206	10.60	1.77 (0.1828)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	24	3.89	81	6.11	75	6.58	6	3.23	105	5.40	4.06 (0.0440)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] -mothers with at least one prescription	422	68.40	901	67.95	781	68.51	120	64.52	1323	68.09	0.04 (0.8441)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	250	40.52	571	43.06	496	43.51	75	40.32	821	42.25	1.12 (0.2907)

	Paternal exposure group										Comparison
NDD	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproatevs Lamotrigine /levetiracetam
Number of offspring	N=617		N=1326		N=1140		N=186		N=1943		-
	N	%	N	%	N	%	N	%	N	%	

NDD: neurodevelopmental disorders; SD- Standard Deviation; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) at index (childbirth)

b) all available data prior to index date

c) during pregnancy (from LMP2 until index date)

d) 12 months lookback from LMP2

e) 3 months lookback from LMP2

* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed

Table 96 Association between potential paternal risk factors/confounders for NDD by paternal exposure group; Primary outcome cohort in Norway

	Paternal exposure group										Comparison
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of offspring	**N=617**		**N=1326**		**N=1140**		**N=186**		**N=1943**		**-**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Paternal risk factors/confounders											
Affective disorder excluding bipolar affective disorder and mania [a]	34	5.51	234	17.65	233	20.44	1	0.54	268	13.79	52.16 (<.0001)
Bipolar affective disorder [a]	66	10.70	294	22.17	294	25.79	0	0.00	360	18.53	36.73 (<.0001)
Mania [a]	7	1.13	7	0.53	7	0.61	0	0.00	14	0.72	2.17 (0.1411)
Neurotic disorder [a]	31	5.02	164	12.37	162	14.21	2	1.08	195	10.04	25.15 (<.0001)
Schizophrenia, schizotypal and delusional disorders [a]	14	2.27	19	1.43	19	1.67	0	0.00	33	1.70	1.76 (0.1842)
Substance abuse [c]	10	1.62	22	1.66	22	1.93	0	0.00	32	1.65	0.00 (0.9507)
Paternal polypharmacy index [d] (categorical)											
0	372	60.29	664	50.08	543	47.63	121	65.05	1036	53.32	-
1-4	233	37.76	615	46.38	554	48.60	61	32.80	848	43.64	-
5-10	12	1.94	44	3.32	40	3.51	4	2.15	56	2.88	-
>10	0	0.00	3	0.23	3	0.26	0	0.00	3	0.15	-
Test statistics	-	-	-	-	-	-	-	-	-	-	19.56 (0.0002)
Paternal polypharmacy index [d] (continuous)											
Mean (SD)	0.72 (1.20)		1.05 (1.53)		1.12 (1.56)		0.66 (1.25)		0.95 (1.44)		548177.50 (<.0001)*

Median (25th - 75th percentile)	0(0.00, 1.00)		0(0.00, 2.00)		1(0.00, 2.00)		0(0.00, 1.00)		0(0.00, 1.00)		-
Min, max	0.00,8.00		0.00,13.00		0.00,13.00		0.00,8.00		0.00,13.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fatherswith at least one prescription	153	24.80	508	38.31	492	43.16	16	8.60	661	34.02	34.26 (<.0001)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	369	59.81	868	65.46	776	68.07	92	49.46	1237	63.66	5.82 (0.0158)
Father's age [e] (categorical)											-
<=20 years	7	1.13	4	0.30	3	0.26	1	0.54	11	0.57	-
21-25	56	9.08	103	7.77	86	7.54	17	9.14	159	8.18	-
26-30	158	25.61	295	22.25	248	21.75	47	25.27	453	23.31	-
31-35	220	35.66	425	32.05	360	31.58	65	34.95	645	33.20	-
36-40	126	20.42	310	23.38	275	24.12	35	18.82	436	22.44	-
>40	50	8.10	189	14.25	168	14.74	21	11.29	239	12.30	-
Test statistics	-	-	-	-	-	-	-	-	-	-	24.32 (0.0002)
Father's age [e] (continuous)											
Mean (SD)	32.58 (5.76)		33.90 (6.34)		34.03 (6.39)		33.13 (5.99)		33.48 (6.19)		554537.50 (<.0001)*
Median (25th - 75th percentile)	32(29.00, 36.00)		33(29.00, 38.00)		34(30.00, 38.00)		33(29.00, 37.00)		33(29.00, 37.00)		-
Min, max	18.00,53.00		18.00,64.00		18.00,64.00		20.00,51.00		18.00,64.00		-
Year of offspring conception [f,g]											
2005-2009	240	38.90	368	27.75	331	29.04	37	19.89	608	31.29	-
2010-2014	219	35.49	506	38.16	438	38.42	68	36.56	725	37.31	-
2015-2019	158	25.61	452	34.09	371	32.54	81	43.55	610	31.39	-

Test statistics	-	-	-	-	-	-	-	-	-	-	27.16 (<.0001)

NDD: neurodevelopmental disorders; SD- Standard Deviation
Legend: Number of offspringrepresentoffspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index (childbirth)
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

10.5.1.5 Association between potential risk factors/confounders and NDD including ASD

Association between covariates (potential risk factors / confounders) and occurrence of NDD was assessed in the Primary outcome cohort for comparative analyses. Results of crude associations are shown in Table 97 to Table 99.

These variables were initially selected based on literature review and clinical expert opinion, see section9.4.4.

For offspring characteristics, only gender (OR: 0.50, 95% CI: 0.32, 0.79; p=0.0031) was associated with NDD including ASD (Table 97); the proportion of events among females were significantly lower than the proportion of events among males.

For maternal characteristics identified as risk factors or confounders (see Table 4 and Table 98) the following variables were statistically significantly associated with occurrence of NDD including ASD event:

- Smoking prior to LMP2 (OR: 2.17, 95% CI: 1.19, 3.96; p=0.0114) and smoking during pregnancy (OR: 2.66, 95% CI: 1.45, 4.88; p=0.0016), were associated with higher risk of NDD including ASD approximately by 2 fold and 3 fold, respectively.
- Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 (OR: 3.08, 95% CI: 1.85, 5.11; p<0.0001) and concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy (OR: 2.12, 95% CI: 1.03, 4.35; p=0.0413), were associated with higher risk of NDD including ASD by approximately 3 fold and 2 fold, respectively.
- Maternal age was associated with NDD including ASD outcome (p=0.0065). Offspring from mothers aged between 31-35 years had a higher risk of NDD including ASD when compared with offspring from mothers aged between 26-30 years (OR: 0.38, 95% CI: 0.20, 0.73).

From paternal characteristics identified as risk factors or confounders (see Table 4 and Table 6), only categories of calendar year of offspring conception (categorical, 2010-2014: [OR: 0.29, 95% CI: 0.17, 0.47] and 2015-2019: [OR: 0.08, 95% CI: 0.03, 0.19] p<0.0001) were statistically significantly associated with occurrence of NDD event (Table 99).

Table 97 Association between potential offspring risk factors/confounders and NDD; Primary outcome cohort in Norway

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Offspring risk factors/confounders								
Gender [a]								
Male	1012	52.08	59	5.83	953	94.17	Reference	-
Female	931	47.92	28	3.01	903	96.99	0.50 (0.32, 0.79)	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Missing	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	8.72,0.0031
Congenital CMV [b]								
No	1943	100.00	87	4.48	1856	95.52	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital rubella [b]								
No	1943	100.00	87	4.48	1856	95.52	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Foetal alcohol syndrome [b]								
No	1943	100.00	87	4.48	1856	95.52	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Fragile X syndrome [b]								
No	1943	100.00	87	4.48	1856	95.52	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Lejeune/cri du chat syndrome [b]								
No	1943	100.00	87	4.48	1856	95.52	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Tuberous sclerosis [b]								
No	1943	100.00	87	4.48	1856	95.52	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-

NDD: neurodevelopmental disorders; CMV: Cytomegalovirus; OR: odds ratio
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at index (childbirth)
b) between index and exit date

Table 98 Association between potential maternal risk factors/confounders and NDD; Primary outcome cohort in Norway

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Maternal risk factors/confounders								
Mother's age [a] (categorical)								
≤20 years	46	2.37	3	6.52	43	93.48	1.29 (0.38, 4.36)	-
21-25	289	14.87	22	7.61	267	92.39	1.52 (0.87, 2.65)	-
26-30	641	32.99	33	5.15	608	94.85	Reference	-
31-35	641	32.99	13	2.03	628	97.97	0.38 (0.20, 0.73)	-
36-40	270	13.90	12	4.44	258	95.56	0.86 (0.44, 1.69)	-
>40	56	2.88	4	7.14	52	92.86	1.42 (0.48, 4.16)	-
Wald test	-	-	-	-	-	-	-	16.12 (0.0065)
Affective disorder [b]								
No	1806	92.95	83	4.60	1723	95.40	Reference	-
Yes	137	7.05	4	2.92	133	97.08	0.62 (0.23, 1.73)	0.82 (0.3648)
Diabetes [b]								
No	1905	98.04	87	4.57	1818	95.43	Reference	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Yes	38	1.96	0	0.00	38	100.00	0.00(0.00,I)	0.00(0.9798)
Gestational diabetes [c]								
No	1840	94.70	84	4.57	1756	95.43	Reference	-
Yes	103	5.30	3	2.91	100	97.09	0.63 (0.19, 2.02)	0.61 (0.4341)
Neurotic disorder [b]								
No	1734	89.24	81	4.67	1653	95.33	Reference	-
Yes	209	10.76	6	2.87	203	97.13	0.60 (0.26, 1.40)	1.38 (0.2393)
Schizophrenia, schizotypal and delusional disorders [b]								
No	1939	99.79	87	4.49	1852	95.51	Reference	-
Yes	4	0.21	0	0.00	4	100.00	0.00(0.00,I)	0.00(0.9849)
Obesity [d]								
No	1927	99.18	87	4.51	1840	95.49	Reference	-
Yes	16	0.82	0	0.00	16	100.00	0.00(0.00,I)	0.00(0.9869)
CMV [c]								
No	1943	100.00	87	4.48	1856	95.52	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Rubella [c]								
No	1943	100.00	87	4.48	1856	95.52	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse prior to LMP2 [d]								
No	1940	99.85	87	4.48	1853	95.52	Reference	-
Yes	3	0.15	0	0.00	3	100.00	0.00(0.00,I)	0.00(0.9869)
Alcohol abuse during pregnancy [c]								
No	1941	99.90	87	4.48	1854	95.52	Reference	-
Yes	2	0.10	0	0.00	2	100.00	0.00(0.00,I)	0.00(0.9893)
Substance abuse prior to LMP2 [d]								
No	1937	99.69	86	4.44	1851	95.56	Reference	-
Yes	6	0.31	1	16.67	5	83.33	4.30 (0.50, 37.25)	1.76 (0.1849)
Substance abuse during pregnancy [c]								
No	1938	99.74	86	4.44	1852	95.56	Reference	-
Yes	5	0.26	1	20.00	4	80.00	5.38 (0.60, 48.68)	2.25 (0.1340)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Smoking prior to LMP2 [d]								
No	1245	64.08	38	3.05	1207	96.95	Reference	-
Yes	250	12.87	16	6.40	234	93.60	2.17 (1.19, 3.96)	-
Missing	448	23.06	33	7.37	415	92.63	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	6.41(0.0114)
Smoking during pregnancy [c]								
No	1554	79.98	61	3.93	1493	96.07	Reference	-
Yes	143	7.36	14	9.79	129	90.21	2.66 (1.45, 4.88)	-
Missing	246	12.66	12	4.88	234	95.12	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	9.92(0.0016)
Maternal polypharmacy index prior to LMP2 [e](categorical)								
0	1261	64.90	49	3.89	1212	96.11	Reference	-
1-4	648	33.35	34	5.25	614	94.75	1.37 (0.87, 2.14)	-
5-10	32	1.65	2	6.25	30	93.75	1.65 (0.38, 7.10)	-
>10	2	0.10	2	100.00	0	0.00	4.28628E10(0.00,I)	-
Wald test	-	-	-	-	-	-	-	2.15(0.5425)
Maternal polypharmacy index during pregnancy [c](categorical)								
0	1002	51.57	39	3.89	963	96.11	Reference	-
1-4	897	46.17	43	4.79	854	95.21	1.24 (0.80, 1.94)	-
5-10	44	2.26	5	11.36	39	88.64	3.17 (1.18, 8.47)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	5.45(0.0654)
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription								
No	1737	89.40	65	3.74	1672	96.26	Reference	-
Yes	206	10.60	22	10.68	184	89.32	3.08 (1.85, 5.11)	18.88(<.0001)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription								
No	1838	94.60	78	4.24	1760	95.76	Reference	-
Yes	105	5.40	9	8.57	96	91.43	2.12 (1.03, 4.35)	4.16 (0.0413)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription								
No	620	31.91	24	3.87	596	96.13	Reference	-
Yes	1323	68.09	63	4.76	1260	95.24	1.24 (0.77, 2.01)	0.78 (0.3770)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription								
No	1122	57.75	43	3.83	1079	96.17	Reference	-
Yes	821	42.25	44	5.36	777	94.64	1.42 (0.92, 2.19)	2.56 (0.1094)

CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; NDD: neurodevelopmental disorders; OR: odds ratio
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2

Table 99 Association between potential paternal risk factors/confounders and NDD; Primary outcome cohort in Norway

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Paternal risk factors/confounders								
Affective disorder [a,b]								
No	1675	86.21	78	4.66	1597	95.34	Reference	-
Yes	268	13.79	9	3.36	259	96.64	0.71(0.35, 1.44)	0.90,0.3421
Bipolar affective disorder [a]								
No	1583	81.47	77	4.86	1506	95.14	Reference	-
Yes	360	18.53	10	2.78	350	97.22	0.56 (0.29, 1.09)	2.91,0.0882
Mania [a]								
No	1929	99.28	87	4.51	1842	95.49	Reference	-
Yes	14	0.72	0	0.00	14	100.0 0	0.00(0.00,I)	0.00,0.9877
Neurotic disorder [a]								
No	1748	89.96	82	4.69	1666	95.31	Reference	-
Yes	195	10.04	5	2.56	190	97.44	0.53 (0.21,	1.80,0.1800

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
							1.34)	
Schizophrenia, schizotypal and delusional disorders [a]								
No	1910	98.30	86	4.50	1824	95.50	Reference	-
Yes	33	1.70	1	3.03	32	96.97	0.66 (0.09, 4.91)	0.16,0.6872
Substance abuse [c]								
No	1911	98.35	86	4.50	1825	95.50	Reference	-
Yes	32	1.65	1	3.13	31	96.88	0.69 (0.09, 5.07)	0.14,0.7117
Paternal polypharmacy index [d] (categorical)								
0	1036	53.32	45	4.34	991	95.66	Reference	-
1-4	848	43.64	38	4.48	810	95.52	1.03 (0.66, 1.61)	-
5-10	56	2.88	4	7.14	52	92.86	1.69 (0.59, 4.89)	-
>10	3	0.15	0	0.00	3	100.0 0	0.00(0.00,I)	-
Wald test	-	-	-	-	-	-	-	0.95,0.8129
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription								
No	1282	65.98	53	4.13	1229	95.87	Reference	-
Yes	661	34.02	34	5.14	627	94.86	1.26 (0.81, 1.95)	1.04,0.3088
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription								
No	706	36.34	29	4.11	677	95.89	Reference	-
Yes	1237	63.66	58	4.69	1179	95.31	1.15 (0.73, 1.81)	0.35,0.5517
Father's age [e] (categorical)								
≤20 years	11	0.57	1	9.09	10	90.91	3.13 (0.38, 25.61)	-
21-25	159	8.18	13	8.18	146	91.82	2.78 (1.35, 5.72)	-
26-30	453	23.31	25	5.52	428	94.48	1.83 (1.00, 3.33)	-
31-35	645	33.20	20	3.10	625	96.90	Reference	-
36-40	436	22.44	16	3.67	420	96.33	1.19 (0.61, 2.32)	-
>40	239	12.30	12	5.02	227	94.98	1.65 (0.79, 3.43)	-
Wald test	-	-	-	-	-	-	-	10.01,0.0750
Year of offspring conception [f,g]								
2005-2009	608	31.29	60	9.87	548	90.13	Reference	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
2010-2014	725	37.31	22	3.03	703	96.97	0.29 (0.17, 0.47)	-
2015-2019	610	31.39	5	0.82	605	99.18	0.08 (0.03, 0.19)	-
Wald test	-	-	-	-	-	-	-	47.13,<.0001

NDD: neurodevelopmental disorders; OR: odds ratio
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index (date of childbirth)
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period

10.5.1.6 Variable estimates from propensity score

Variables found to be associated with the outcome were included in the PS models for the analyses of the Primary outcome cohort. This means all specified confounders for which an association with both the outcome and the exposure was observed and all specified risk factors (associated with the outcome but not the exposure) are included in the PS models. Notably some maternal characteristics appeared to be associated with the exposure as well as the outcome; further evaluation of the impact of these variables were undertaken to minimise introduction of bias. If any unbalance for these variables remained after performing PS weighting, they were also included in the final Cox regression model.

In the PS model estimated from logistic regression (Table 100), offspring gender was not associated with the paternal exposure to valproate when compared to lamotrigine/levetiracetam (OR: 1.14, 95% CI: 0.91, 1.42, p=0.2437). From maternal risk factors/confounders, no covariate was associated with the study exposure. Offspring with fathers with affective disorders (OR: 0.41, 95% CI: 0.25, 0.67, p=0.0004), neurotic disorders (OR: 0.46, 95% CI: 0.27, 0.81, p=0.0068), concomitant medications associated with valproate-indicated psychiatric conditions (OR: 0.56, 95% CI: 0.42, 0.75, p<0.0001), and years of offspring conception 2010-2014 (OR: 0.71, 95% CI: 0.54, 0.94, p=0.0155) and 2015-2019 (OR: 0.62, 95% CI: 0.46, 0.83, p<0.0015) had a lower probability of being in the valproate exposure group. A random forest propensity score was performed to identify variable importance metrics, i.e. two-way interactions, and variables presenting low index importance were not included in the PS logistic informed by random forest model.

Variables or interactions associated with NDD including ASD in the PS model from logistic regression informed by random forest were paternal affective disorder (OR: 0.41, 95% CI: 0.25, 0.67, p=0.0004), neurotic disorder (OR: 0.46, 95% CI: 0.26, 0.80, p=0.0063), at least one prescription concomitant medications associated with valproate-indicated psychiatric conditions (OR: 0.56, 95% CI: 0.42, 0.75,

p<0.0001), and categories of calendar year of offspring conception 2010-2014 (OR: 0.71, 95% CI: 0.54, 0.94, p=0.0163) and 2015-2019 (OR: 0.62, 95% CI: 0.46, 0.83, p=0.0016).

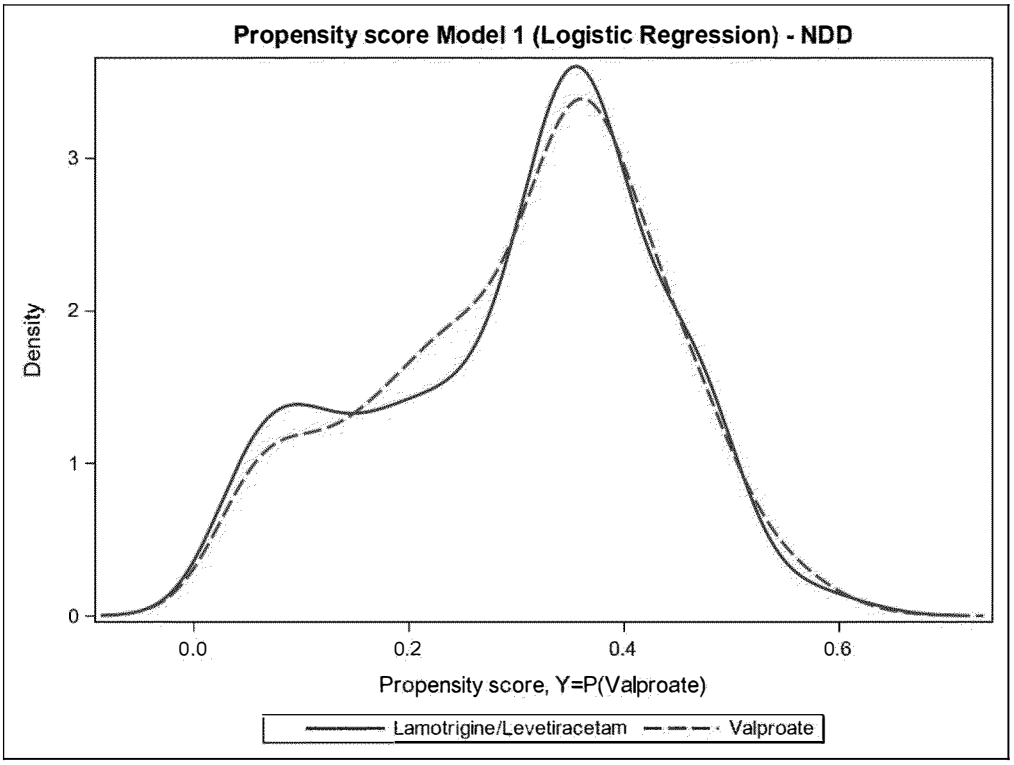
The PS model that best achieved a balance in the weighted exposure groups after using inverse probability of treatment weights was the PS model estimated from logistic regression, please see Table 240 and Figure 24. Thus, the logistic regression model was used to apply inverse probability of treatment weights in the effect estimation analysis (presented in Section 10.5.1.7).

Table 100 Variable estimates from logistic regression propensity score model; Primary outcome cohort in Norway

Exposure group (valproate vs lamotrigine/levetiracetam)	Estimate		
Variable (or interaction)[a]	OR	95% CI	P-value
Offspring risk factors/confounders			
Gender [b]			
Male	Reference	-	-
Female	1.14	0.91, 1.42	0.2437
Maternal risk factors/confounders			
Mother's age [b] (categorical)			
≤20 years	1.28	0.65, 2.53	0.4741
21-25	0.94	0.67, 1.31	0.7215
26-30	Reference	-	-
31-35	0.97	0.74, 1.27	0.8086
36-40	0.79	0.55, 1.15	0.2198
>40	0.51	0.24, 1.11	0.0896
Affective disorder [d]	0.58	0.33, 1.03	0.0635
Diabetes [d]	1.17	0.45, 3.05	0.7452
Gestational diabetes [e]	0.79	0.43, 1.47	0.4644
Neurotic disorder [d]	1.33	0.89, 1.98	0.1577
Obesity [f]	0.76	0.15, 3.96	0.7480
Smoking during pregnancy [e]			
No	Reference	-	-
Yes	1.43	0.96, 2.14	0.0785
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.75	0.47, 1.20	0.2275
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.58	0.28, 1.18	0.1321
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] -mothers with at least one prescription	1.07	0.84, 1.37	0.5701
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.94	0.74, 1.18	0.5835
Paternal risk factors/confounders			
Affective disorder [d,g]	0.41	0.25, 0.67	0.0004
Bipolar affective disorder [d]	0.73	0.50, 1.07	0.1041
Mania [d]	0.47	0.05, 4.19	0.4988
Neurotic disorder [d]	0.46	0.27, 0.81	0.0068
Schizophrenia, schizotypal and delusional disorders [d]	2.43	0.94, 6.28	0.0662
Substance abuse [f]	0.28	0.04, 2.21	0.2292
Concomitant medications associated with valproate-indicated psychiatric conditions [f] – fathers with at least one prescription	0.56	0.42, 0.75	<.0001
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with at least one	1.00	0.79, 1.27	0.9946

Exposure group (valproate vs lamotrigine/levetiracetam)	Estimate		
Variable (or interaction)[a]	OR	95% CI	P-value
prescription			
Year of offspring conception [i,j]			
2005-2009	Reference	-	-
2010-2014	0.71	0.54, 0.94	0.0155
2015-2019	0.62	0.46, 0.83	0.0015

CI: Confidence Interval; LMP2: Last Menstrual Period Date Plus 2 weeks; OR: odds ratio
Legend: Odds ratios (OR), 95% confidence intervals (CI) and p-values were represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model were listed here, however some of the variables might not be included in the final set of variables.
a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.
b) at index (childbirth)
d) all available data prior to index date
e) during pregnancy (from LMP2 until index date)
f) 12 months lookback from LMP2
g) excluding bipolar affective disorder and mania
h) 3 months lookback from LMP2
i) at mother's LMP2
j) calendar years were grouped in each country according to the length of the study period



NDD: neurodevelopmental disorders.

Figure 24 Balance of PS Model 1- Logistic Regression; Primary outcome cohort in Norway

10.5.1.7 Effect estimation for NDD including ASD

The effect estimation for NDD including ASD was assessed using crude Cox regression model as presented in Table 101. In this model 1,943 subjects were included, 617 offspring of the valproate group and 1,326 of lamotrigine/levetiracetam group, and no influential subject was identified. Respectively, 6.2% (N=38) of offspring of the valproate group and 3.7% (N=49) of the lamotrigine/levetiracetam group presented a NDD including ASD event. In the crude analysis, no increased risk for NDD including ASD was observed in offspring of fathers exposed to valproate compared to offspring of fathers exposed to lamotrigine/levetiracetam (HR: 1.40, 95% CI: 0.90, 2.18).

The effect estimation for NDD including ASD using PS-weighted Cox regression model was assessed in a total of 1670 offspring, 505 offspring of valproate group and 1165 of lamotrigine/levetiracetam group. Respectively, 6.3% (N=32) of offspring of the valproate group and 3.6% (N=42) of the lamotrigine/levetiracetam group presented an NDD including ASD event. In the PS-weighted Cox regression model, no increased risk for NDD including ASD was observed in offspring of fathers exposed to valproate compared to offspring of fathers exposed to the lamotrigine/levetiracetam group (HR: 1.52, 95% CI: 0.93, 2.49) (Table 102).

Table 103 presents the effect estimation for NDD including ASD using PS-weighted Cox regression model adjusted for the K-means exposure cluster (i.e. trajectories with constant high exposure (A), and with constant low exposure (B), for further details on the K-means cluster please check Figure 22 and Table 91). In order to obtain estimates of the effect of valproate *vs* lamotrigine/levetiracetam in each cluster identified by the K-means algorithm, an interaction term between the K-means clusters variable and the main exposure variable was included in the model. The effect estimation was assessed in a total of 1670 offspring. No increased risk for NDD including ASD was observed, for offspringoffspringoffspring of fathers exposed to valproate compared to offspring of fathers exposed to lamotrigine/levetiracetam, in the different cluster of exposure. Likewise, no interaction between exposure and paternal K-means cluster was observed.

In the analysis of effect estimation in cluster A (i.e. trajectories with constant high exposure) 349 offspring from the valproate group, of which 6.9% (N=24) presented a NDD including ASD event and 877 from lamotrigine/levetiracetam, of which 3.4% (N=30) presented a NDD including ASD event, were considered. In cluster A, no increased risk for NDD including ASD was observed for offspring from fathers exposed to the valproate compared to offspring from fathers exposed to lamotrigine/levetiracetam (HR: 1.60, 95% CI: 0.90, 2.85). The effect estimated in cluster B (i.e. constant low exposure) considered 156 offspring from the valproate group, of which 5.1% (N=8) presented a NDD including ASD event and 288 from lamotrigine/levetiracetam, of which 4.2% (N=12) presented a NDD including ASD event. In cluster B, no increased risk for NDD including ASD was observed for offspring from fathers exposed to the valproate compared to offspring from fathers exposed to lamotrigine/levetiracetam (HR: 1.36, 95% CI: 0.53-3.47) (Table 103).

Table 101 Effect estimation for neurodevelopmental disorders (NDD) using crude Cox regression model; Primary outcome cohort in Norway

Variable	Total	Number of events	Number of subjects included in the model (after excluding influential subjects) [a]		Model estimates		
	N	N	N	%	HR	95% CI	P-value
Valproate	617	38					
Lamotrigine/levetiracetam	1326	49					

Variable	Total N	Number of events N	Number of subjects included in the model (after excluding influential subjects) [a] N	%	Model estimates HR	95% CI	P-value
Valproate	617	38					
Lamotrigine/levetiracetam	1326	49					
Paternal exposure: valproate vs lamotrigine/levetiracetam	1943		1943	100.00	1.40	(0.90, 2.18)	0.1411

CI: Confidence Interval; HR: Hazard Ratio
a) Influential subjects were identified using the dfbetas for the main exposure coefficient.

Table 102 Effect estimation for neurodevelopmental disorders (NDD) using Propensity Score weighted Cox regression model; Primary outcome cohort in Norway

Variable	Total N	Number of events	Model estimates[1] HR	95% CI	P-value
Valproate	505	32			
Lamotrigine/levetiracetam	1165	42			
Paternal exposure: valproate vs lamotrigine/levetiracetam	1670		1.52	(0.93, 2.49)	0.0947

CI: Confidence Interval; HR: Hazard Ratio
[1]**The logistic regression PS model includes all variables from Table 100, following described: Offspring risk factors/confounders:** "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception"

Table 103 Effect estimation for neurodevelopmental disorders (NDD) using Propensity Score weighted Cox regression model adjusted for K-means exposure cluster; Primary outcome cohort in Norway

Variable	Total N	Number of events	Model estimates[1] HR	95% CI	P-value
Valproate – cluster A	349	24			
Lamotrigine/levetiracetam – cluster A	877	30			
Valproate – cluster B	156	8			
Lamotrigine/levetiracetam – cluster B	288	12			
Paternal exposure: valproate vs lamotrigine/levetiracetam	1670		-	-	0.1084
K-means exposure cluster:					
K-means exposure cluster B	-		-	-	0.7130
Paternal exposure * cluster:					
Valproate * cluster B	-		-	-	0.7718
Effect of valproate across K-means cluster:					
Valproate vs lamotrigine/levetiracetam in cluster A	-		1.60	(0.90, 2.85)	-
Valproate vs lamotrigine/levetiracetam in cluster B	-		1.36	(0.53, 3.47)	-

CI: Confidence Interval; HR: Hazard Ratio
Cluster A: constant high exposure; Cluster B: constant low exposure.
[1] **The logistic regression PS model includes all variables from Table 100, following described: Offspring risk factors/confounders:** "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with

valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception"

10.5.1.8 Case assessment

Overall, considering all the groups of paternal exposure, 5.0% of the offspring were identified as cases of NDD including ASD, of which the majority (81.2%) were considered in the case assessment as a probable case (meeting the criteria of multiple diagnosis for NDD including ASD recorded during the follow-up). The same was observed considering valproate and lamotrigine/levetiracetam group, with a slightly higher percentage of NDD including ASD being observed in the valproate group. Considering the valproate group, 6.8% of the offspring were identified as cases of NDD including ASD, of which 83.3% were classified in the case assessment as probable cases. Considering the lamotrigine/levetiracetam group, 4.1% of the offspring were identified as cases of NDD including ASD, of which 79.6% were classified in the case assessment as probable cases (Table 104).

Table 104 Case assessment in Norway

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of offspring	**N=616**		**N=1318**		**N=1128**		**N=190**		**N=1934**	
Nr of offspring identified as cases of NDD including ASD *	42	6.82%	54	4.10%	47	4.17%	7	3.68%	96	4.96%
Case assessment										
Possible **	7	16.67%	11	20.37%	10	21.28%	1	14.29%	18	18.75%
Probable **	35	83.33%	43	79.63%	37	78.72%	6	85.71%	78	81.25%

NDD: neurodevelopmental disorders; ASD: Autism Spectrum Disorders
* Percentages were calculated over the total pregnancies in each group
** percentages were calculated over the total number of offspring identified as cases of NDD including ASD in each group

Possible case: The offspring aged ≤12 years were considered a possible case if they satisfy the criteria that only one diagnosis record for NDD including ASD was recorded during follow-up.
Probable case: The offspring aged ≤12 years were considered a probable case if they satisfy the criteria that multiple diagnoses for NDD including ASD were recorded during follow-up, regardless of whether the same code was recorded multiple times or different codes are recorded.

10.5.1.9 Exploratory Analyses – NDD including ASD cohort

10.5.1.9.1 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Exploratory analysis 5 for NDD including ASD)

Results from exploratory analysis 5 are presented in Table 242 to Table 253 in section 15.3.4 (see Appendix). The analyses were performed in order to answer Exploratory Objective 5, which aimed to describe the risk factors and frequency of NDD, including ASD in offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine/levetiracetam) and lamotrigine/levetiracetam (in combination with other AEDs excluding valproate) at the time of the conception. The analysis was performed in the Primary outcome cohort for explorative objective 5. Findings were compared to results obtained from the Primary cohort for comparative analysis (main analysis).

For the exploratory analyses 5, the inclusion criterion was all offspring from the Primary outcome cohort (N=4,648). After additional exclusions, a total of 290 offspring were included in this analysis, with 69 in valproate and 221 in lamotrigine/levetiracetam group (Figure 43).

None of the offspring was born extremely preterm (gestational age <28 weeks) or had extremely low (<1000g) birth weight in the valproate polytherapy group, while these counts were one (0.5%) and 2 (0.9%) offspring in the lamotrigine/levetiracetam polytherapy group, respectively. Gestational age and birth weight were similarly distributed between the exposure groups. Compared with the valproate monotherapy in the main analysis (Table 94), a higher proportion of females were observed in the valproate polytherapy group (52.2% vs. 47.9% female in the main analyses) (Table 242).

The proportion of NDD including ASD was higher in the offspring paternally exposed to polytherapy (10.1% valproate and 5.4% lamotrigine/levetiracetam) (Table 243) compared with those on monotherapy in the main analysis (6.2% valproate and 3.7% lamotrigine/levetiracetam) (section 10.5.1.7).

Compared with the main analyses (Table 95), in this exploratory analysis mothers presented similar median age (30 years), and lower proportion of comorbidities was also observed in the lamotrigine/levetiracetam polytherapy (when compared to lamotrigine/levetiracetam monotherapy group) such as neurotic disorders (5.0% vs. % 11.2%) and affective disorders (4.5% vs 8.4%). The frequency of these comorbidities was similar in this exploratory analysis compared with the main analysis in the valproate group (Table 244 and Table 245).

Compared to those included in the main analyses, fathers included in this exploratory analysis (Table 96) presented similar median age in the valproate (33 years vs. 32 years, respectively) and in the lamotrigine/levetiracetam groups (32 years vs. 33 years, respectively) (Table 246). Higher proportion of comorbidities was observed in the valproate group in the main analysis as compared with the valproate group in the exploratory analysis 5: bipolar disorder (10.7% vs. 1.5%), and neurotic disorder (5.0% vs. 2.9%). Similar observation was also noted in the lamotrigine/levetiracetam monotherapy (main analysis) and lamotrigine/levetiracetam polytherapy (exploratory analysis 5): affective disorder excluding bipolar affective disorder and mania (17.7% vs. 4.1%), bipolar affective disorder (22.2% vs. 3.2%), and neurotic disorder (12.4% vs. 6.3%). The most frequent indication for AED treatment was epilepsy in the exploratory analysis 5 (valproate 56.5% and lamotrigine/levetiracetam polytherapy 63.8%) (Table 247).

The distribution of potential risk factors and confounders for NDD including ASD by paternal exposure of polytherapy group were examined for the Primary outcome cohort for Explorative Objective 5. Results of univariable analyses are presented in Table 248-Table 249.

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

As observed in the main analyses (Table 94), none of the offspring characteristics were associated with paternal polytherapy exposure (Table 248).

When compared to the main analysis (Table 95), less maternal characteristics were associated to paternal exposure in the exploratory analyses 5 (Table 249). One maternal risk factor, was statistically associated with paternal polytherapy exposure: age (categorical, p=0.0062),

Also, less paternal characteristics were associated to paternal exposure in the exploratory analyses 5 (Table 250), when compared to the main analyses (Table 96). One paternal characteristic, concomitant medications associated with valproate-indicated psychiatric conditions – fathers with at least one prescription (p=0.0125) was statistically associated with paternal polytherapy exposure, this characteristics was not associated in the main analysis.

The distribution of potential risk factors and confounders were examined by NDD including ASD group in the Primary outcome cohort for explorative objective 5. Results of univariable analyses are presented from Table 251 to Table 253. All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

For the offspring characteristics, only gender (OR: 0.17, 95% CI: 0.05, 0.61, p=0.0062) was associated with NDD including ASD event (Table 251); the proportion of events among males were significantly higher than the proportion of events among females, and the same was observed in the main analyses (Table 97).

For maternal characteristics (Table 252), smoking 3 months prior to LMP2 (OR: 6.45, 95% CI: 1.99, 20.86; p=0.0019) and smoking during pregnancy (OR: 3.96, 95% CI: 1.16, 13.56; p=0.0284) were associated with higher risk of NDD including ASD. Smoking during pregnancy was also associated with NDD including ASD in the main analysis (Table 98).

For paternal characteristics (Table 253), one risk factor/confounder, paternal polypharmacy index (categorical, polypharmacy index 1-4 [OR: 1.14, 95% CI: 0.40, 3.24] and polypharmacy index 5-10 [13.12, 95% CI: 2.58, 66.78]; p=0.0072), was statistically significantly associated with NDD event., This risk factor/confounder was not associated with NDD in the main analysis (Table 99).

10.5.1.9.2 Paternal exposure to valproate or lamotrigine/levetiracetam in discordant siblings (Exploratory analysis 6 for NDD including ASD)

Results from exploratory analysis 6 are presented in Table 254 to Table 262 in section 15.3.6. The analysis was performed in the Primary outcome cohort for explorative objective 6. This objective aimed to describe the risk factors and frequency of NDD including ASD, in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception. Findings were compared to results obtained from the Primary cohort for comparative analysis (main analyses).

For the exploratory analyses 6, the inclusion criterion was all offspring from the Primary outcome cohort for comparative analysis (N=1943). After additional exclusions, a total of 8 offspring were included in this analysis, with 4 in valproate and 4 in lamotrigine/levetiracetam group (Figure 44).

In exploratory analysis 6, the sample size was significantly lower than the main analysis, hence direct comparison with the main analysis may not be ideal. But overall, all offspring were born at term in the valproate group (100%) while 75% born at term in the lamotrigine/levetiracetam group (Table 254). In exploratory analysis 6, the mean follow-up time was longer in the valproate group (8.43 years) than lamotrigine/levetiracetam group (6.56 years) (Table 254). Regarding clinical characteristics, none of the offspring had comorbidities which might be attributed to the small sample size (Table 255).

In this cohort, only 1 event of NDD including ASD was observed: in the valproate group (Table 255).

Median age of mothers at childbirth was lower in the valproate than in the lamotrigine/levetiracetam group (28.5, IQR 23.5, 32.5 vs. 31, IQR 28, 35.5, respectively) (Table 256). None of the mothers in the valproate group had comorbidities, and in the lamotrigine/levetiracetam group, one mother had diabetes and another mother had gestational diabetes in exploratory analysis 6. Median maternal polypharmacy index prior to LMP2 was 0.0 (IQR 0.0, 0.5) in valproate and 0.5 (IQR 0.0, 1.0) in lamotrigine/levetiracetam group (Table 257).

Median age of fathers was lower in the valproate than in the lamotrigine/levetiracetam group (29.5, IQR 24.5, 31.0 vs. 32, IQR 29, 34.0, respectively) (Table 258). None of the fathers in the valproate group had comorbidities, and in the lamotrigine/levetiracetam group, one father had neurotic disorder in exploratory analysis 6. Median paternal polypharmacy index prior to LMP2 was 0.0 (IQR 0.0, 0.5) in valproate and 2.0 (IQR 1.0, 2.5) in lamotrigine/levetiracetam group (Table 259). Due to small sample size (8), comparing these findings with the main analysis may not be informative.

The distribution of potential risk factors and confounders for NDD including ASD by paternal exposure to valproate and levetiracetam were examined for the Primary outcome cohort for explorative objective 6. Results of univariable analyses are presented in Table 260-Table 262.

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

As observed in the main analyses (Table 94), none of the offspring characteristics were associated with paternal exposure (Table 260).

Also, none of the maternal and paternal characteristics were not associated with paternal exposure to valproate or lamotrigine/levetiracetam (Table 261 and Table 262).

10.5.1.10 Sensitivity Analyses for NDD including ASD

Multiple sensitivity analyses were performed to examine the robustness of the main analysis findings. Summary tables of the main results for each of sensitivity analysis are presented in this section. All tables produced for each of the sensitivity analyses are presented in a separate document.

Findings from extending the exposure window for the primary outcome to 6 months (sensitivity analysis 1), excluding offspring with low birth weight or born prior to 8th month for the primary cohort (sensitivity analysis 3), simple pairwise comparisons for the exposure groups (valproate vs lamotrigine, sensitivity analysis 5), comparing PS-matched model with covariate adjusted model for the primary cohort

(sensitivity analysis 6) and examining the effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy (sensitivity analysis 7) were similar with the results observed in the main analyses (see Table 105). In sensitivity analysis 5, offspring in the levetiracetam exposure group had no NDD event resulting non-interpretable HR for crude Cox regression model and PS-weighted Cox regression model adjusted for K-means exposure model (cluster B). See Table 105 for further details.

Table 105 Summary of main analysis and sensitivity analysis of Neurodevelopmental Disorders (NDD) including Autism Spectrum Disorders (ASD) in Norway

Analyses*	Population considered	HR (95% CI) estimates		HR (95% CI) estimates by cluster of exposure	
		Crude*	Adjusted**	Cluster A	Cluster B
Main analysis N sample = 1943	Please check Section 9.3	1.40 (0.90, 2.18)	1.52 (0.93, 2.49)	1.60 (0.90, 2.85)	1.36 (0.53, 3.47)
Sensitivity analysis 1 N sample = 2034	Extended risk window of paternal valproate exposure (6 months)	1.33 (0.87, 2.03)	1.57 (0.97, 2.53)	1.64 (0.90, 3.01)	1.45 (0.67, 3.15)
Sensitivity analysis 3 N sample = 1928	Exclusion of offspring with low birth weight or born prior to 8th months	1.42 (0.91, 2.22)	1.52 (0.93, 2.49)	1.61 (0.90, 2.87)	1.36 (0.53, 3.47)
Sensitivity analysis 5[A] N sample = 1757	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	1.39, (0.88, 2.18)	1.41 (0.85, 2.32)	1.50 (0.83, 2.71)	1.23 (0.48, 3.12)
Sensitivity analysis 5[B] N sample = 798	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)		3.58 (0.82, 15.60)	3.12 (0.71, 13.71)	
Sensitivity analysis 6 N sample = 1697	Comparison of PS-weighted model with covariate adjustment model		1.47 (0.91, 2.37)		
Sensitivity analysis 7 N sample = 1977	Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy	1.39 (0.90, 2.13)*	1.46 (0.91, 2.34)	1.59 (0.92, 2.72)	1.23 (0.48, 3.13)
Sensitivity analysis 11 N sample = 1942	Narrow definition of NDD	1.52 (0.96, 2.40)	1.61 (0.97, 2.69)	1.75 (0.95, 3.23)	1.35 (0.53, 3.42)

HR: Hazard Ratio; CI: Confidence Interval; 5A analysis comparing valproate and lamotrigine; 5B analysis comparing valproate and levetiracetam; AED: Antiepileptic Drug; ASD: Autism Spectrum Disorders; NDD: Neurodevelopmental Disorders

* For sensitivity analysis 7 the "crude" hazard ratio was adjusted for offspring epilepsy and offspring exposure AED

****The logistic regression PS models used in sensitivity analysis include variables following described:**

Sensitivity analysis 1: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age", "Diabetes", "Neurotic disorder", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Year of offspring conception"

Sensitivity analysis 3: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age at childbirth", "Affective disorder" "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", mothers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception".

Sensitivity analysis 5[A]: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age at childbirth", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", Substance abuse prior to LMP2", fathers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Father's age", "Year of offspring conception"
Sensitivity analysis 5[B]: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age", "Neurotic disorder", mother with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2" "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** Fathers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Year of offspring conception"
Sensitivity analysis 6: No PS weighting performed
Sensitivity analysis 7: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", Mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", father exposed to at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Year of offspring conception "
Sensitivy analysis 11: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders**: "Mother's Age", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception"

Validation of the assumption that individuals are exposed to one DDD per day (sensitivity analysis 8) was performed among fathers who had prescriptions of AED for epilepsy, the estimated treatment durations (estimated from the number of prescriptions as described in section 9.9.4.8) was longer for fathers treated with levetiracetam 196.6 (±142.2) days followed by those treated with lamotrigine 186.7 (±132.3) days and valproate 135.7 (±83.5) days. The actual observed time between prescriptions was longer for fathers prescribed with valproate 98.7 (±33.9) days followed by levetiracetam 89.6 (±34.0) days and lamotrigine 87.7 (±34.7) days. The ratio (observed vs estimated) was 1.00 for valproate, 0.76 for lamotrigine, and 0.69 for levetiracetam. Under the assumption of perfect compliance of each father, the ratio for valproate was within the approximation range 0.8-1.20 which indicate the real daily dose prescribed in congruence with the WHO DDD. However, the ratio for lamotrigine and levetiracetam depart from the range indicating the real daily dose prescribed diverge from the WHO DDD (see Table 106 for further details).

Sensitivity analysis 8 was also performed among fathers who had prescriptions of AED without indication for epilepsy, the estimated treatment durations (expected) was longer for fathers treated with levetiracetam 191.8 (±95.2) days followed by those treated with lamotrigine 183 (±175.1) days, and valproate 129.8 (±106.9) days. Time between prescriptions (observed) was similar for fathers prescribed with valproate 92.9 (±30.6) days, lamotrigine 94.1 (±34.3) days, and levetiracetam 91.9 (±37) days. The ratio (observed vs expected) was 1.23 for valproate, 0.98 for lamotrigine and 0.56 for levetiracetam (Table 106). Under the assumption of perfect compliance of each father, the ratio for lamotrigine was within the approximation range 0.80-1.20 which indicate the real daily dose prescribed was in congruence with the WHO DDD. However, the ratios for valproate and levetiracetam depart from the range indicating the real daily dose prescribed diverge from the WHO DDD (see Table 106 for further details).

Table 106 Distribution of estimated treatment durations and time between prescriptions for fathers with/without an indication for epilepsy; Primary outcome cohort in Norway

	Distribution of estimated treatment durations and time between prescriptions for fathers with an indication for epilepsy			**Distribution of estimated treatment durations and time between prescriptions for fathers without an indication for epilepsy; primary outcome**		
	Paternal exposure group			**Paternal exposure group**		
NDD	**Valproate**	**Lamotrigine**	**Levetiracetam**	**Valproate**	**Lamotrigine**	**Levetiracetam**
Number of offspring	**N=250**	**N=308**	**N=155**	**N=390**	**N=877**	**N=39**
Estimated treatment durations (expected)	135.74 (83.47)	186.67 (132.34)	196.64 (142.22)	129.76 (106.90)	182.98 (175.11)	191.78 (95.18)
Time between prescriptions (observed)	98.73 (33.92)	87.72 (34.66)	89.63 (33.95)	92.86 (30.55)	94.06 (34.32)	91.85 (36.97)
Ratio (observed vs expected)	0.99	0.76	0.69	1.23	0.98	0.56

NDD: neurodevelopmental disorders

In sensitivity analysis 10, the mean paternal cumulative exposure to valproate was 63.8 (±24.1) days, while in the lamotrigine/levetiracetam group mean paternal cumulative exposure 68.1 (±23.8) days (See Table 107). Comparing paternal cumulative exposure to valproate with lamotrigine/levetiracetam at specific cumulative exposure level (mean cumulative exposure 67.3 days) showed higher risk of NDD in the offspring (HR: 2.75, 95% CI: 1.03, 7.33). However, the confidence interval was wide and the lower bound was slightly above one. At this particular mean cumulative exposure, the number of events reported in the valproate group and lamotrigine/levetiracetam group were 27 and 36, respectively. See Table 108 for further detail.

Among fathers exposed to valproate, comparing medium cumulative exposure to low cumulative exposure to valproate, no NDD events (0 events) were observed in the medium cumulative exposure while one event was reported for the low cumulative exposure to valproate (HR 0.00, 95% CI: 0.00, 0.00). Comparison between high paternal exposure to valproate and low paternal exposure to valproate showed

higher risk of NDD in the offspring (HR: 14.49, 95% CI: 1.99, 105.46). However, the confidence interval was wide and the number of NDD events reported to the high cumulative exposure to valproate group was 18 compared with a single event for the low cumulative exposure to valproate which may have influenced the HR. See Table 109 for further description.

Among fathers exposed to lamotrigine, comparing medium cumulative exposure to low cumulative exposure to lamotrigine, no NDD events (0 events) reported in the medium cumulative exposure while 8 events were reported for the low cumulative exposure to lamotrigine (HR: 0.00, 95% CI: 0.00, 0.00). Comparison between high paternal exposure to low paternal exposure to lamotrigine showed no higher risk of NDD in the offspring (HR: 2.11, 95% CI: 0.96, 4.66). The number of NDD events reported in the high paternal exposure were 23. See Table 109 for further description.

Table 107. Paternal cumulative exposure to Antiepileptic Drugs (AEDs) by paternal exposure group; Primary outcome cohort in Norway

Paternal exposure group										
NDD **Number of offspring**	**Valproate** **N=930**		**Lamotrigine/levetiracetam** **N=1425**		**Lamotrigine** **N=1207**		**Levetiracetam** **N=218**		**Total (valproate + lamotrigine/levetiracetam) N=2355**	
Cumulative exposure to AEDs	N	%	N	%	N	%	N	%	N	%
Low	204	33.06	438	33.03	377	33.07	60	32.26	638	32.84
Medium	148	23.99	124	9.35	125	10.96	126	67.74	276	14.20
High	265	42.95	764	57.62	638	55.96	0	0.00	1029	52.96
Mean (SD)	63.77 (24.13)		68.05 (23.84)		67.07 (24.32)		74.08 (19.67)		66.69 (24.01)	
Median (25^{th} - 75^{th} percentile) Min, max	75(45.00, 84.00) 1.00, 84.00		84(55.00, 84.00) 2.00, 84.00		84(52.00, 84.00) 2.00, 84.00		84(75.00, 84.00) 2.00, 84.00		84(51.00, 84.00) 1.00, 84.00	

AED: antiepileptic drugs; NDD: neurodevelopmental disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

Table 108. Effect estimation for neurodevelopmental disorders (NDD) using Cox covariate adjustment model; Primary outcome cohort in Norway

NDD	Model estimates		
Number of subjects included in analysis prior to exclusion influential subjects [a]	1697		
Number of subjects included in the model (after excluding influential subjects) [b]	1674 (98.64%)		
	HR	**95% CI**	**P-value**
Effect of valproate at a specific cumulative exposure level:			
Valproate vs lamotrigine/levetiracetam at the mean cumulative exposure=67.32139	2.75	(1.03, 7.33)	-

Legend: Hazard ratios (HR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders included in the covariate adjustment model. All variables potentially included in the model are listed here, however some of the variables might not be included in the final set of variables.
a) Number of subjects included represents the total number of subjects in the cohort of interest minus those subjects who have at least one missing value for any of the variables included in each model.
b) Influential subjects were identified using the dfbetas for the exposure coefficient.

Table 109. Effect estimation for neurodevelopmental disorders (NDD) using Cox covariate adjustment model for valproate and lamotrigine treatment group; Primary outcome cohort in Norway

	Valproate			**Lamotrigine**		
	N	**HR (95% CI)**	**P-value**	**N**	**HR (95% CI)**	**P-value**
Number of subjects included in analysis prior to exclusion influential subjects [a]	617			1207		
Number of subjects included in the model (after excluding influential subjects) [b]	598 (96.92%)			1184 (98.09%)		
Paternal cumulative exposure						
Low		Reference			Reference	Reference
Medium		0.00 (0.00, 0.00)	<0.0001		0.00 (0.00, 0.00)	0.9854
High		14.49 (1.99, 105.46)	0.0083		2.11 (0.96, 4.66)	0.0649

Legend: Hazard ratios (HR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders included in the covariate adjustment model. All variables potentially included in the model are listed here, however some of the variables might not be included in the final set of variables.
a) Number of subjects included represents the total number of subjects in the cohort of interest minus those subjects who have at least one missing value for any of the variables included in each model.
b) Influential subjects were identified using the dfbetas for the exposure coefficient.

10.5.2 Congenital Malformations

10.5.2.1 Description of the offspring, maternal and paternal characteristics by paternal exposure group

The results presented below (Table 110 to Table 115) are of analyses performed in the Secondary outcome cohort for descriptive analyses (see Figure 21).

Overall, the majority of offspring were male (52.2%; 50.3% in those paternally exposed to valproate and 53.1% in those paternally exposed to lamotrigine/levetiracetam), born at term between 37-41 weeks of gestational age (89.3%; 87.7% in those paternally exposed to valproate and 90.0% in those paternally exposed to lamotrigine/levetiracetam) and weighing ≥2500 g (96.4%, similar in both exposure groups) (Table 110). Regarding CM, 15.6% were diagnosed with CM during the overall study follow-up. In the group paternally exposed to valproate, 9.2% had a major CM while 9.0% had a diagnosis of minor CM. In the lamotrigine/levetiracetam paternally exposed group, 8.9% had a major CM while 8.0% had a diagnosis of minor CM (Table 111).

The most frequent adverse pregnancy outcome associated with a diagnosis of CM was intrauterine growth retardation, both for the valproate paternal exposure group (10.3%) and the lamotrigine/levetiracetam paternal exposure group (8.13%) (Table 111).

Overall, the median (IQR) age of mothers from the Secondary outcome cohort for descriptive analyses at childbirth was 30 (26, 34) years, similar in both exposure groups (Table 112).

The most prevalent clinical characteristics recorded in mothers prior to childbirth were diabetes (observed in 1.9% of mothers of offspring paternally exposed to valproate and 2.1% of mothers of offspring paternally exposed to lamotrigine/levetiracetam) and gestational diabetes (observed in 1.7% of mothers of offspring paternally exposed to valproate and 1.9% of mothers of offspring paternally exposed to lamotrigine/levetiracetam) (Table 113).

Smoking prior to LMP2 was recorded 14.6% in mothers of offspring paternally exposed to valproate and 12.6% in mothers of offspring paternally exposed to lamotrigine/levetiracetam; however, the corresponding proportions of missing values were 27.2% and 21.0%, respectively. Smoking during pregnancy was recorded in 9.2% in mothers of offspring paternally exposed to valproate and 6.7% in the lamotrigine/levetiracetam exposed counterparts (Table 113); the corresponding proportions of missing values were 14.3% and 11.4%. Exposure to AEDs in mothers prior to LMP2 and during pregnancy was very low.

Concomitant medications associated with teratogenic activity/foetal toxicity prior to LMP2 were reported in 27.0% of mothers of offspring paternally exposed to valproate and 29.2% mothers of offspring exposed to lamotrigine/levetiracetam were reported. Correspondingly, concomitant medications associated with teratogenic activity/foetal toxicity during pregnancy were reported in 24.8% of mothers of offspring paternally exposed to valproate and 31.2% of mothers of offspring exposed to lamotrigine/levetiracetam

(Table 113). Nevertheless, these exposures were considered as risk factors for CM and excluded for the comparative analysis.

Regarding fathers' demographic characteristics, the overall median (IQR) age of fathers at childbirth was 32 (29, 37) years (32 (28-36) in the valproate group and 33 (29-37) in the lamotrigine/levetiracetam group). A larger proportion of offspring in the lamotrigine/levetiracetam group were conceived in the latest year of the study time period, compared with the valproate group (Table 114). Regarding fathers' indication for AED treatment, epilepsy was reported in 39.0% of paternal valproate exposed group and in 33.6% of paternal lamotrigine/levetiracetam exposed group (Table 115).

The K-means algorithm, analysing DDD trajectories in fathers exposed to AEDs 3 months prior to conception (i.e. prior to LMP2) identified 2 different clusters (Figure 25), one with constant high exposure (cluster A) and one with constant low exposure to AEDs (cluster B). A higher proportion of fathers were in cluster A (68.2%) as compared to cluster B (31.8%) in the valproate exposed group. In the lamotrigine/levetiracetam exposed group, similar proportions were observed in cluster A (74.4%) and cluster B (25.6%).

Paternal exposure to teratogenic activity/foetal toxicity 3 months lookback from LMP2 was 31.1% in the valproate group and 41.7% in the lamotrigine/levetiracetam group (Table 115). Nevertheless, this exposure was considered as risk factor for CM and excluded for the comparative analysis.

Table 110 Offspring demographic characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=2027)

	Paternal exposure group									
CM **Number of offspring**	**Valproate** **N=644**		**Lamotrigine/levetiracetam** **N=1383**		**Lamotrigine** **N=1188**		**Levetiracetam** **N=195**		**Total (valproate + lamotrigine/levetiracetam)** **N=2027**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Gestational age (weeks)										
<28 (extremely preterm)	2	0.31	7	0.51	7	0.59	0	0.00	9	0.44
28-31 (very preterm)	3	0.47	8	0.58	7	0.59	1	0.51	11	0.54
32-36 (moderate to late preterm)	36	5.59	56	4.05	47	3.96	9	4.62	92	4.54
37-41 (at term)	565	87.73	1244	89.95	1067	89.81	177	90.77	1809	89.25
≥42 (post-term)	38	5.90	68	4.92	60	5.05	8	4.10	106	5.23
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	3	0.47	10	0.72	9	0.76	1	0.51	13	0.64
1000-1499 (very low)	2	0.31	6	0.43	5	0.42	1	0.51	8	0.39
1500-2499 (low)	18	2.80	35	2.53	29	2.44	6	3.08	53	2.61
≥2500	621	96.43	1332	96.31	1145	96.38	187	95.90	1953	96.35
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gender										
Male	324	50.31	734	53.07	620	52.19	114	58.46	1058	52.20
Female	320	49.69	648	46.85	567	47.73	81	41.54	968	47.76
Missing	0	0.00	1	0.07	1	0.08	0	0.00	1	0.05

CM: Congenital Malformations
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

Table 111 Offspring clinical characteristics paternal exposure group; Secondary outcome cohort in Norway (N=2027)

	Paternal exposure group									
CM **Number of offspring**	**Valproate** **N=644**		**Lamotrigine/levetiracetam** **N=1383**		**Lamotrigine** **N=1188**		**Levetiracetam** **N=195**		**Total (valproate + lamotrigine/levetiracetam)** **N=2027**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**

Comorbidities [a]										
Congenital CMV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital Herpes Simplex	0	0.00	1	0.07	1	0.08	0	0.00	1	0.05
Congenital rubella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital varicella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Foetal alcohol syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Outcomes										
CM	107	16.61	209	15.11	180	15.15	29	14.87	316	15.59
Major CM (at any time)	59	9.16	123	8.89	106	8.92	17	8.72	182	8.98
Minor CM (at any time)	58	9.01	111	8.03	94	7.91	17	8.72	169	8.34
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]										
Stillbirth	4	3.74	5	2.39	4	2.22	1	3.45	9	2.85
Spontaneous abortion	0	0.00	3	1.44	3	1.67	0	0.00	3	0.95
Intrauterine growth retardation	11	10.28	17	8.13	15	8.33	2	6.90	28	8.86
Perinatal mortality	5	4.67	6	2.87	5	2.78	1	3.45	11	3.48

CM: Congenital Malformations; CMV: Cytomegalovirus
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) between 12th week of gestation in Norway and exit date
b) Denominator for the percentage is the number of offspring with CM.

Table 112 Maternal demographic characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=2027)

	Paternal exposure group									
CM **Number of offspring**	**Valproate** **N=644**		**Lamotrigine/levetiracetam** **N=1383**		**Lamotrigine** **N=1188**		**Levetiracetam** **N=195**		**Total (valproate + lamotrigine/levetiracetam)** **N=2027**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Mother's age [a]										
≤20 years	24	3.73	39	2.82	35	2.95	4	2.05	63	3.11
21-25	117	18.17	226	16.34	192	16.16	34	17.44	343	16.92
26-30	231	35.87	466	33.69	386	32.49	80	41.03	697	34.39
31-35	191	29.66	423	30.59	374	31.48	49	25.13	614	30.29
36-40	73	11.34	200	14.46	181	15.24	19	9.74	273	13.47
>40	8	1.24	29	2.10	20	1.68	9	4.62	37	1.83
Mean (SD)	29.48 (5.13)		30.20 (5.21)		30.26 (5.19)		29.84 (5.36)		29.97 (5.20)	

	Paternal exposure group									
CM **Number of offspring**	**Valproate** **N=644**		**Lamotrigine/levetiracetam** **N=1383**		**Lamotrigine** **N=1188**		**Levetiracetam** **N=195**		**Total (valproate + lamotrigine/levetiracetam)** **N=2027**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Median (25th - 75th percentile)	29.5(26.00, 33.00)		30(27.00, 34.00)		30(27.00, 34.00)		29(26.00, 33.00)		30(26.00, 34.00)	
Min, max	16.00, 46.00		17.00, 45.00		17.00, 45.00		17.00, 44.00		16.00, 46.00	
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM: Congenital Malformations; SD- Standard Deviation
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at 12th week of gestation in Norway

Table 113 Maternal clinical characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=2027)

Paternal exposure group										
CM **Number of offspring**	**Valproate** **N=644**		**Lamotrigine/levetiracetam** **N=1383**		**Lamotrigine** **N=1188**		**Levetiracetam** **N=195**		**Total (valproate + lamotrigine/levetiracetam)** **N=2027**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Comorbidities										
Diabetes [a]	12	1.86	29	2.10	28	2.36	1	0.51	41	2.02
Epilepsy [a]	7	1.09	17	1.23	14	1.18	3	1.54	24	1.18
Obesity [b]	6	0.93	11	0.80	11	0.93	0	0.00	17	0.84
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Folate deficiency [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gestational diabetes [c]	11	1.71	26	1.88	24	2.02	2	1.03	37	1.83
Herpes simplex virus [c]	2	0.31	1	0.07	1	0.08	0	0.00	3	0.15
Rubella [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Toxoplasmosis [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Varicella [c]	0	0.00	1	0.07	1	0.08	0	0.00	1	0.05
Lifestyle characteristics										
Alcohol abuse prior to LMP2 [b]	1	0.16	2	0.14	2	0.17	0	0.00	3	0.15
Alcohol abuse during pregnancy [c]	1	0.16	1	0.07	1	0.08	0	0.00	2	0.10
Substance abuse prior to LMP2 [b]	2	0.31	4	0.29	4	0.34	0	0.00	6	0.30
Substance abuse during pregnancy [c]	2	0.31	2	0.14	2	0.17	0	0.00	4	0.20
Smoking prior to LMP2 [b]										
Yes	94	14.60	174	12.58	158	13.30	16	8.21	268	13.22
No	375	58.23	919	66.45	774	65.15	145	74.36	1294	63.84
Missing	175	27.17	290	20.97	256	21.55	34	17.44	465	22.94
Smoking during pregnancy [c]										
Yes	59	9.16	93	6.72	91	7.66	2	1.03	152	7.50
No	493	76.55	1133	81.92	961	80.89	172	88.21	1626	80.22
Missing	92	14.29	157	11.35	136	11.45	21	10.77	249	12.28
Medication use										
Exposure to AEDs prior to LMP2 [d]										
Valproate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lamotrigine	0	0.00	19	1.37	19	1.60	0	0.00	19	0.94
Levetiracetam	0	0.00	2	0.14	2	0.17	0	0.00	2	0.10
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	1	0.16	1	0.07	1	0.08	0	0.00	2	0.10
Carboxamide derivatives	3	0.47	2	0.14	1	0.08	1	0.51	5	0.25

Paternal exposure group										
CM **Number of offspring**	**Valproate** **N=644**		**Lamotrigine/levetiracetam** **N=1383**		**Lamotrigine** **N=1188**		**Levetiracetam** **N=195**		**Total (valproate + lamotrigine/levetiracetam)** **N=2027**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	0	0.00	22	1.59	21	1.77	1	0.51	22	1.09
Exposure to AEDs during pregnancy [c]										
Valproate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lamotrigine	0	0.00	17	1.23	17	1.43	0	0.00	17	0.84
Levetiracetam	0	0.00	2	0.14	2	0.17	0	0.00	2	0.10
Barbiturates and derivatives	1	0.16	0	0.00	0	0.00	0	0.00	1	0.05
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	1	0.07	1	0.08	0	0.00	1	0.05
Carboxamide derivatives	3	0.47	3	0.22	2	0.17	1	0.51	6	0.30
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	0	0.00	20	1.45	19	1.60	1	0.51	20	0.99
K-means cluster prior to LMP2 [d]										
Unexposed	641	99.53	1359	98.26	1166	98.15	193	98.97	2000	98.67
Cluster A[1]	2	0.31	17	1.23	15	1.26	2	1.03	19	0.94
Cluster B[1]	1	0.16	7	0.51	7	0.59	0	0.00	8	0.39
K-means cluster during pregnancy [c]										
Unexposed	640	99.38	1359	98.26	1166	98.15	193	98.97	1999	98.62
Cluster A[2]	2	0.31	15	1.08	13	1.09	2	1.03	17	0.84
Cluster B[2]	2	0.31	9	0.65	9	0.76	0	0.00	11	0.54
Maternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [d] - mothers with at least one prescription	174	27.02	404	29.21	350	29.46	54	27.69	578	28.52
Maternal exposure to teratogenic activity/foetal toxicity during pregnancy [d] - mothers with at least one prescription	160	24.84	431	31.16	371	31.23	60	30.77	591	29.16

AED: antiepileptic drug; CM: Congenital Malformations; LMP2: Last Menstrual Period Date Plus 2 weeks; SD- Standard Deviation
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) all available data prior to 12th week of gestation in Norway
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Norway during the study period

Cluster A[1]: constant moderate exposure, Cluster B[1]: constant low exposure
Cluster A[2]: constant low exposure, Cluster B[2]: moderate to low exposure

Table 114 Paternal demographic characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=2027)

	Paternal exposure group									
CM	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=644**		**N=1383**		**N=1188**		**N=195**		**N=2027**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Father's age [a]										
≤20 years	9	1.40	12	0.87	9	0.76	3	1.54	21	1.04
21-25	70	10.87	116	8.39	97	8.16	19	9.74	186	9.18
26-30	179	27.80	348	25.16	293	24.66	55	28.21	527	26.00
31-35	220	34.16	443	32.03	376	31.65	67	34.36	663	32.71
36-40	119	18.48	294	21.26	263	22.14	31	15.90	413	20.37
>40	47	7.30	170	12.29	150	12.63	20	10.26	217	10.71
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mean (SD)	32.11 (5.81)		33.31 (6.32)		33.46 (6.37)		32.40 (5.98)		32.93 (6.19)	
Median (25th - 75th percentile)	32(28.00, 36.00)		33(29.00, 37.00)		33(29.00, 37.00)		32(28.00, 36.00)		32(29.00, 37.00)	
Min, max	17.00, 52.00		17.00, 63.00		17.00, 63.00		20.00, 51.00		17.00, 63.00	
Year of offspring conception [b]										
2005	42	6.52	44	3.18	40	3.37	4	2.05	86	4.24
2006	46	7.14	63	4.56	60	5.05	3	1.54	109	5.38
2007	63	9.78	79	5.71	70	5.89	9	4.62	142	7.01
2008	56	8.70	109	7.88	96	8.08	13	6.67	165	8.14
2009	45	6.99	91	6.58	82	6.90	9	4.62	136	6.71
2010	46	7.14	118	8.53	109	9.18	9	4.62	164	8.09
2011	43	6.68	89	6.44	78	6.57	11	5.64	132	6.51
2012	51	7.92	110	7.95	95	8.00	15	7.69	161	7.94
2013	42	6.52	104	7.52	83	6.99	21	10.77	146	7.20
2014	47	7.30	114	8.24	96	8.08	18	9.23	161	7.94
2015	49	7.61	116	8.39	93	7.83	23	11.79	165	8.14
2016	40	6.21	111	8.03	96	8.08	15	7.69	151	7.45
2017	34	5.28	101	7.30	81	6.82	20	10.26	135	6.66
2018	32	4.97	109	7.88	89	7.49	20	10.26	141	6.96
2019	8	1.24	25	1.81	20	1.68	5	2.56	33	1.63

CM: Congenital Malformations

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

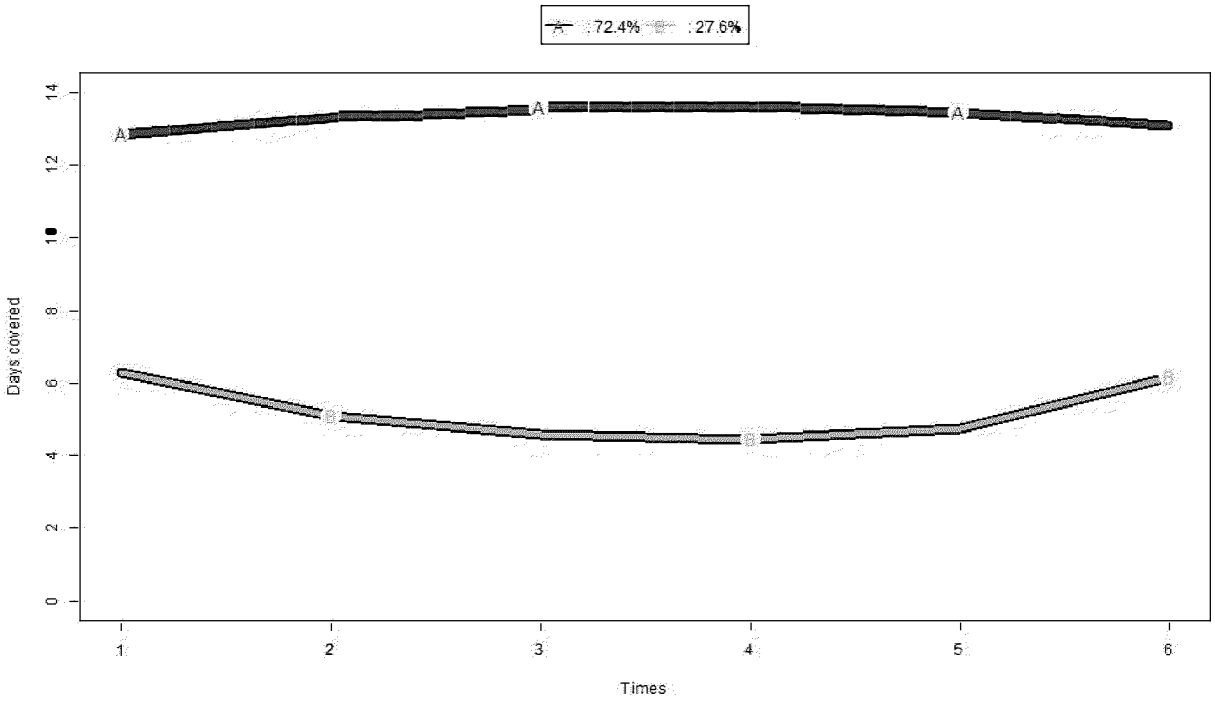
a) at 12th week of gestation in Norway
b) at mother's LMP2

Table 115 Paternal clinical characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=2027)

	Paternal exposure group									
CM **Number of offspring**	**Valproate** **N=644**		**Lamotrigine/levetiracetam** **N=1383**		**Lamotrigine** **N=1188**		**Levetiracetam** **N=195**		**Total (valproate + lamotrigine/levetiracetam)** **N=2027**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Medication use										
AED indication										
Epilepsy	251	38.98	465	33.62	309	26.01	156	80.00	716	35.32
Bipolar affective disorder and mania	66	10.25	303	21.91	303	25.51	0	0.00	369	18.20
Other/unknown	327	50.78	615	44.47	576	48.48	39	20.00	942	46.47
K-means cluster [a]										
Cluster A	439	68.17	1029	74.40	864	72.73	165	84.62	1468	72.42
Cluster B	205	31.83	354	25.60	324	27.27	30	15.38	559	27.58
Paternal exposure to teratogenic[a] activity/foetal toxicity [a]	200	31.06	577	41.72	526	44.28	51	26.15	777	38.33

AED: antiepileptic drugs; CM: Congenital Malformations
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) 3 months lookback from LMP2

Cluster A: constant high exposure; Cluster B: constant low exposure



Legend: Times refers to the 14-days interval during which exposure is assessed (in this case, 6 14 days interval [i.e. 3 months]); Days covered refers to days covered in each 14-day interval; Defined Daily Dose (DDD) trajectories: Cluster A: constant high exposure; Cluster B: constant low exposure. The percentage shows the proportion of fathers exposed to valproate and lamotrigine/levetiracetam in each cluster.

Figure 25 Mean defined daily dose (DDD) trajectories for fathers exposed to Antiepileptic Drugs (AEDs) in the 3 months lookback prior to Last Menstrual Period Date Plus 2 weeks LMP2 in Norway

10.5.2.2 Cumulative incidence proportion

Considering the overall study follow-up, the incidence proportion of CM (major and minor as composite) among offspring paternally exposed to valproate (n=107, 16.6%, 95% CI: 13.7, 19.5) appeared to be higher than those paternally exposed to lamotrigine/levetiracetam (n=209, 15.1, 95% CI: 13.2, 17.0). The CIs were slightly overlapping, which does not support differences between exposure groups (Table 116).

Table 116 Cumulative incidence proportion (risk) of CM by paternal exposure group; Secondary outcome cohort in Norway (N=2027)

CM		Paternal exposure group				
		Valproate	**Lamotrigine /levetiracetam (composite)**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	644	1383	1188	195	2027
0-1 years	n	61	126	107	19	187
	n/N*100	9.47(7.21, 11.73)	9.11(7.59, 10.63)	9.01(7.38, 10.63)	9.74(5.58, 13.91)	9.23(7.97, 10.49)
	N	572	1206	1039	167	1778
1-2 years	n	10	26	23	3	36
	n/N*100	1.75(0.67,2.82)	2.16(1.34,2.98)	2.21(1.32,3.11)	1.80(-0.22,3.81)	2.02(1.37,2.68)
	N	530	1089	945	144	1619
2-3 years	n	8	9	8	1	17
	n/N*100	1.51(0.47,2.55)	0.83(0.29,1.36)	0.85(0.26,1.43)	0.69(-0.66,2.05)	1.05(0.55,1.55)
	N	489	992	865	127	1481
3-4 years	n	4	15	13	2	19
	n/N*100	0.82(0.02,1.62)	1.51(0.75,2.27)	1.50(0.69,2.31)	1.57(-0.59,3.74)	1.28(0.71,1.86)
	N	448	878	766	112	1326
4-5 years	n	2	8	7	1	10
	n/N*100	0.45(-0.17,1.06)	0.91(0.28,1.54)	0.91(0.24,1.59)	0.89(-0.85,2.64)	0.75(0.29,1.22)
	N	405	779	686	93	1184
5-6 years	n	5	5	5	0	10
	n/N*100	1.23(0.16,2.31)	0.64(0.08,1.20)	0.73(0.09,1.37)	0.00(0.00,0.00)	0.84(0.32,1.37)
	N	364	668	590	78	1032
6-7 years	n	3	5	4	1	8
	n/N*100	0.82(-0.10,1.75)	0.75(0.09,1.40)	0.68(0.02,1.34)	1.28(-1.21,3.78)	0.78(0.24,1.31)
	N	322	571	511	60	893
7-8 years	n	7	5	3	2	12
	n/N*100	2.17(0.58,3.77)	0.88(0.11,1.64)	0.59(-0.08,1.25)	3.33(-1.21,7.88)	1.34(0.59,2.10)
	N	267	480	435	45	747
8-9 years	n	2	5	5	0	7
	n/N*100	0.75(-0.29,1.78)	1.04(0.13,1.95)	1.15(0.15,2.15)	0.00(0.00,0.00)	0.94(0.25,1.63)
	N	233	396	361	35	629
9-10 years	n	2	2	2	0	4
	n/N*100	0.86(-0.33,2.04)	0.51(-0.19,1.20)	0.55(-0.21,1.32)	0.00(0.00,0.00)	0.64(0.01,1.26)
	N	199	305	275	30	504

		Paternal exposure group				
CM		**Valproate**	**Lamotrigine /levetiracetam (composite)**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
10-11 years	n	1	1	1	0	2
	n/N*100	0.50(-0.48,1.48)	0.33(-0.31,0.97)	0.36(-0.35,1.08)	0.00(0.00,0.00)	0.40(-0.15,0.95)
	N	154	223	201	22	377
11-12+[a] years	n	2	2	2	0	4
	n/N*100	1.30(-0.49,3.09)	0.90(-0.34,2.13)	1.00(-0.38,2.37)	0.00(0.00,0.00)	1.06(0.03,2.10)
	N	644	1383	1188	195	2027
Overall (0-12+ years)	n	107	209	180	29	316
	n/N*100	16.61(13.74, 19.49)	15.11(13.22, 17.00)	15.15(13.11, 17.19)	14.87(9.88, 19.87)	15.59(14.01, 17.17)

CM: Congenital Malformations

Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with 95% confidence interval (CI) are presented.

a) For countries where the index date was the 12th week of pregnancy, follow-up time in years were longer than age in years, therefore some offspring were >12 years of follow-up by the time they were censored upon 12th birthday. For this reason, the table shows '12+ years'.

10.5.2.3 Association between potential offspring risk factors/confounders for CM and paternal exposure group

Association between potential covariates (risk factors and counfounders) for CM and paternal exposure group was assessed in the Secondary outcome cohort for comparative analyses. Results of the crude associations are shown in Table 117 to CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; SD: Standard Deviation

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed

Table 119.

For the offspring, none of the characteristics considered was associated with paternal exposure (Table 117).

None of maternal characteristic previously identified as a risk factor or confounder (see Table 5) were significantly associated with paternal exposure to valproate or lamotrigine/levetiracetam (Table 118).

The only paternal characteristic identified as a confounder/risk factor (Table 5) that was statistically significantly associated with paternal exposure was year of conception, earlier years of conception more frequent in the valproate group and more recent years in the lamotrigine/levetiracetam exposure group (p=0.0046) (CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; SD: Standard Deviation

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed

Table 119).

Table 117 Association between potential offspring risk factors/confounders for CM by paternal exposure group; Secondary outcome cohort in Norway (N=705)

	Paternal exposure group										Comparison
CM	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**		**Valproatevs Lamotrigine /levetiracetam**
Number of offspring	**N=262**		**N=443**		**N=363**		**N=80**		**N=705**		**N=705**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Offspring risk factors/confounders[a]											
Congenital CMV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital Herpes Simplex	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital rubella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital toxoplasmosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital varicella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Foetal alcohol syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-

CM: Congenital Malformations; CMV: Cytomegalovirus

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) between 12th week of gestation in Norway and exit date

* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 118 Association between potential maternal risk factors/confounders for CM by paternal exposure group; Secondary outcome cohort in Norway (N=705)

	Paternal exposure group										Comparison
CM	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Vaproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=262		N=443		N=363		N=80		N=705		N=705
	N	%	N	%	N	%	N	%	N	%	
Maternal risk factors/confounders											
Mother´s age [a](categorical)											
<=20 years	6	2.29	16	3.61	13	3.58	3	3.75	22	3.12	-
21-25	41	15.65	73	16.48	59	16.25	14	17.50	114	16.17	-
26-30	105	40.08	157	35.44	122	33.61	35	43.75	262	37.16	-
31-35	82	31.30	132	29.80	113	31.13	19	23.75	214	30.35	-
36-40	27	10.31	56	12.64	50	13.77	6	7.50	83	11.77	-
>40	1	0.38	9	2.03	6	1.65	3	3.75	10	1.42	-
Test statistics	-	-	-	-	-	-	-	-	-	-	5.99 (0.3073)
Mother´s age [a](continuous)											
Mean (SD)	29.60 (4.60)		29.81 (5.16)		29.92 (5.14)		29.33 (5.26)		29.73 (4.95)		91441.50 (0.6889)*
Median (25th - 75th percentile)	30 (27.00, 33.00)		30 (26.00, 33.00)		30 (27.00, 34.00)		29 (26.00, 32.00)		30 (27.00, 33.00)		-
Min, max	16.00,42.00		17.00,44.00		17.00,43.00		17.00,44.00		16.00,44.00		-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Diabetes [b]	2	0.76	3	0.68	3	0.83	0	0.00	5	0.71	1.00 (1.0000)*

CM	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Vaproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=262		N=443		N=363		N=80		N=705		N=705
	N	%	N	%	N	%	N	%	N	%	
Obesity [c]	2	0.76	2	0.45	2	0.55	0	0.00	4	0.57	0.63 (0.6305)*
Alcohol abuse prior to LMP2 [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Alcohol abuse during pregnancy [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [c]	0	0.00	1	0.23	1	0.28	0	0.00	1	0.14	1.00 (1.0000)*
Substance abuse during pregnancy [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Smoking prior to LMP2 [c]											
No	163	62.21	308	69.53	250	68.87	58	72.50	471	66.81	-
Yes	28	10.69	45	10.16	36	9.92	9	11.25	73	10.35	-
Missing	71	27.10	90	20.32	77	21.21	13	16.25	161	22.84	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	0.39 (0.5324)
Smoking during pregnancy [d]											
No	207	79.01	365	82.39	294	80.99	71	88.75	572	81.13	-
Yes	21	8.02	22	4.97	21	5.79	1	1.25	43	6.10	-
Missing	34	12.98	56	12.64	48	13.22	8	10.00	90	12.77	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	2.74 (0.0977)
CMV [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Folate deficiency [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Gestational diabetes [d]	3	1.15	3	0.68	3	0.83	0	0.00	6	0.85	0.67 (0.6757)*
Herpes simplex virus [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Rubella [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Toxoplasmosis [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-

CM Number of pregnancies	Paternal exposure group Valproate N=262		Lamotrigine/ levetiracetam N=443		Lamotrigine N=363		Levetiracetam N=80		Total (valproate + lamotrigine/ levetiracetam) N=705		Comparison Vaproate vs Lamotrigine /levetiracetam N=705
	N	%	N	%	N	%	N	%	N	%	
Varicella [d]	0	0.00	1	0.23	1	0.28	0	0.00	1	0.14	1.00 (1.0000)*

CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; SD: Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed

Table 119 Association between potential paternal risk factors/confounders for CM by paternal exposure group; Secondary outcome cohort in Norway (N=705)

CM Number of offspring	Paternal exposure group Valproate N=262		Lamotrigine/levetiracetam N=443		Lamotrigine N=363		Levetiracetam N=80		Total (valproate + lamotrigine/levetiracetam) N=705		Comparison Valproatevs Lamotrigine /levetiracetam N=705
	N	%	N	%	N	%	N	%	N	%	
Paternal risk factors/confounders **Father´s age [a](categorical)**											
≤20 years	2	0.76	5	1.13	3	0.83	2	2.50	7	0.99	-
21-25	22	8.40	45	10.16	35	9.64	10	12.50	67	9.50	-
26-30	78	29.77	113	25.51	88	24.24	25	31.25	191	27.09	-
31-35	88	33.59	148	33.41	120	33.06	28	35.00	236	33.48	-

	Paternal exposure group										Comparison
CM **Number of offspring**	**Valproate** **N=262**		**Lamotrigine/levetiracetam** **N=443**		**Lamotrigine** **N=363**		**Levetiracetam** **N=80**		**Total (valproate + lamotrigine/levetiracetam)** **N=705**		**Valproatevs Lamotrigine /levetiracetam** **N=705**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
36-40	57	21.76	92	20.77	81	22.31	11	13.75	149	21.13	-
>40	15	5.73	40	9.03	36	9.92	4	5.00	55	7.80	-
Test statistics	-	-	-	-	-	-	-	-	-	-	4.24 (0.5148)
Father´s age [a] (continuous)											
Mean (SD)	32.34 (5.44)	-	32.61 (5.91)	-	32.91 (5.99)	-	31.24 (5.37)	-	32.51 (5.74)	-	90944.50 (0.5548)*
Median (25th - 75th percentile)	32(29.00, 36.00)	-	32(29.00, 36.00)	-	32(29.00, 37.00)	-	32(28.00, 35.00)	-	32(29.00, 36.00)	-	-
Min, max	19.00, 52.00	-	20.00, 53.00	-	20.00, 53.00	-	20.00, 44.00	-	19.00, 53.00	-	-
Year of offspring conception [b,c]											
2005-2009	103	39.31	122	27.54	107	29.48	15	18.75	225	31.91	-
2010-2014	98	37.40	190	42.89	154	42.42	36	45.00	288	40.85	-
2015-2019	61	23.28	131	29.57	102	28.10	29	36.25	192	27.23	-
Test statistics	-	-	-	-	-	-	-	-	-	-	10.75 (0.0046)

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) at 12th week of gestation in Norway
b) at mother's LMP2
c) calendar years were grouped in each country according to the length of the study period

	Paternal exposure group										Comparison
CM **Number of offspring**	**Valproate** **N=262**		**Lamotrigine/levetiracetam** **N=443**		**Lamotrigine** **N=363**		**Levetiracetam** **N=80**		**Total (valproate + lamotrigine/levetiracetam)** **N=705**		**Valproatevs Lamotrigine /levetiracetam** **N=705**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	

***** A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

10.5.2.4 Association between potential offspring risk factors/confounders and CM

Association between covariates (potential risk factors / confounders) and occurrence of CM was assessed in the Secondary outcome cohort for comparative analyses. Results of crude associations are shown in Table 120 to Table 122.

None of the offspring, maternal or paternal characteristics were found to be associated with CM event in Norway.

Table 120 Association between potential offspring risk factors/confounders and CM; Secondary outcome cohort in Norway (N=705)

CM	Overall		Event		Non-event		Event vs non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Offspring risk factors/confounders [a]								
Congenital CMV								
No	705	100.00	105	14.89	600	85.11	_	_
Yes	0	0.00	0	0.00	0	0.00	_	_
Congenital Herpes Simplex								
No	705	100.00	105	14.89	600	85.11	_	_
Yes	0	0.00	0	0.00	0	0.00	_	_
Congenital rubella								
No	705	100.00	105	14.89	600	85.11	_	_
Yes	0	0.00	0	0.00	0	0.00	_	_
Congenital toxoplasmosis								
No	705	100.00	105	14.89	600	85.11	_	_
Yes	0	0.00	0	0.00	0	0.00	_	_
Congenital varicella								
No	705	100.00	105	14.89	600	85.11	_	_
Yes	0	0.00	0	0.00	0	0.00	_	_
Foetal alcohol syndrome								
No	705	100.00	105	14.89	600	85.11	_	_
Yes	0	0.00	0	0.00	0	0.00	_	_

CM: Congenital Malformations; CMV: Cytomegalovirus; OR: Odds ratio; CI: Confidence Interval
Legend: Percentages are calculated over the total number of offspring. The overall column represents the number and percentage of offspring with each characteristic (percentage is calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome is tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test are reported. a) between 12th week of gestation in Norway and exit date

Table 121 Association between potential maternal risk factors/confounders and CM; Secondary outcome cohort in Norway

CM	Overall		Event		Non-event		Event vs Non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, (p-value)
Maternal risk factors/confounders								
Mother's age [a] (categorical)								
≤20 years	22	3.12	5	22.73	17	77.27	1.73(0.60, 4.98)	-
21-25	114	16.17	17	14.91	97	85.09	1.03(0.56, 1.92)	-
26-30	262	37.16	38	14.50	224	85.50	Reference	-
31-35	214	30.35	30	14.02	184	85.98	0.96(0.57, 1.61)	-
36-40	83	11.77	14	16.87	69	83.13	1.20(0.61, 2.34)	-
>40	10	1.42	1	10.00	9	90.00	0.65(0.08, 5.32)	-
Wald test	0	0.00	0	0.00	0	0.00	-	1.64,0.8964
Diabetes [b]								
No	700	99.29	103	14.71	597	85.29	Reference	-
Yes	5	0.71	2	40.00	3	60.00	3.86(0.64, 23.41)	2.16,0.1414
Obesity [c]								
No	701	99.43	104	14.84	597	85.16	Reference	-
Yes	4	0.57	1	25.00	3	75.00	1.91(0.20, 18.57)	0.31,0.5757
Alcohol abuse prior to LMP2 [c]								
No	705	100.00	105	14.89	600	85.11	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse during pregnancy [d]								
No	705	100.00	105	14.89	600	85.11	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Substance abuse prior to LMP2 [c]								
No	704	99.86	105	14.91	599	85.09	Reference	-
Yes	1	0.14	0	0.00	1	100.00	0.00(0.00,I)	0.00,0.9865
Substance abuse during pregnancy [d]								
No	705	100.00	105	14.89	600	85.11	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Smoking prior to LMP2 [c]								
No	471	66.81	63	13.38	408	86.62	Reference	-
Yes	73	10.35	12	16.44	61	83.56	1.27(0.65, 2.50)	-
Missing	161	22.84	30	18.63	131	81.37	-	-

CM	Overall		Event		Non-event		Event vs Non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, (p-value)
Wald test without 'Missing' category	-	-	-	-	-	-	-	0.50,0.4808
Smoking during pregnancy [d]								
No	572	81.13	80	13.99	492	86.01	Reference	-
Yes	43	6.10	9	20.93	34	79.07	1.63(0.75, 3.52)	-
Missing	90	12.77	16	17.78	74	82.22	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	1.53,0.2159
CMV [d]								
No	705	100.00	105	14.89	600	85.11	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Folate deficiency [d]								
No	705	100.00	105	14.89	600	85.11	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Gestational diabetes [d]								
No	699	99.15	104	14.88	595	85.12	Reference	-
Yes	6	0.85	1	16.67	5	83.33	1.14(0.13, 9.89)	0.01,0.9026
Herpes simplex virus [d]								
No	705	100.00	105	14.89	600	85.11	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Rubella [d]								
No	705	100.00	105	14.89	600	85.11	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Toxoplasmosis [d]								
No	705	100.00	105	14.89	600	85.11	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Varicella [d]								
No	704	99.86	105	14.91	599	85.09	Reference	-
Yes	1	0.14	0	0.00	1	100.00	0.00(0.00,I)	0.00,0.9865

CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; OR: Odds ratio; CI: Confidence Interval

Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.

a) at 12th week of gestation in Norway
b) all available data prior to index date
c) 12 months lookback from LMP2
d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)

Table 122 Association between potential paternal risk factors/confounders and CM; Secondary outcome cohort in Norway

CM	Overall		Event		Non-event		Event vs non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Paternal risk factors/ confounders for CM Father's age [a] (categorical)								
≤20 years	7	0.99	1	14.29	6	85.71	1.06 (0.12, 9.12)	-
21-25	67	9.50	10	14.93	57	85.07	1.12 (0.52, 2.41)	-
26-30	191	27.09	29	15.18	162	84.82	1.14 (0.66, 1.96)	-
31-35	236	33.48	32	13.56	204	86.44	Reference	-
36-40	149	21.13	22	14.77	127	85.23	1.10 (0.61, 1.98)	-
>40	55	7.80	11	20.00	44	80.00	1.59 (0.75, 3.40)	-
Wald test	-	-	-	-	-	-	-	1.46,0.9171
Year of offspring conception [b,c]								
2005-2009	225	31.91	39	17.33	186	82.67	Reference	-
2010-2014	288	40.85	41	14.24	247	85.76	0.79 (0.49, 1.28)	-
2015-2019	192	27.23	25	13.02	167	86.98	0.71 (0.41, 1.23)	-
Wald test	-	-	-	-	-	-	-	1.68,0.4320

CM: Congenital Malformations; OR: Odds ratio; CI: Confidence Interval
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.

a) at index (at 12th week of gestation in Norway)
b) at mother's LMP2
c) calendar years were grouped in each country according to the length of the study period

10.5.2.5 Variable estimates from propensity score

Variables pre-identified as risk factors/confounders in this study and associated with the study outcome in the univariate analyses were candidates for variable estimates in the propensity score.

In the PS model estimated from logistic regression (Table 123), no maternal risk factors were associated with the paternal exposure.

Variable importance metric from random forest propensity score model and variable estimates from logistic regression informed by random forest propensity score model are not presented due to the fact that none of the offspring included in these models had any of the risk factors (i.e. offspring included had no risk factors and as a result the random forest propensity score and/or the logistic regression informed by random forest propensity score models could not be created and neither variable importance metric).The balance of the PS model estimated from logistic regression is depicted in Figure 26 and Table

241, which was used to apply inverse probability of treatment weights in the effect estimation analysis (presented in Section 10.5.1.7).

Table 123 Variable estimates from logistic regression propensity score model; Secondary outcome cohort in Norway

Exposure group (valproate vs lamotrigine/levetiracetam)	**Estimate**		
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
Maternal risk factors/confounders			
Substance abuse prior to LMP2 [b]	0.00	0.00 – I	0.9869
Smoking during pregnancy [c]			
No	Reference	-	-
Yes	1.60	0.84 - 3.06	0.1501
Varicella [f]	0.00	0.00 – I	0.9864

CM: Congenital Malformations; OR: Odds ratio; CI: Confidence Interval
Legend: Odds ratios (OR), 95% confidence intervals (CI); LMP2: Last Menstrual Period Date Plus 2 weeks; and p-values are represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.
a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.

b) 12 months lookback from LMP2

c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)

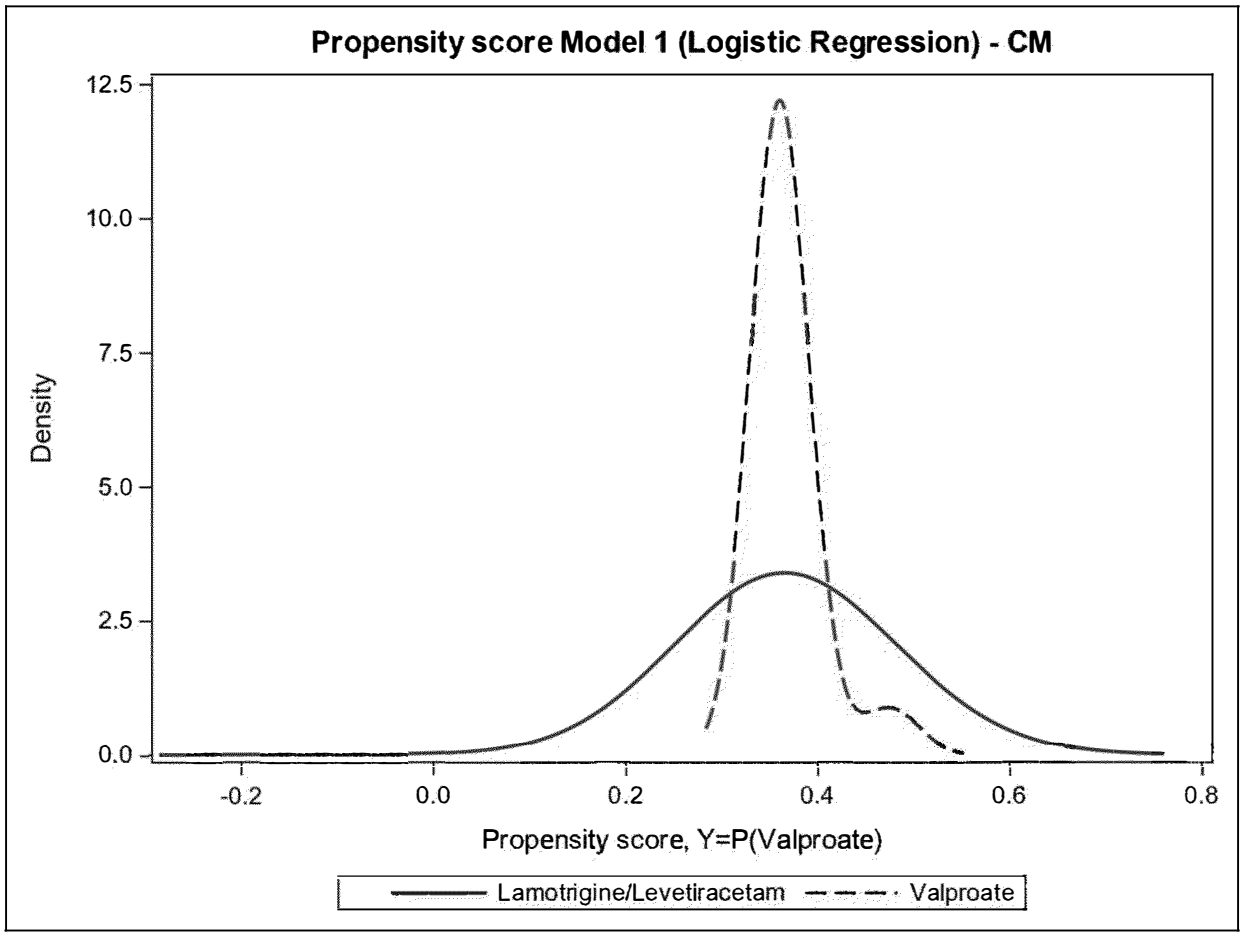


Figure 26 Balance of PS Model 1- Logistic Regression; Secondary outcome cohort in Norway.

CM: Congenital Malformations

10.5.2.6 Effect estimation for Congenital Malformation

The effect estimation for CM was assessed by using crude logistic regression model as presented in Table 124. In this model were included 705 subjects, with 262 offspring in the valproate group and 443 in the lamotrigine/levetiracetam group, and no influential subjects were identified. The number of offspring with CM in the valproate and lamotrigine/levetiracetam group was 41 (15.6%) and 64 (14.4%), respectively. The OR of CM was 1.10 (95% CI: 0.72, 1.68) between offspring of fathers exposed to valproate when compared to offspring of fathers exposed to lamotrigine/levetiracetam.

The effect estimation for CM using PS-weighted logistic regression model was assessed in a total of 605 offspring, with 222 (36.7%) offspring in the valproate group and 383 (63.3%) in the lamotrigine/levetiracetam group. The number of offspring with a CM in the valproate and lamotrigine/levetiracetam group was 32 (14.4%) and 54 (14.1%), respectively. The OR of CM observed between the 2 groups was 1.00 (95% CI: 0.62, 1.61) (Table 125).

Table 126 presents the effect estimation for CM using PS-weighted logistic regression model adjusted for the K-means exposure cluster (i.e. Cluster A: constant high exposure; Cluster B: constant low exposure, for further details on the K-means cluster in the main analyses please check Figure 25 and Table 115).The estimate was assessed in a total of 605 offspring, with 443 in cluster A (159 in valproate group and 284 in lamotrigine/levetiracetam group) and 162 (63 in valproate group and 99 in lamotrigine/levetiracetam group) in cluster B. The number of offspring with a CM in cluster A and cluster B was 65 (26 in the valproate group and 39 in the lamotrigine/levetiracetam group) and 21 (6 in the valproate group and 15 in the lamotrigine/levetiracetam group), respectively. The OR for CM was 0.55 (95% CI: 0.20, 1.51) for cluster A and 1.21 (95% CI: 0.70, 2.09) for cluster B, when compared offspring of fathers exposed to valproate to those exposed to lamotrigine/levetiracetam. Likewise, no interaction between exposure and paternal K-means cluster was observed.

Table 124 Effect estimation for congenital malformations (CM) using crude logistic model; Secondary outcome cohort in Norway.

Variable	Total N	Number of events	Model estimates		
	N	N	OR	95% CI	P-value
Valproate	262	41			
Lamotrigine/levetiracetam	443	64			
Paternal exposure: valproate vs lamotrigine/levetiracetam	705		1.10	(0.72, 1.68)	0.6629

OR: Odds ratio; CI: Confidence Interval

Variable	Total N	Number of events	Model estimates		
	N	N	OR	95% CI	P-value
Valproate	262	41			
Lamotrigine/levetiracetam	443	64			
Paternal exposure: valproate vs lamotrigine/levetiracetam	705		1.10	(0.72, 1.68)	0.6629

OR: Odds ratio; CI: Confidence Interval

Table 125 Effect estimation for congenital malformations (CM) using Propensity Score weighted logistic model; Secondary outcome cohort in Norway.

Variable	Total N	Number of events	Model estimates[1]		
	N	N	OR	95% CI	P-value
Valproate	222	32			
Lamotrigine/levetiracetam	383	54			
Paternal exposure: valproate vs lamotrigine/levetiracetam	605		1.00	(0.62, 1.61)	0.9974

OR: Odds ratio; CI: Confidence Interval

[1] **The logistic regression PS model includes all variables from Table 123, following described: Maternal risk factors/confounders:** "Substance abuse prior to LMP2", "Smoking during pregnancy", "Varicella during pregnancy"

Table 126 Effect estimation for congenital malformations (CM) using Propensity Score weighted logistic model on offspring with concordant K-means exposure cluster; Secondary outcome cohort in Norway.

Variable	Total N	Number of events	Model estimates[1]		
			OR	95% CI	P-value
Valproate - cluster A	159	26			
Lamotrigine/levetiracetam - cluster A	284	39			
Valproate - cluster B	63	6			
Lamotrigine/levetiracetam - cluster B	99	15			
Paternal exposure: valproate vs lamotrigine/levetiracetam	605		-	-	0.4924
K-means exposure cluster:					
K-means exposure cluster B	-		-	-	0.7168
Paternal exposure * cluster:					
Valproate * cluster B	-		-	-	0.1803
Effect of valproate across K-means cluster:					
Valproate vs lamotrigine/levetiracetam in cluster A	-		0.55	(0.20, 1.51)	-
Valproate vs lamotrigine/levetiracetam in cluster B	-		1.21	(0.70, 2.09)	-

OR: Odds ratio; CI: Confidence Interval

Cluster A: constant high exposure; Cluster B: constant low exposure

[1] **The logistic regression PS model includes all variables from Table 123, following described: Maternal risk factors/confounders:** "Substance abuse prior to LMP2", "Smoking during pregnancy", "Varicella during pregnancy"

10.5.2.7 Exploratory Analyses - CM cohort

10.5.2.7.1 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Exploratory analysis 5 for CM)

Results from exploratory analysis 5 are presented in Table 263 to Table 271 in section 15.3.7. The analysis was performed in the Secondary outcome cohort for explorative objective 5, in order to answer Exploratory Objective 5, which aimed to describe the risk factors and frequency of CM in offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine/levetiracetam) and lamotrigine/levetiracetam (in combination with other AEDs excluding valproate) at the time of the conception.

For the exploratory analyses 5, the inclusion criterion was all offspring from the Secondary outcome cohort (N=4676). After additional exclusions, a total of 51 offspring were included in this analysis, with 6 in valproate and 45 in lamotrigine/levetiracetam group (Figure 45).

In exploratory analysis 5, the sample size was significantly lower than the main analysis, hence direct comparison with the main analysis may not be ideal. Overall, all offspring were born at term in the valproate polytherapy group (100%) while 91.1% born at term in the lamotrigine/levetiracetam polytherapy (Table 263). Majority of offspring in the main analysis was also born at term (Table 110).

Regarding clinical characteristics, none of the offspring had comorbidities which might be attributed to the small sample size (Table 264).

Median age of mothers at childbirth was higher in the valproate polytherapy than in the lamotrigine/levetiracetam polytherapy (31.0, IQR 26.0, 32.0 vs. 28.0, IQR 26, 33.0, respectively) (Table 265). None of the mothers in the valproate polytherapy had comorbidities, and in the lamotrigine/levetiracetam polytherapy, one mother had gestational diabetes in exploratory analysis 5. Smoking prior to LMP2 was 0.0% and 2.2% in the valproate and lamotrigine/levetiracetam polytherapy, respectively. Smoking during pregnancy was 16.7% in the valproate polytherapy and 6.7% in the lamotrigine/levetiracetam polytherapy (Table 266). Due to small sample size (N=51), comparing these findings with the main analysis may not be informative.

Median age of fathers was lower in the valproate polytherapy than in the lamotrigine/levetiracetam polytherapy (32.0, IQR 27.0, 34.0 vs. 32, IQR 28, 35.0, respectively) in exploratory analysis 5 (Table 267). Paternal comorbidities were not reported (Table 268). Epilepsy was the most common indication for valproate (66.7%) polytherapy and lamotrigine/levetiracetam polytherapy (68.9%).

The distribution of potential risk factors and confounders for CM by paternal exposure to valproate polytherapy and lamotrigine/levetiracetam polytherapy were examined for the Secondary outcome cohort for explorative objective 5. Results of univariable analyses are presented in Table 269-Table 271.

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 for an overview.

As observed in the main analyses (Table 117, Table 118 and CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; SD: Standard Deviation

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed

Table 119), none of the offspring, maternal and paternal characteristics were associated with paternal exposure (Table 269, Table 270, and Table 271).

10.5.2.7.2 Paternal exposure to valproate or lamotrigine/levetiracetam in discordant siblings (Exploratory analysis 6)

Results from exploratory analysis 6 are presented in Table 272 to Table 277 in section 15.3.8. The analysis was performed in the Secondary outcome cohort for explorative objective 6. This objective aimed to describe the risk factors and frequency of CM, in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception.

For the exploratory analyses 6, the inclusion criterion was all offspring from the Secondary outcome cohort for comparative analysis (N=705). After additional exclusions, a total of 4 offspring were included in this analysis, with zero in valproate and 4 in lamotrigine/levetiracetam group (Figure 36).

In exploratory analysis 6, the sample size is significantly lower than the main analysis and there was no single offspring in the valproate group, hence direct comparison with the main analysis may not be ideal. But overall, 75% (3 out of 4 offspring) born at term and had birth weight ≥2500 gram in the lamotrigine/levetiracetam group (Table 272). All study participants were female. No comorbidities were reported in this exploratory analysis, and one offspring had minor CM (Table 273).

The median age of mothers at childbirth was 29 (26.5, 31.5) years in the lamotrigine/levetiracetam group (Table 274). No maternal comorbidies reported and 25% (one out of 4 mothers) smoked in either prior to LMP2 or during pregnancy (Table 275).

The median age of fathers at childbirth was 29.5 (29.0, 30.5) years in the lamotrigine/levetiracetam group (Table 276). Three fathers had AED indication for epilepsy while one father had other/unknown AED indication in the lamotrigine/levetiracetam group (Table 277).

Results for exploratory analysis 8 are not reported in this final report. For further details, please see section 9.9.2.4.3.

10.5.2.8 Sensitivity analyses for CM

Multiple sensitivity analyses were performed to examine the robustness of the main analysis finding. Summary tables of the main results for each of sensitivity analysis were prepared and are presented in this section. All tables produced for each of the sensitivity analysis are presented in a separate document.

Sensitivity analysis 4 was performed for the CM handling missing CM diagnosis comparing valproate with lamotrigine/levetiracetam. Overall, the findings in the crude logistic regression model (OR: 1.08, 95% CI: 0.71, 1.65) and PS-weighted logistic model on offspring with concordant K-means exposure cluster (cluster A (constant high exposure to AEDs): OR 0.55, 95% CI: 0.20, 1.51; and cluster B (constant low exposure to AEDs): OR 1.17, 95% CI: 0.68, 2.02) were consistent with the main analyses. No increase in the risk of CM observed in the PS-weighted adjusted logistic regression model (OR: 0.98, 95% CI: 0.61, 1.57).

Sensitivity analysis 5 was performed for the CM outcome comparing valproate with lamotrigine, and valproate with levetiracetam separately as presented in Table 127. The crude logistic regression model estimation for CM in the sensitivity analysis 5, for both simple pairwise comparison between valproate and lamotrigine, and valproate and levetiracetam, was consistent with the estimate observed in the main analysis. See Table 127 for further detail.

In the PS adjusted logistic regression model, the simple pairwise comparisons between valproate and lamotrigine showed a non significant lower risk of CM in the offspring (OR of valproate and lamotrigine 0.91, 95% CI: 0.56, 1.48), but a non significant higher risk of CM when comparing offspring exposed to valproate and levetiracetam (OR of valproate and levetiracetam 1.62, 95% CI: 0.64, 4.09). The number of offspring with CM in the simple pairwise comparison between valproate and lamotrigine was 32 and 48, respectively. For simple pairwise comparison between valproate and levetiracetam the number of offspring with CM was 34 and 6, respectively (Data not shown). See Table 127 for further details.

In sensitivity analysis 6, there were zero patients with CM after removing outliers. It was not possible to perform logistic regression with 0 CM events. OR, 95% CI and p-values were not presented.

Sensitivity analysis 9 focused on live births for CM outcome. Findings from this analysis produced similar estimates as with the main analysis (live-birth or non-live-birth) in the crude logistic regression model, PS adjusted logistic regression model and PS-weighted logistic model on offspring with concordant K-means exposure cluster. See Table 127 for further details.

In sensitivity analysis 10, the mean paternal cumulative exposure to valproate was 65.1 (±22.6) days, while in the lamotrigine/levetiracetam group mean paternal cumulative exposure 68.3 (±23.7) days reported (see Table 128). Comparing paternal cumulative exposure to valproate with lamotrigine/levetiracetam showed no higher risk of CM to the offspring (OR 0.95, 95% CI: 0.14, 6.49). The number of events reported in the valproate group and lamotrigine/levetiracetam group were 20 and 35, respectively (data not shown).

Among fathers exposed to valproate, all CM events were observed in offspring of fathers with high cumulative exposure to valproate (20 events). However, no CM event was reported for low cumulative exposure and medium exposure groups. Hence, the logistic regression covariate adjustment model did not converge, and the confidence intervals and p-values were not created. The OR were not possible to interpret (Table not shown).

Likewise, among fathers exposed to lamotrigine, all CM events were observed in offspring of fathers high cumulative exposure to lamotrigine (29 events). However, no CM event was reported for low cumulative exposure and medium exposure groups. Hence, the logistic covariate adjustment model did not converge, and the confidence intervals and p-values were not created. The OR were not possible to interpret (Table not shown).

Table 127. Summary of main analysis and sensitivity analyses for the Secondary outcome cohort in Norway

Analyses*	Population considered	OR (95% CI) estimates		OR (95% CI) estimates by cluster of exposure	
		Crude	Adjusted*	Cluster A	Cluster B
Main analysis N sample = 705	Please check Section 9.3	1.10 (0.72, 1.68)	1.00 (0.62, 1.61)	0.55 (0.20, 1.51)	1.21 (0.70, 2.09)
Sensitivity analysis 4 N sample = 705	Handling of missing CM diagnosis	1.08 (0.71, 1.65)	0.98 (0.61, 1.57)	0.55 (0.20, 1.51)	1.17 (0.68, 2.02)
Sensitivity analysis 5[A] N sample = 625	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	1.04 (0.67, 1.61)	0.91 (0.56, 1.48)		
Sensitivity analysis 5[B] N sample = 342	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	1.46 (0.68, 3.13)	1.62 (0.64, 4.09)		
Sensitivity analysis 9 N sample = 705	Narrow case definition for secondary outcome	1.10 (0.72, 1.67)	1.00 (0.62, 1.60)	0.55 (0.20, 1.51)	1.21 (0.70, 2.08)

OR: Odds ratio; CI: confidence intervals; **5[A]** analysis comparing valproate and lamotrigine; **5[B]** analysis comparing valproate and levetiracetam

***The logistic regression PS models used in sensitivity analysis include variables following described:**
Sensitivity analysis 4: Maternal risk factors/confounders: "Substance abuse prior to LMP2", "Smoking during pregnancy", "Varicella during pregnancy"
Sensitivity analysis 5[A]: Maternal risk factors/confounders: "Smoking during pregnancy", "Varicella during pregnancy"
Sensitive analysis 5[B]: Maternal risk factors/confounders: "Diabetes", "Obesity", "Smoking during pregnancy", "Gestational diabetes". In sensitivity analysis 5[B], HR were further adjusted for "Maternal smoking during pregnancy"
Sensitivity analysis 9: Maternal risk factors/confounders: "Substance abuse prior to LMP2", "Smoking during pregnancy", "Varicella during pregnancy"

Table 128. Paternal cumulative exposure to Antiepileptic drugs (AEDs) by paternal exposure group; Secondary outcome cohort in Norway

Paternal exposure group										
CM	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of offspring	**N=262**		**N=443**		**N=363**		**N=80**		**N=705**	
Cumulative exposure to AEDs										
Low	88	33.59	147	33.18	122	33.61	26	32.50	236	33.48
Medium	62	23.66	39	8.80	29	7.99	9	11.25	100	14.18
High	112	42.75	257	58.01	212	58.40	45	56.25	369	52.34

Paternal exposure group										
CM **Number of offspring**	**Valproate** **N=262**		**Lamotrigine/levetiracetam** **N=443**		**Lamotrigine** **N=363**		**Levetiracetam** **N=80**		**Total (valproate + lamotrigine/levetiracetam)** **N=705**	
Mean (SD)	65.06 (22.57)		68.34 (23.65)		68.18 (23.70)		69.05 (23.55)		67.12 (23.29)	
Median (25^{th} - 75^{th} percentile) Min, max	76(48.00, 84.00) 1.00, 84.00		84(55.00, 84.00) 2.00, 84.00		84(54.00, 84.00) 2.00, 84.00		84(59.00, 84.00) 2.00, 84.00		84(53.00, 84.00) 1.00, 84.00	
	88	33.59	147	33.18	122	33.61	26	32.50	236	33.48

AED: antiepileptic drugs; CM: Congenital Malformations; SD: Standard Deviation

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

Table 129. Effect estimation for Congenital Malformations using logistic covariate adjustment model; Secondary outcome cohort in Norway

CM	Model estimates		
Number of subjects included in analysis prior to exclusion influential subjects	705		
Number of subjects included in the model (after excluding influential subjects)	654 (92.77%)		
Variable	OR	95% CI	P-value
Effect of valproate at a specific cumulative exposure level:			
Valproate vs lamotrigine/levetiracetam	0.95	(0.14, 6.49)	0.9551
Paternal cumulative exposure to AEDs	1.03	(1.01-1.05)	0.0005
Paternal exposure * Paternal cumulative exposure to AEDs	0.98	(0.96-1.00)	0.0660

Legend: Odds ratios (OR), 95% confidence intervals (CI); CM: congenital malfortions and p-values are represented for risk factors and confounders included in the covariate adjustment model. All variables potentially included in the model are listed here, however some of the variables might not be included in the final set of variables.
* Influential subjects were identified using Cook's distance.

11. Discussion

Valproate-containing medicines are approved in the European Union to treat epilepsy and bipolar disorder (27). In October 2014, PRAC published an assessment report (EMEA/H/A-31/1387) with a review of all available information from non-clinical, clinical, and pharmacoepidemiological studies, published literature, spontaneous reports, and the opinions of the relevant experts on the safety and efficacy of valproate use (28). In this review, the teratogenic effect of valproate use during pregnancy, suggested that children born to women who received valproate during pregnancy had a significantly higher risk of congenital malformations (CM) involving various body system.

Besides, the PRAC reviewed the evidence from a number of prospective and retrospective observational studies on the effects of valproate on cognitive development in pregnancy, despite limited data available on long-term outcomes (28). The available data showed that valproate exposure during pregnancy may harm a child's mental and physical development (2). Whereas AED may have potential teratogenic effects, the precise mode of action of valproate causing NDD, including ASD, or CM, is still unclear. As suggested by Christensen and colleagues, potential mechanisms include neuronal death or plasticity, impairment of folic acid metabolism, histone deacetylase inhibition, interference with neurotransmitter function (2). Therefore, due to the observed increased risk of CM and of NDD in offspring after valproate exposure in utero, the use of valproate in women of childbearing potential (suffering of epilepsy and bipolar disorder) and in pregnant women suffering of epilepsy has been restricted to circumstances where there is no other effective alternative treatment available, and it has been contraindicated during pregnancy for bipolar disorder (27, 28). Despite the increased attention for the role of maternal exposure there have been few studies on the effects of paternal AED exposure on offspring (4,10,31,32). So far, only 4 studies have been published addressing the paternal exposure to AEDs on birth outcomes (4,10,31,32). Engeland et al. found a higher risk of birth defects of the urinary system in offspring paternally exposed to AEDs, though they could not differentiate among this class of medications (4). In a Danish nationwide cohort study, Yang et al. observed no higher risk of CM in the offspring paternally exposed to AEDs though these authors also did not differentiate among AED classes (31). Velby and colleagues found no evidence of negative effects of paternal exposure to AEDs on the NDD risk of the offspring, though the study did not differentiate between various AEDs (10). Only the study of Tomson and colleagues assessed the risk of major congenital malformation MCM as well as risk of different subtypes of NDDs (diagnoses of (i) autism spectrum disorder, (ii) attention deficit hyperactivity disorder and (iii) intellectual disability, separately) in the offspring from fathers exposed to valproate, on monotherapy, for epilepsy, during conception, compared with offspring from fathers with epilepsy unexposed to AEDs during conception (32). The authors found no association between paternal exposure to valproate, or other AEDs, at the time of conception, and MCM or NDDs in the offspring.

The potential impact of paternal use of valproate was discussed during the PRAC referral conducted in 2018, and in an effort to increase knowledge on the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders, including autism, in offspring, a retrospective observational study was recommended (33).

Therefore, a PASS was conducted, to assess the risk of NDD, including ASD, and CM in the offspring from fathers exposed to valproate in monotherapy at conception, compared to offspring from fathers

exposed to lamotrigine/levetiracetam in monotherapy. This final report presents the results of this PASS. Paternal exposure to valproate (monotherapy) was compared to paternal exposure to lamotrigine/levetiracetam (composite monotherapy) as they were considered the safer treatment (11–14). The primary outcome of interest was NDD including ASD and the secondary outcome was CM (minor and major). The multivariable adjusted associations were described independently of potential impact of measured clinical and demographic characteristics of the study population. This study was conducted in 3 countries, Sweden, Norway and Denmark, as these were the only available databases with father-offspring linkage.

11.1 Key Results

11.1.1 Primary outcome cohort - Neurodevelopmental disorders including autism spectrum disorder

Country-specific results pooled in a meta-analysis were computed to achieve a more precise summary estimate of the observed effect size. Pooled risk ratios and hazard ratios of NDD including ASD in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam were calculated across the 3 countries. However, only the PS-weighted models HR are reported in this section, as the estimate was less biased and more useful for inference from observational data.

The pooled hazard ratios were estimated and no higher risk was observed (HR 1.15, 95% CI: 0.90-1.48) in the crude model, but after pooling the PS-adjusted HRs, a significantly higher risk of NDD including ASD among offspring from fathers exposed to valproate in comparison to lamotrigine/levetiracetam group (HR 1.47, 95% CI: 1.10-1.96) was observed.

Main analysis – Effect estimation of the association between paternal exposure to valproate and NDD including ASD

When assessing the association of paternal exposure to valproate in each of the 3 study countries separately, no difference in the risk of experiencing NDD including ASD events was observed in offspring from the valproate group compared with the lamotrigine/levetiracetam group.

The crude Cox regression models showed a non-significant HR of 0.94 (95% CI: 0.60-1.46, N=1950) in Denmark, 1.16 (95% CI: 0.76-1.76, N=2355) in Sweden, and 1.40 (95% CI: 0.90-2.18, N=1670) in Norway.

These results showed that for all countries, in earlier years of the study showed a higher proportion of offspring was conceived in the valproate group, while in more recent years, a higher proportion of offspring was conceived in the lamotrigine/levetiracetam group. For example, in Denmark: year of offspring conception 1996-2001: valproate 26.1%, N=207 vs. lamotrigine/levetiracetam 5.0%, N=58, and year of offspring conception 2013-2018: valproate 15.6%, N=124 vs. lamotrigine/levetiracetam 39.2%, N=381. In Sweden: year of offspring conception 2006-2010: valproate 39.8%, N=370 vs. lamotrigine/levetiracetam 21.8%, N=311, and year of offspring conception 2016-2019: valproate 19.6%, N=182 vs. lamotrigine/levetiracetam 36.6%, N=521. In Norway: year of offspring conception 2005-2009:

valproate 38.9%, N=240 vs. lamotrigine/levetiracetam 27.8%, N=368, and year of offspring conception 2015-2019: valproate 25.6%, N=158 vs. lamotrigine/levetiracetam 34.1%, N=452.

Besides, in Sweden, 83% of offspring in the valproate group were identified as probable cases vs. 63.5% in the lamotrigine/levetiracetam group; in Norway, these figures were 83.3% and 79.6%, respectively. This may be attributed to a shorter follow-up period in the lamotrigine/levetiracetam group leading to the detection of fewer probable cases than in the valproate group. For Denmark, an opposite trend was observed, with 60% of offspring in the valproate group identified as probable cases vs. 70% in the lamotrigine/levetiracetam group. Also, compared to Sweden and Norway, in Denmark the maternal risk factor profile were worse in the lamotrigine/levetiracetam groups (e.g. more smokers, a higher percentage of IUGR, higher exposure to teratogens), which might also contribute to the divergent findings. Overall, this finding may indicate a decrease in valproate use in recent years, and suggests that the longer the follow-up, the higher the possibility of detecting NDD including ASD.

To minimise this bias as well as to account for other confounders, a PS-weighted Cox PH regression model was used to estimate the HR of NDD. This model was adjusted for differences in follow-up time, and the year of conception was considered in the PS model. Yet, the HR may change over time and by reporting a single average HR, the distribution of events during follow-up was not taken into consideration (34). Therefore, the different length of the follow-up may have significantly influenced these findings. Adjusted survival curves, or adjusted cumulative risk curves, would have been more informative than the average HR measure (34). Over the study period, the frequency of events was lower than 10% in the 3 study countries, thus making the adjusted Kaplan-Meier curve difficult to compute and interprete.

Besides, considering the observational nature of the study, the potential biases caused by confounding by indication were unavoidable. Indeed, different AEDs are prescribed for different types and severity of epilepsy (and bipolar disorders). However, measures of severity of the treated disorders were not available in the data sources precluding adjustment for this in the regression models.

In line with the findings observed in the crude models, no significant higher risk of NDD, including ASD, in offspring from fathers exposed to valproate vs. those from fathers exposed to lamotrigine/levetiracetam was observed in the PS-weighted Cox regression models, in each of the 3 study countries: HR of 1.34 (95% CI: 0.79, 2.25) in Denmark, 1.54 (95% CI: 0.95, 2.51) in Sweden, and of 1.52 (95% CI: 0.93, 2.49) in Norway. For Denmark, the PS-weighted Cox regression model was additionally adjusted for variables considered as risk factors and/or confounders that were still unbalanced after PS weighting (i.e. maternal affective disorder, and maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy). For maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy that remained unbalanced after weighting, the HR was 3.29 (95% CI: 1.38, 7.83). Despite the fact that when unbalanced covariates are included in PS-weighted models, double adjustment, as performed in the current study, reduces residual confounding (35). Given the magnitude of the effect observed for maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy, either stratification or exclusion would have provided both an evaluation and a control for this confounder. Finally, an analysis adjusted for clusters of exposure was performed to account for intensity and evolution of exposure over time. No higher risk of NDD including ASD was observed whatever the trajectories of exposure, but higher estimates were observed at higher doses and prolonged treatment trajectories in all study countries.

Stronger associations were observed in adjusted models compared with crude models for all 3 countries. This trend moving the point estimates away from the null, may reflect handling of confounding effects in the PS models. In particular, since the crude non-significant association no longer captures the partial effect of the omitted confounders (i.e. omitted variable bias), as suggested by higher rates of confounding factors in the levetiracetam/lamotrigine group than in the valproate group, after adjustment, it rather reflects the "less biased" effect of the association between the exposure and the outcome (36).

Additionally, to assess the impact of the PS-weighted model computed for each country, a Cox regression model adjusted for the set of identified confounders in each country was computed to estimate the HR of NDD, including ASD. Results from this sensitivity analysis (sensitivity analysis 6) showed similar adjusted HRs compared to those obtained from the PS-weighted models, in all 3 countries.

Several other sensitivity analyses were performed aiming to explore the robustness of the estimated risk of the study outcomes. For most of the sensitivity analyses, the results overall described similar results when compared to those observed in the main analysis.

An association between paternal valproate exposure and the occurrence of NDD, was also found in another sensitivity analysis (sensitivity analysis 11), in which a narrow composite NDD case definition was used. In this definition, major NDD diagnoses (excluding mental disorder, not otherwise specified, other specified behavioural and emotional disorders with onset usually occurring in childhood and adolescence disorders, tic disorders, stereotyped movement disorders, essential tremor, other specified forms of tremor, myoclonus, other chorea, other specified extrapyramidal and movement disorders, extrapyramidal and movement disorder, unspecified, Idiopathic nonfamilial dystonia, spasmodic torticollis, idiopathic orofacial dystonia, blepharospasm, other dystonia, dystonia, unspecified, extrapyramidal and movement disorders in diseases classified elsewhere), including ASD, were considered. A significant, moderate, association was observed between paternal exposure to valproate in the 3 months before conception and the occurrence of diagnoses of major NDD, including ASD in Sweden (PS-weighted HR: 1.70, 95% CI: 1.02, 2.81), a similar but non-significant point estimates were observed in Norway (PS-weighted HR: 1.65, 0.99, 2.76), and a non-significant result in Denmark (PS-weighted HR: 1.59, 0.89, 2.86). Results from the main analysis, considering all NDD, including ASD showed a gradient towards risk dilution (in Sweden, HR: 1.54 [95% CI: 0.95, 2.51]), possibly masking the association with ASD.
When assessing a wider exposure window (6 months) to investigate whether there was an effect of valproate beyond the spermatogenic cycle, the results, although not statistically significant, were similar to those observed in the main analysis as presented in section 10.3.1.10 for Denmark, section 10.4.1.9 for Sweden, and section 10.5.1.10 for Norway. However, in Denmark, offspring born to fathers who had constant low valproate exposure had a non-significantly lower risk of NDD, including ASD (when compared to those who had constant high valproate exposure).

We furthermore investigate the possibility of a mediator effect of preterm birth in the association between exposure to AEDs and NDD occurrence could be present. Thus, a sensitivity analysis excluding extremely low birth weight, very preterm and extremely preterm new-born was done to explore the potential impact introduced in the main analysis by inclusion of this sub-population of offspring, because conditioning on mediators may lead to a biased estimate. This sensitivity analysis produced very similar results compared to the main results. Since low birth weight, very preterm, and extremely preterm new-born were used as proxies for IUGR, the likelihood that bias was introduced as a consequence of the inclusion of this subpopulation in the Primary outcome comparative cohort in the 3 study countries cannot be ruled out. Nevertheless, considering that ultrasound biometry is essential for the diagnosis of IUGR

(37) and the difficulty of obtaining good quality data in real-world studies, low birth weight, very preterm, and extremely preterm are reasonable proxies, and have been used in several perinatal epidemiological studies (38--40).

For the main analysis the comparator group included irrespectively of exposure to either lamotrigine or levetiracetam. Thus, a sensitivity analysis was performed comparing valproate paternal exposure to separately lamotrigine (sensitivity analysis 5a) and levetiracetam (sensitivity analysis 5b) paternal exposure to evaluate differential effect of using one or the other comparator. The 3 AEDs are usually used for different type of epilepsy or potentially for other indications. For instance, lamotrigine may be prescribed for depression in the setting of bipolar disorder, but levetiracetam is not. Valproate could be used in acute mania in the context of bipolar disorder. Additionally, levetiracetam is approved and used in monotherapy for focal epilepsy and, despite not being approved, is used in monotherapy for generalized seizures, while valproate is now essentially used as a first-line treatment in cases of idiopathic generalized epilepsy and lamotrigine in cases of refractory partial epilepsy and generalized epilepsy not responding to valproate. Another issue relates to the different periods of licencing, resulting in systematic differences in the treated populations. The results of the comparison between those exposed to valproate and those exposed to lamotrigine were similar to the association estimated in the main analysis. When the HRs were estimated by clusters of exposure, the same trend was observed, although the association between Cluster A, constant high exposure in Sweden was even stronger than the one observed in the main analysis. The comparison results with the levetiracetam exposure group were difficult to interpret, with contradictory findings between the 3 countries. It should be noted that this was the smallest group of exposure in all 3 countries, and the number of events in this exposure group was also very small.

The WHO DDD is the assumed average maintenance dose per day for a drug used for its main indication, i.e. epilepsy for the studied AEDs, in adults. However, this may not represent the suggested or prescribed daily dose. Due to individual characteristics (such as indication, age, weight, ethnic variations, kind and severity of disease), pharmacokinetic considerations, and other factors, therapeutic doses for certain patients and patient groups will commonly deviate from the DDD. In this study, a comparison between the estimated treatment durations and time between prescriptions was provided, acknowledging that this would necessarily be affected by the DDD methodology approximation. To better provide an estimate of the impact of this approach, a sensitivity analysis (Sensitivity Analysis 8) was performed. stratifying patients with and without epilepsy, the main indication used by the WHO DDD. Overall, this sensitivity analysis showed a lower agreement with the WHO DDD among fathers with AED prescription without an indication of epilepsy, specially in the valproate group.

Finally, a sensitivity analysis (sensitivity 10) was done to investigate the risk of NDD, including ASD using a cumulative exposure to treatment. Cumulative exposure was calculated as the total amount of DDD intake that a father was exposed to over the 3 months time window prior to conception (this corresponded to the sum of the DDD in all 14-day intervals). As a continuous variable, the cumulative exposure to valproate was associated with a higher risk of NDD including ASD in Norway (Table 108), but not in Denmark and Sweden. When the cumulative exposure was categorised, cumulative higher doses of valproate seemed also associated to higher risk of NDD, including ASD, in Norway (Table 109), but not in Denmark (Table 39) and Sweden (Table 82). In the main analysis' multivariate K-Means adjusted Cox regression model, the associations in cluster with higher exposure were numerically stronger than those in clusters with lower exposure, but the analyses were limited by the loss of power when subdividing into

strata. The dose-effect association thus remains unclear; besides, considering the small number of events in each of the cumulative exposure categories, no conclusion can be drawn.

11.1.2 Secondary outcome cohort - Congenital malformations

Meta-analysis

Country-specific results were pooled in a meta-analysis in order to achieve a more precise summary estimate of the observed effect size. Pooled OR of CM in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam were calculated across 2 countries, Denmark and Norway.

No higher risk of CM in the valproate vs. the lamotrigine/levetiracetam was observed in any of the follow-up periods and for the overall study period in both countries.

The pooled results, suggested no higher risk of CM associated with paternal exposure to valproate 3 months prior to conception compared to lamotrigine/levetiracetam exposure, both in the crude and adjusted models (OR: 0.84, 95% CI: 0.48, 1.48 and OR: 0.79, 95% CI: 0.49, 1.29, respectively). It should be noted, that considerable heterogeneity was observed between country-specific estimates for the overall period of study follow-up and for 0-1 years of follow-up. Hence, the pooled results should be interpreted with caution, since they may be a reflection of this heterogeneity, explained by the small sample size (only 2 countries are included) but also by the diverging results observed (OR of 0.62 [95% CI: 0.37, 1.04] for Denmark, and OR of 1.10 [95% CI: 0.72, 1.68] for Norway).

Main analysis – Effect estimation of the association between paternal exposure to valproate and CM

When assessing the association of paternal exposure to valproate in the 2 study countries, Denmark and Norway, no difference in the risk of CM was observed in offspring from the valproate group compared with the lamotrigine/levetiracetam group. Considering the overall study follow-up, the incidence proportion of the first CM event (major and minor as composite) among offspring paternally exposed to valproate appeared to be lower than that of those paternally exposed to either lamotrigine or levetiracetam in Denmark (respectively, 9.3%, [95% CI: 6.9%, 11.7%] vs. 14.1%, [95% CI: 12.1%, 16.2%]). In contrast, in Norway, the incidence proportion of CM among offspring paternally exposed to valproate appeared to be higher than that among those paternally exposed to either lamotrigine or levetiracetam (respectively, 16.6%, 95% CI: 13.7, 19.5 vs. 15.1%, [95% CI: 13.2, 17.0]). In Denmark, when focusing on the first year of follow-up - due to the small number of events and masking rules, the incidence proportion of first CM event was 5.3% (95% CI: 3.4%, 7.2%, n=29) among offspring paternally exposed to valproate and 9.1% (95% CI: 7.4%, 10.8%, n=101) in those paternally exposed to lamotrigine/levetiracetam. In Norway, in the first year of follow-up, the incidence proportion of first CM event was 9.5% (95% CI: 7.2%, 11.7%, n=61) among offspring paternally exposed to valproate and 9.1% (95% CI: 7.6%, 10.6%, n=126) among those paternally exposed to lamotrigine/levetiracetam. Nonetheless, these figures should be interpreted with caution, even though the overlapping CIs do not support differences between exposure groups. It is worth mentioning that the incidence proportions estimated in these descriptive cohorts, refer to offspring born from fathers and/or mothers exposed to teratogenic drugs in the preconception period or during pregnancy, thus an overestimation of the incidence of CM is highly probable.

For the crude logistic regression models, it was observed a non-significant OR of 0.62 (95% CI: 0.37, 1.04) in Denmark, and 1.10 (95% CI: 0.72, 1.68) in Norway. The opposite direction in the OR observed between Denmark and Norway may be explained by the higher risk factors potentially linked to CM observed in the lamotrigine/levetiracetam group vs. the valproate group. Similar to what was observed for the crude models, in the PS-weighted logistic regression models, no higher risk of CM was observed in offspring from fathers of valproate group compared with lamotrigine/levetiracetam group, in both study countries, OR of 0.61 (95% CI: 0.36, 1.06) in Denmark, 1.00 (95% CI: 0.62, 1.61) in Norway.

Finally, no higher risk of CM was observed in the analysis adjusted for clusters of exposure to account for intensity and evolution of exposure over time, regardless of exposure trajectories.

The evaluation of CM described above, comprised a population of live births, stillbirths, and spontaneous abortions during gestation, for Norway and Denmark. In Sweden, as linkage with fathers was only possible for live births, no information was available on stillbirths, and spontaneous abortions during gestation. Thus, an exploratory objective was designed in Sweden to assess the risk of CM in offspring paternally exposed to valproate compared to lamotrigine or levetiracetam at the time of conception. Also for this exploratory analysis no association was observed between exposure to valproate at the time of conception and the occurrence of a CM when compared to live offspring from fathers exposed to lamotrigine or levetiracetam. A crude OR of 1.01 (95% CI: 0.66, 1.55) and a PS-weighted adjusted OR of 0.61 (95% CI: 0.36, 1.06) were observed. Furthermore, no higher risk of CM was observed regardless of the trajectories of exposure. Additionally, to confirm the robustness of the results, a sensitivity analysis was performed on the live-birth population for Norway and Denmark, as we expect that the distribution of CM observed in this population likely reflected functional defects and minor morphological abnormalities. Results from this sensitivity analysis were also similar to the ones observed in the main analysis, confirming the main observed association.

Additional sensitivity analyses were performed in this study aiming to explore the risk of CM in offspring born to fathers exposed to valproate, in different study populations. These analyses can be used to challenge the robustness of the study results, which can then be compared to the main findings to provide a quantitative assessment of the robustness of the original analysis. The following sensitivity analysis results overall describe similar associations when compared to the those observed in the main analysis.

As several diagnoses for spontaneous abortions and stillbirths could be missing due to under-reporting, a sensitivity analysis was performed to investigate the risk of CM using a broader definition of the outcome.

For this sensitivity analysis (sensitivity analysis 4) all the ICD-10 codes of interest for live births and spontaneous abortions or stillbirths as well as all spontaneous abortions or stillbirths without an ICD-10 code for the diagnosis were included. In both countries, similar results as to the estimated risk of CM were observed when this broader definition of CM was applied. Thus, the impact of the expected underreporting does not seem to have impacted the results reported in the main analysis.

The comparator group in the main analysis included irrespectively, exposure to either lamotrigine or levetiracetam in monotherapy. As for the primary outcome, in order to evaluate differential effect of using lamotrigine or levetiracetam, a sensitivity analysis was performed comparing paternal exposure to valproate to paternal exposure to lamotrigine (sensitivity analysis 5a) and levetiracetam (sensitivity analysis 5b), separately. The results for the comparison between the offspring exposed to valproate vs. those exposed to lamotrigine, and between the offspring exposed to valproate vs. those exposed to levetericetam, were similar to the associations estimated in the main analysis. However, because of the

very small number of events, in this sensitivity analysis the estimation of the association by clusters of exposure was not possible.

A sensitivity analysis was planned to assess the impact of the PS-weighted model computed for each country, by computing a logistic regression model adjusted for a set of identified confounders in each country (sensitivity analysis 6). Since no PS weighting is applied in this analysis, the dfbetas (statistics that indicate the effect that deleting each observation has on the estimates for the regression coefficients) for the exposure coefficient was calculated for each offspring after fitting the adjusted model in order to identify influential subjects, and excluded them from the model, before re-estimating the model (23). However, this sensitivity analysis was not possible to compute as there were no observed CM events in the population after removing outliers.
Finally, a sensitivity analysis was done to investigate the risk of CM using a cumulative exposure to treatment (sensitivity analysis 10), similar to what was computed for the Primary outcome cohort. Also, for this analysis, due to the small number of events, no conclusions could be drawn.

11.2 Limitations and strengths

This observational retrospective study was conducted in 3 Nordic countries using data sources that were not primarily collected to address the study objectives, therefore, the following limitations must be acknowledged.

- Data were collected only for administrative purposes in Denmark and Sweden, therefore, some medical information not directly related to reimbursement may be incomplete or not available at all. In Norway, most of the confounders assessed were from the birth registry, a database designed for research purposes, although we also used data from the patient registry, a database established for administrative purposes.
- As the data was extracted from different country registries, some differences were expected in terms of variables collected, coverage and missing data patterns. This was indeed the case as presented above, however many of the descriptive analyses showed similar trends.
- Paternal linkage might be incorrectly classified when the registered father is not the child's biological father. The ability to identify adoption or IVF is available in the registers of all countries of interest. Children born through IVF or adoption are not considered in this study. However, this proportion is likely not be different between AEDs.
- Information about spontaneous abortions and stillbirths (linked to mother and father) were not available for Denmark before 22nd week of pregnancy and for Norway before the 12th week of pregnancy. Accordingly, diagnoses of CM leading to a spontaneous abortion and elective terminations of pregnancies which occurred before these weeks of gestation were not detectable and not included in this study. This may have led to a

selection of cases and to a survivor bias as the distribution of type of CM and severity is likely to be different.

- Information on medicines without a prescription purchased were not available in the databases. This is an important limitation, particularly regarding folic acid, which has a significative impact on frequency of neural tube defects and congenital heart defects. Randomised trial evidence indicate that periconceptional folic acid supplementation prevented a major proportion (about 90%) of neural tube defects as well as a certain proportion (about 40%) of congenital heart defects (41). The impact of failing to account for folic acid supplementation could bias risk estimates in the comparative analyses of CM, if exposure differed across to exposure groups.
- Despite paternal exposure to medications has not been associated with birth defects, offspring from fathers exposed to drugs with known teratogenic effects 3 months prior to conception, were excluded from the comparative, sensitivity and exploratory objective analyses. The exclusion of a large number of patients may have introduce a bias and decreased the precision of the effect size estimates.
- Misclassification of exposure can also not be ruled out. In this study, paternal exposure to antiepileptic drugs was defined using a risk window of 3 months prior to the estimated date of conception. First, the date of conception could have been incorrectly estimated. Second, and related to AED's, given the longest half-life (no longer than 118 hours) and the estimated five half-life's (not more than 1 month), the window of exposure of 3 months prior to conception used in this study may have been conservative, and exposed males at the time of conception could have been classified as unexposed. Offspring exposed to AEDs and/or diagnosed with epilepsy after birth are included in the Primary outcome for descriptive analysis but excluded from the primary outcome for comparative analysis. Epilepsy and bipolar disorders are strong risk factors for NDD, and offspring with epilepsy or receiving AEDs are already at increased risk of NDD regardless of paternal exposure. Other known risk factors for NDD include genetic disorders, some congenital infectious disease, and perinatal asphyxia. It was assumed that these characteristics were balanced between the 2 exposure groups, though we could not verify this. There could have been a differences in the distribution of these characteristics between the 2 exposure groups, resulting in bias in the HR estimate.
- Indications for medications were not available in all the data sources used for this study. Epilepsy was assumed to be the primary indication for the three AEDs of interest (valproate, lamotrigine, and levetiracetam) at the time of study design and protocol development. The indication for paternal epilepsy was considered a proxy for the AED's prescription; hence, this clinical characteristic was not accounted for in the comparative analyses. Nonetheless, our results showed that epilepsy was the AED indication in 63.5%, 55.8%, and 35.1% of the

cases in Denmark, Sweden, and Norway, respectively. Thus, a confounding effect of the paternal epilepsy indication cannot be ruled out based on the estimates.

- It should also be considered that some AEDs may be continued or discontinued more frequently than others. Fathers with more severe epilepsy are more likely to continue their AED intake. In the present study, patients switching or discontinuing their medication were considered as polytherapy, and the offspring of these fathers were excluded from the main analyses, which might have introduced selection bias.
- Bipolar disorders in the parents can have an impact on offspring development. Bipolar disorders in fathers were taken into account in the primary outcome analyses, but bipolar disorders in mothers were not.
- Lifestyle factors (such as paternal and maternal smoking, substance abuse or alcohol consumption) were missing in a high proportion in both countries. The exception is smoking before pregnancy which was well recorded in Sweden. The negative effects of prenatal alcohol exposure on the developing brain and the resulting neurological and/or cognitive, behavioural, emotional, and adaptive functioning deficits in offspring maternally exposed *in utero* are well recognised (42). It is also well established that prenatal nicotine exposure, even though maternal smokeless tobacco use, is associated with numerous post-natal adverse health outcomes in new-born – not only low birth weight, preterm delivery, and sudden infant death syndrome but also severe neuropsychiatric disorders (Tourette syndrome and chronic tic disorder, as well as Tourette syndrome with comorbid psychiatric conditions including attention deficit/hyperactivity disorder [ADHD]) (43). The limited information on these factors will preclude complete adjustment in the final model, however, this misclassification is anticipated to be non-differential, affecting both exposed groups equally.
- For Denmark, when the outcome for a specific analysis had <5 cases/observations, the specific result and other potentially related results that could lead to the identification of those patients were masked by the data provider. This might sometimes lead to incomplete descriptive analyses, for example, the minimum and maximum values could not be reported, as well as strata with very few counts.
- The major malformations were defined per protocol based on the exclusion of minor using EUROCATs classification. This approach is well described and accepted. However, the list of exclusions (minor) was based on the British Paediatric Association (BPA) extension of ICD-10. Country-specific adaptations of ICD-10 in Denmark and Norway may have led to a failure in excluding minor malformations, and consequently, a high proportion of overall CM was observed.

- Offspring with CM are more at risk of NDD. Not having excluding offspring suffering from CM in the primary outcome cohorts might have biased the estimate of the association between exposure and risk of NDD.
- NDD was considered as a composite outcome therefore it may be challenging to understand the clinical relevance of the observed findings. The main issue is the potential of misinterpretation when there is heterogeneity of response among components of composite endpoints. For instance, less clinically significant endpoint(s) included in the definition of the composite outcome may drive the overall observed effect (i.e. less important outcomes may account for the majority of events). This may have had an impact on the estimate in the main analysis.
- The incidence proportions and the incidence rates estimated in the descriptive cohort are unadjusted, therefore should be interpreted with caution. Yet, the interpretation of the findings for the effect of paternal exposure to valproate (compared with lamotrigine/levetiracetam) on NDD, including ASD or CM risk, was based on the results from the PS-weighted adjusted Cox regression models. However, despite the very comprehensive and through adjustments implemented in the multivariable models, residual confounding cannot be completely ruled out.

Also, results were pooled in a meta-analysis and, the following limitations should be considered when interpreting the findings:

- In some instances the I^2 statistic suggested low heterogeneity, however, very broad CI were observed suggesting large uncertainty in this assessment, added to which the meta-analysis is conducted only using 3 and 2 sets of results, i.e. Denmark, Sweden, and Norway, and Denmark and Norway, respectively for primary and secondary outcome. Specifically, in the pooled results of the secondary outcome analysis, significant heterogeneity and risk estimates in opposite directions in the 2 countries make the results difficult to interpret.
- There are differences in the healthcare systems and healthcare policy, such as the screening for the outcomes of interest, as well as country-specific risk factors and confounders considered in the PS adjusted model.
- The study-specific results from which the pooled HR were derived may be biased due to residual confounding because the degree of adjustment may differ by country depending on the availability of the selected variables and the strength of the relationships between exposure and outcome(s).
- In crude analyses no risk for NDD including ASD was observed in offspring from the paternal exposure to valproate group compared to the paternal exposure to lamotrigine/levetiracetam group. A slight and non-significant higher HR was observed, which may be attributable to paternal underlying psychiatric indications that were not considered in the crude analysis.

With regard to the research methods the following strengths should also be acknowledged:

- Data sources are based on live births with medical record linkage to mother and father available in multiple registry databases in Denmark, Sweden, and Norway for NDD including ASD. The choice of minimal inclusion and exclusion criteria were applied in this study to minimise potential selection bias and capture a comprehensive sample that could represent the nationwide real practice.
- The study is based on data of offspring with linkage data to both parents from national health registries in Denmark, Norway and Sweden.
- An adequate number of offspring was reached for each study cohort in all study countries with an 80% of power, and the follow-up of the study was up to 12 years of age of the offspring, enabling the identification of the safety outcomes of interest during the infancy and childhood period.
- In the present study paternal exposure to valproate was compared to paternal exposure to lamotrigine/levetiracetam, a comparator group with similar indications without evidence, so far, of an association with NDD nor CM. Therefore, the threat of a systematic bias was minimised by the choice of a robust active comparator group. Also, the implementation of appropriate statistical techniques (PS weighting, double adjustment, adjustment for K-means cluster of exposure) likely reduced the likelihood of confounding. The observed findings regarding higher incidence rates in specific age groups, corresponding with "Real life practice": less than 2 years correspond to the most severe cases, 5-6 years first years of mandatory school, 7-8 years age of first national school learning level tests (Europewide aligned).
- The robustness of the main findings was corroborated by the consistency of the largely similar findings observed in sensitivity and exploratory analyses across the 3 study countries.

11.3 Interpretation

It is well recognised that maternal exposure to valproate during pregnancy significantly increases the risk of congenital malformations, including neural tube, cardiac, skeletal and limb, or-facial cleft, and craniofacial deformities (44). Results from a Danish population-based study of children born alive, Christensen and colleagues (2), investigated potential association of prenatal exposure to valproate with risk of ASD. They observed a higher risk of ASD and childhood autism, and the association was observed among offspring of mothers with and without epilepsy, and after further adjustment for parental psychiatric disease. According to the animal model study, maternal valproate therapy in mice increases the occurrence of features similar to ASD at the molecular, cellular, and behavioural levels. Besides, offspring with in utero exposure to valproate presented health and behavioural outcomes such as NDD, including ASD-related deficits (11,45–47). On the other hand, it is unclear how exposure to paternal valproate will affect the behaviours of the offspring, and human studies investigating this association among offspring from fathers exposed are still scarce (48). Nevertheless, recent findings suggest that paternal exposure to valproate during the spermatogenesis of mice may disturb the histone acetylation balance in the brain of offspring through changes in the germline epigenome, leading to behavioural alterations in offspring (5).

However, whether the same mechanisms apply to humans is not yet known. There are indeed concerns whether paternally exposed offspring to valproate, during conception may be at increased risk of NDD including ASD and CM.

So far, only 4 population-based studies have been published assessing the paternal exposure to AEDs on birth outcomes (10,31,32,49). In a prospective population base-cohort study, children born to parents with epilepsy had a significantly higher risk of scores on tests of personal social skills (OR: 2.3, 95% CI: 1.3, 4.1) and a measure of autistic traits compared to children whose parents had epilepsy but were untreated. However, the study did not differentiate between the various AEDs; therefore, the findings cannot be extended to valproate (10). Interestingly, all the groups exposed to AEDs, including lamotrigine, were associated with more autistic traits at 36 months. Results from a cohort study based on the Norwegian Prescription Database and the Medical Birth Registry of Norway, suggest no association between paternal exposure to AEDs and higher risk of unfavourable pregnancy outcomes (4). Further results from a cohort study based on Danish national registers found that children whose fathers used AEDs during the 3 months before conception had a 23% higher risk of congenital anomalies (adjusted OR 1.23, 95% CI: 1.10, 1.37), compared to those unexposed (31). Despite this study did not differentiate between AEDs, the results of the negative-control analysis suggested that the higher risk was also observed in children whose fathers were former users (i.e. those using AEDs only from 1 year to 3 months before conception) (OR 1.29, 95% CI: 1.03, 1.61) and later users (i.e. those using AEDs only during pregnancy) (OR 1.35, 95% CI: 1.12, 1.65). The authors concluded that the risk of congenital anomalies in the offspring paternally exposed to AEDs before conception may be attributable to the underlying condition rather than to the effects of AEDs (31). Yet, so far, only one study has examined potential associations between valproate exposure and major CM or NDD in offspring (32).This study was conducted using the Swedish registries to investigate the association between paternal use of AEDs and adverse neurodevelopmental outcomes and major CM in the offspring (32). The results found that offspring of fathers exposed to AEDs did not show a higher risk of autism (adjusted HR [aHR] 0.9, [95% CI: 0.5, 1.7]), ADHD (aHR 1.1, [95% CI: 0.7, 1.9]) or intellectual disability (aHR 1.3, 95% CI: 0.6, 2.8) compared with offspring of fathers with epilepsy who were not exposed to AEDs. Among offspring of fathers with epilepsy who used valproate in monotherapy during conception, rates of autism and intellectual disability up to 11 years of follow-up were slightly higher compared to those of the offspring of fathers with epilepsy who did not use AEDs during conception. However, after adjustment for PS the estimated risk lost its statistical significance, leading the authors to conclude that exposure to valproate, or other AEDs, during conception was not associated with a higher risk of major CM or NDD in the offspring. To test the robustness of their findings, the authors investigated whether children of mothers with epilepsy had higher rates of major malformations, autism, ADHD and intellectual disability than those whose mothers were not exposed to AEDs during pregnancy. These findings were confirmed (aHR 4.8, 95% CI: 2.1, 10.8), and most cases of the observed association were among offspring of mothers who used valproate in monotherapy during pregnancy. The authors concluded that the higher risk of NDD was more likely caused by factors associated with epilepsy and partly genetically determined (32).

To the best of our knowledge, this study is the first extensive population-based study, comprising 3 countries, showing a significantly increased risk of neurodevelopmental disorders in children from fathers with epilepsy exposed to valproate, compared to those from fathers with epilepsy exposed to lamotrigine/levetiracetam. The significant association with NDD, became stronger when the outcome of interest was restricted to ASD though only investigated in the Swedish data (aHR 2.68, 95% CI: 1.17, 6.12), with a consistent pattern of association according to a constant high and a constant moderate

exposure to valproate. Since the outcome investigated was a composite of any NDD it was not possible to evaluate neither the proportion of the different type of NDDs nor the comparative risk for each NDD subtype. Besides, this study was not designed to fully characterise this risk, rather to identify if one existed. Yet, interpreting the findings of the present study (showing a significant higher risk of composite NDD, and higher risk of ASD, in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam), and compare to those observed by Tomson and colleagues (no association with NDD), both for Sweden, is challenging. Only one study based on Danish national registers has reported an increased risk of ASD following paternal use of selective serotonin reuptake inhibitors (SSRIs) before conception (7). Offspring of fathers who used SSRIs before conception had a 1.62-fold greater risk of developing autism spectrum disorders (ASD) than those who did not. The risk was reduced after controlling for possible confounders, particularly fathers' mental disorders (HR: 1.43; 95% CI: 1.18, 1.74). Extending the exposure window to 3 months before conception did not change the observed higher risk, but no risk was observed for the offspring of fathers who only used SSRIs during the last 3 months before conception. The authors concluded that the increased risk of ASD in the offspring associated with paternal SSRI use before conception may be attributable to paternal underlying psychiatric indications related to SSRI use or other unmeasured confounding factors (7).

In the study of Tomson et al., performed in Sweden in live-born singleton children between 2006-2016, 1.7% of offspring paternally exposed to valproate (n=8) were diagnosed with an ASD vs. 1.3% of offspring paternally unexposed (n=32) (32). In the present study, also in Sweden ASD as the first NDD diagnosis - although maybe not reliable as methods of diagnosis may have changed over time - during all the study period (2007-2019), was observed in 1.7% of offspring paternally exposed to valproate and in 0.6% of offspring paternally exposed to lamotrigine/levetiracetam. All ASD diagnoses (i.e. not only as a first diagnosis) were observed in 2.2% of offspring paternally exposed to valproate and in 0.9% of offspring paternally exposed to lamotrigine/levetiracetam. However, in the study by Tomson et al., no information about lamotrigine or levetiracetam was available, making comparison difficult.

Considering the observational nature of the studies, several biases might have affected the findings, the most important of which related to the choice of the comparator group. In the current study, the risk of systematic bias was reduced by using a robust active comparator group (i.e. paternal exposure to lamotrigine/levetiracetam with basically similar indications as valproate, but with no evidence of an association with NDD or CM), as opposed to Tomson and colleagues' where a non-user comparator group was selected (32). Non-users had epilepsy but were not treated, and this comparator group most likely included subjects with a very mild disease, for example only those with sporadic seizures. Despite the authors' adjustments for PS, added to the models as a continuous variable, a richer set of variables and the implementation of a high-dimensional propensity score would have provided a more robust adjustment, further reducing the likelihood of confounding by indication on the observed estimates (50). According to Yang et al., additional sensitivity analyses using inactive comparators or the use of a negative control by assessing the risk of NND or ASD in former valproate users (i.e. 1-3 months prior to conception, thus outside the spermatogenesis window of inseminating sperm) could have provided evidence that the observed outcome was the result of the underlying indication rather than valproate (31). Although the current study did not estimate the effect based on ASD events, epilepsy was the most common indication for either valproate and lamotrigine/levetiracetam in all study countries. As a result of this, large differences in effect estimation are not expected but cannot be ruled out.

In the present PASS, a follow-up up to 12 years of age was considered, and some NDD, especially autism disorder, may not be readily diagnosed in childhood (51). Thus, the likelihood of detecting such NDD diagnosis increases with the entry in school (52). Although data on offspring starting school were not present in the included data sources, and thus results could not be adjusted for this characteristic, we found a pattern of higher incidence of NDD, including ASD rates, at ages when children begin formal schooling. Even if the model was adjusted for year of conception, an unbalanced year of conception in the 2 paternal exposure groups may have influenced the likelihood of being detected with NDD, including ASD, in the lamotrigine/levetiracetam group due to the shorter three-year follow-up in this group. Indeed, the mean age of an ASD diagnosis is around 4-5 years old, and in the lamotrigine/levetiracetam group, roughly 74% had at least 4 years of follow-up (conceived before 2006) vs. 86% in the valproate group. Similarly, regarding NDD outcome, we observed in this study 3 age peaks for detection of NDD (1-2 years, 5-6 years, and 7-8 years); in the lamotrigine/levetiracetam group, 29% had at least 8 years of follow-up (conceived before 2011) vs. 54% in the valproate group. Hence, offspring of the valproate group appeared to have a higher chance of being diagnosed with NDD or ASD.

With the aim to explore the genetic role in the development of NDD, including ASD, an analysis was performed in each study country to describe risk factors and the frequency of NDD, including ASD, in paternally-matched but exposure-discordant siblings (exploratory analysis 6). However, no conclusion was possible to draw since the small sample sizes (Denmark N=21; Sweden N=29; Norway N=8) precluded the observation of the outcome of interest or the calculation of its effect on NDD, including ASD.

As reported by Thomas, the majority of mothers with epilepsy treated with valproate have genetic generalised epilepsy types, which raises the question of whether women with generalised epilepsy are at higher risk of NDD in their offspring than those with focal epilepsy, difficult to disentangle considering that valproate is the primary drug for idiopathic generalised epilepsy (53). It is unclear, though, which definition the author used of "genetic generalised epilepsy" and whether the same author was referring to "idiopathic generalised epilepsy," a type of epilepsy known to have a genetic basis. Yet, it would be of interest to learn whether this hypothesis can be applied to fathers as well, considering that for male patients with idiopathic generalised epilepsy, valproate is the treatment of choice. However, the findings published so far related to the paternal exposure to valproate and the risk of NDD or ASD in their offspring, or lack thereof, need to be further investigated.

Although the effects of maternal exposure to AEDs on CM outcomes have been extensively examined, only a few studies have been able to include data related to drug ingestion by fathers prior to conception. A study using a composite of valproic acid, phenytoin, and phenobarbital found no association between paternal exposure and safety outcomes related to congenital malformation (i.e. spontaneous abortion, preterm birth, perinatal mortality, small gestational age, and birth defects) (4). In line with the present findings, Tomson and colleagues (32) found no risk for major CM in Sweden (adjusted OR 0.9, 95% CI: 0.7, 1.2).

The authors observed 4.8% of major CM diagnosed in offspring paternally exposed to valproate vs. 4.9% in offspring paternally unexposed. In the present study, where a more specific definition of major CM was used, we observed that 5.6% of offspring paternally exposed to valproate were diagnosed with major CM vs. 5.9% of those paternally exposed to lamotrigine or levetiracetam in Sweden. The effect of paternal exposure to valproate on offspring congenital malformation was evaluated in our study using logistic models, and the coefficient observed was lower than the null both in the meta-analysis and in the Danish

population. Besides, in a Danish nationwide cohort study, Yang and colleagues found that the use of valproate in the 3-month period prior to conception was not associated with an increased risk of CM, while lamotrigine exposure in the same time period was associated with a higher risk of CM (31).

These results from the only available real-world sources with paternal linkage, are the first to find an increased risk of NDD in offspring from fathers exposed to valproate, compared to those from fathers exposed to lamotrigine or levetiracetam and they have several limitations; hence more studies are warranted to confirm these findings.

11.4 Generalizability

Data sources are based on live births with medical record linkage to mother and father available in multiple registry databases recording longitudinal medical data in Denmark, Sweden, and Norway for NDD including ASD cohort; and live births, stillbirths, and spontaneous abortions during gestation with medical record linkage to mother and father available within such registries, for Norway and Denmark for congenital malformations. In this study, minimal inclusion and exclusion criteria were used with the goal of minimising potential selection bias and capturing a comprehensive sample that could best represent nationwide real practice in the selected countries.

The included data sources are representative of the country's total population and patient lifetime data, and they have been demonstrably used for research to reveal the real-world patterns. This study has used offspring data with linkage data to both parents. A high rate of paternal linkage data is available in those registries, 97.5% for Denmark, 97% for Norway, and 90% for Sweden (see section 9.5).

An adequate number of offspring was reached for each study cohort in all study countries to reach the precision of 5% of significance and 80% of power (see Section 9.5 of Protocol V6.0). Further, the follow-up of the study was up to the age of 12 years for the offspring, enabling the identification of the safety outcomes of interest during the infancy and childhood period.

Finally, it needs to be considered that, although differences from specific-country characteristics of databases, the healthcare system, and the diagnosis and screening of outcomes of interest, the estimates obtained from the meta-analysis may be generalisable for the risk of NDD including ASD in children of the study countries. Regarding the CM, high heterogeneity and risk estimates in opposite directions in the 2 countries would make the results difficult to generalise.

11.5 Additional discussion

11.5.1 Descriptive analysis for the primary outcome for Denmark, Sweden, and Norway

The total number of offspring selected in the Primary outcome cohort, considering all 3 countries, was 16081 (including 5034 from Denmark, 6664 from Sweden, and 4648 from Norway).

Offspring characteristics

Overall, offspring characteristics from the descriptive cohort were similar in all 3 countries, with an expected distribution of the gestational age, ratio of males to females, and the offspring weight (54,55). Although offspring with epilepsy were excluded from the Primary outcome cohort for comparative analysis, a higher proportion of this condition was observed in offspring paternally exposed to valproate than in those exposed to lamotrigine or levetiracetam. This might be due to the fact that valproate is the treatment of choice (or first-line drug) for male patients with idiopathic generalised epilepsy, a type of epilepsy known to have a genetic basis and that, as such, can be found in several members of the same family. On the other hand, lamotrigine and levetiracetam are used for a wide range of conditions, including focal epilepsy (56).

The diagnosis of NDD, including ASD, was higher in offspring exposed to valproate than in those exposed to lamotrigine or levetiracetam consistently across the 3 countries (Denmark: 6.6% vs. 3.7%; Sweden: 5.4% vs. 3.5%; and Norway: 6.7% vs. 4.0%). A similar trend was observed when ASD was considered as a first NDD diagnosis or when all ASD diagnoses were considered (i.e. not only as a first diagnosis) in both Sweden (2.2% vs. 0.9%, respectively, for valproate vs. lamotrigine/levetiracetam) and Norway (1.6% vs. 0.7%, respectively, for valproate vs. lamotrigine/levetiracetam), but not in Denmark (1.6% vs. 1.8%, respectively, for valproate vs. lamotrigine/levetiracetam). The median age in years at the first ASD diagnosis [6.1, 6.3, 4.9 vs. 7.5, 4.5, 4.8 (respectively for Denmark, Sweden, and Norway and for valproate vs. lamotrigine/levetiractem groups)] is in line with the global mean age at ASD diagnosis (from 38 to 120 months) (57). Several factors may influence the age at diagnosis, including, but not limited to, the type and severity of ASD diagnosis, gender, ethnicity, calendar year of diagnosis (as detection methods have improved overtime), etc. This, however, was not within the scope of the present study; therefore, we cannot provide a conclusive explanation considering that these are crude data that have not been adjusted for other variables.

Maternal characteristics

With regard to maternal characteristics, maternal age distribution was similar in all countries (median [IQR] of 30 [27-34] years for Denmark, 31 [27-35] years for Sweden, and 30 [27-34] for Norway, respectively) and aligned with previous studies (55). The number of pregnancies in more recent years was lower than in earlier years, and can reflect more cautious behaviour and a general European trend of declining birth rates (58). The most frequent maternal comorbidities diagnosed prior to childbirth in Denmark, Sweden, and Norway were neurotic disorders (6.8%, 11.8%, and 10.9% respectively), affective disorder (4.0%, 9.9%, and 7.5%, respectively), and gestational diabetes (3.7%, 3.0%, and 5.3%, respectively).

Smoking during pregnancy was observed among 16.1% mothers in Denmark, 6.4% in Sweden, and 7.5% in Norway. However, large differences in the proportion of missing information on smoking particularly before pregnancy (masked numbers in Denmark, 5.1% in Sweden, and 22.9% in Norway), and during pregnancy (4.0% in Denmark, 3.0% in Sweden, and 12.3% in Norway) were observed, which impairs direct comparisons between countries. The lowest proportion of missing information was observed in Sweden, since recording of smoking is a standard procedure during maternal clinic visits. The observed differences in prevalence of smoking percentage might also be influenced by different recording and data collection in the 3 countries, as outlined in Section 9.

In Denmark, Sweden, and Norway, similar proportions of the offspring's mothers were found within a polypharmacy index during pregnancy between 1 and 4 (48.5%, 47.0%, and 46.3%, respectively). The

prevalence of medications associated with neuropsychiatric adverse events during pregnancy was high in all 3 countries: 44.2% in Denmark, 45.2% in Sweden, and 42.6% in Norway. This result may be explained by the fact that the list of medications for this category is lengthy and includes common medications such as ibuprofen and paracetamol. In contrast, maternal exposure to AED during pregnancy was very low (masked values in Denmark, 2.7% in Sweden, 2.5% in Norway). As expected, only a very small proportion of offspring would be both paternally and maternally exposed to AEDs, and this was confirmed in the data.

Paternal characteristics

Regarding paternal characteristics, the median (IQR) age of fathers at childbirth was similar in all countries (32 [29-36] years for Denmark, 34 [30-38] years for Sweden, and 33 [29-37] for Norway). The most common paternal comorbidities diagnosed prior to the childbirth in Denmark, Sweden, and Norway were neurotic disorders (9.2%, 21.9%, and 10.2%, respectively), affective disorder (excluding bipolar affective disorder and mania) (9.2%, 22.7%, and 14.0%, respectively), and bipolar affective disorders (5.5% and 22.9%, and 18.5%, respectively). The proportions of fathers with a polypharmacy index between 1 and 4 were similar in all countries (43.3 % for Denmark, 40.9% for Sweden, and 43.6% for Norway). Likewise, the prevalence of paternal concomitant medications associated with neuropsychiatric adverse events prior to LMP2 was high in all countries (53.2% in Denmark, 57.9% in Sweden, and 63.7% in Norway). Fathers exposed to either lamotrigine or levetiracetam generally presented a higher proportion of clinical comorbidities (i.e. paternal psychiatric disorders) in all 3 countries. For instance, among fathers exposed to valproate, 6.3% from Denmark, 13.5% from Sweden, and 5.0% from Norway presented neurotic disorders and 3.7% from Denmark, 11.0% from Sweden, and 5.5% from Norway presented affective disorder excluding bipolar and mania. Among fathers exposed to either lamotrigine or levetiracetam, 11.3% from Denmark, 27.4% from Sweden, and 12.7% from Norway presented neurotic disorders, and 13.0% from Denmark, 30.3% from Sweden, and 17.96% from Norway presented affective disorder excluding bipolar and mania. All mental health diagnoses were more frequent in Sweden than in Denmark and Norway; however, this does not necessarily illustrate a higher true prevalence, but rather potential differences in coding and clinical practice.

The K-means algorithm, analysing DDD trajectories in fathers exposed to AEDs 3 months prior to conception (before LMP2), identified 2 different clusters: A (constant high exposure to AEDs) and B (constant low exposure) in both Denmark and Norway, and 3 different clusters: A, B, and C in Sweden [constant high exposure (A), low-to-high exposure (B), and high-to-low exposure (C)]. Overall, fathers were treated quite similarly in the exposure groups, although in Norway a lower proportion of fathers in the valproate group was in cluster A (68.2%) as compared to lamotrigine/levetiracetam (74.4%), and a higher proportion of fathers in the valproate group was in cluster B (31.8%) as compared to lamotrigine/levetiracetam (25.6%).

Frequency of the outcome of NDD including ASD

From the total of 2031 offspring from *the* Primary outcome cohort for descriptive Analysis in Denmark, 2451 offspring from the Primary outcome cohort for descriptive analysis in Sweden, and 2019 offspring from Primary outcome cohort for descriptive analysis in Norway, the overall cumulative incidence

proportions (95% CI) of NDD including ASD for the total group (valproate + lamotrigine/levetiracetam) were 4.9% (3.9%, 5.8%), 4.2% (3.4%, 5.0%), and 4.8% (3.9%, 5.8%) respectively which are aligned with previous studies investigating prevalence of NDD in general population (59,60). For instance, a meta-analysis found the prevalence (95% CI) of intellectual disability national level of high income countries of 5.8% (5.5%, 7.0%) (60). However, the overall cumulative incidence proportion appears to be higher in offspring paternally exposed to valproate than in those paternally exposed to lamotrigine/levetiracetam, across the 3 study countries, though these are unadjusted data that should be interpreted with caution.

The crude incidence rates for the first diagnosis of NDD, including ASD, in the follow-up period (0-12 years) in the cohort for descriptive analysis were slightly higher in the valproate group than in lamotrigine/levetiracetam group: n=55, incidence rate: 6.6, (95% CI: 4.9, 8.3) per 1000 PY vs n=44, incidence rate: 3.7 (95% CI: 2.6, 4.7) per 1000 PY in Denmark; n=52, incidence rate: 5.4 (95% CI; 3.9, 6.8) per 1000 PY vs n=52 incidence rate: 3.5 (95% CI: 2.6, 4.4) per 1000 PY in Sweden; n=43, incidence rate: 9.6 (95% CI: 6.9, 12.9) per 1000 PY vs n=55 incidence rate: 6.4 (95% CI: 4.8, 8.4) per 1000 PY in Norway. For Denmark, the total patient-years of follow-up were 15605.72 (7691.63 for valproate and 7914.08 for lamotrigine/levetiracetam group), and the mean follow-up in years per patient was 9.2 for the valproate group and 6.6 for the lamotrigine/levetiracetam group. For Sweden, the total patient-years of follow-up were 13975.92 (6483.28 for valproate and 7492.64 for lamotrigine/levetiracetam group), and the mean follow-up in years per patient was 6.7 for the valproate group and 5.0 for the lamotrigine/levetiracetam group. For Norway, the total patient-years of follow-up were 13072.38 (4490.96 for valproate and 8581.42 for lamotrigine/levetiracetam group), and the mean follow-up in years per patient was 7.0 for the valproate group and 6.2 for the lamotrigine/levetiracetam group. Also here, a trend towards higher incidence rates was observed in the valproate group vs. the lamotrigine/levetiracetam group, which are unadjusted and therefore should be interpreted with caution.

The crude incidence proportion and rates of NDD, including ASD, appeared higher in males compared to females in all 3 countries, which is consistent with the known epidemiology of the diseases (60–62). In addition, in Denmark and Sweden, males were diagnosed earlier (based on 5th and 10th percentiles of time to NDD distribution from Kaplan-Meier estimates). This can be explained by the fact that males display hyperactivity symptoms and are more likely to be diagnosed at younger age, which could trigger earlier investigations and diagnosis (61).

The overall median age in years at the first diagnosis of NDD including ASD in offspring of fathers from valproate group was 6.6 (IQR 4.7, 7.9) in Denmark, 6.2 (IQR 4.1, 8.7) in Sweden, and 6.6 (IQR 4.7, 7.9) in Norway for the valproate paternal exposure group. The corresponding numbers for the lamotrigine/levetiracetam group were 6.1 (IQR 3.9, 8.3) in Denmark, 5.2 (IQR 3.4, 8.2) in Sweden, and 6.1 (3.9, 8.3) in Norway. Also, offspring in the lamotrigine/levetiracetam group were conceived in the later period of the study compared to those in the valproate group in all countries, particularly in Denmark and Sweden. This is aligned with previous research that showed a declining trend for valproate use during pregnancy in the Nordic countries in more recent years (63). This slight difference in the rate of NDD between exposure groups likely reflects longer follow-up time in the valproate group (more offspring conceived in the early years of study period), and subsequently can also partly explain the higher risk of observing NDD in older children. Likewise, previous literature has shown that a child's birth-year may impact the first diagnosis of NDD (64). We hypothesise that improvements in the awareness, screening and diagnosis of NDD including ASD in more recent years, may explain the earlier diagnosis in children

from lamotrigine/levetiracetam group (65,66). Other explanation could be more severe form of NDD in the lamotrigine/levetiracetam.

Risk factors and potential confounders

In the current study, potential risk factors and confounders were initially selected based on the literature and clinical expert opinion. These characteristics were related to the offspring, father, and mother, and their assessment was needed to decide which would be considered in the multivariable analysis. The distributions of potential risk factors and confounders for the association between NDD including ASD and paternal exposure group were examined for those offspring within the Primary outcome cohort for comparative analysis.

As per the protocol definition, confounders are all those variables associated with both the exposure and the outcome of interest but that are not intermediate factors on the causal path between exposure and outcome; a variable is considered a risk factor if it is associated with the outcome independently of the paternal exposure and of the magnitude of the association.

Characteristics associated with the exposure

Gender of the offspring was associated with exposure group in Norway, indicating an unequal gender distribution between exposure groups (proportions of male offspring: 50.1% in the valproate group vs. 53.0% in the comparator group).

Maternal characteristics associated with the exposure were the mother's age, affective disorder in Denmark and Norway, maternal polypharmacy index prior to LMP2 in all study countries, and during pregnancy. In Denmark and Norway only, concomitant medications associated with valproate-indicated psychiatric conditions were approved prior to LMP2 in Denmark and Sweden and during pregnancy in Denmark and Norway. The following risk factors for maternal neurotic disorders were considered in Sweden but not in other countries: the mother's alcohol abuse prior to LMP2 and during pregnancy; smoking prior to LMP2 and during pregnancy; and the maternal polypharmacy index during pregnancy.

Similar to what was observed for fathers, regarding the above mentioned maternal characteristics, mothers of offspring from the valproate exposure group presented a lower proportion of comorbidities, a lower polypharmacy index, a lower proportion of concomitant medications, and a slightly lower age. In Sweden, the proportion of alcohol, substance abuse, and smoking prior to LMP2 and during pregnancy was higher among mothers of offspring from the valproate exposure group.

Paternal characteristics associated with the exposure to valproate or lamotrigine/levetiracetam were the same in all study countries and comprised affective disorder excluding bipolar affective disorder and mania, bipolar affective disorder, neurotic disorder, paternal polypharmacy index, concomitant medications associated with valproate-indicated psychiatric conditions, concomitant medications associated with neuropsychiatric adverse events, father's age, and year of offspring conception.

Fathers from valproate group presented a lower proportion of comorbidities, polypharmacy index, proportion of concomitant medications, and a slightly lower age, and earlier years of offspring conception than fathers from the comparator group.

Characteristics associated with the primary outcome

Gender of the offspring was a risk factor for NDD, including ASD, with male offspring having a higher likelihood of the outcome than female offspring.

Mother's age, smoking during pregnancy, maternal polypharmacy index prior to LMP2 and during pregnancy, and concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 and during pregnancy were all linked to the primary study outcome and thus considered a risk factor for NDD, including ASD, in Denmark and Norway. In Denmark and Sweden, maternal affective disorder was also a risk factor for NDD, including ASD. Moreover, only in Denmark were certain factors considered risk factors for NDD, including ASD, maternal schizophrenia, schizotypal and delusional disorders (marginally significant), and substance abuse prior to LMP2; in Norway, smoking prior to LMP2.

Regarding paternal characteristics, the year of offspring conception was associated with NDD, including ASD, in all the study countries, and thus considered a risk factor, with more recent years of conception presenting a lower odds of the study's primary outcome. This association likely reflects the difference in the length of the follow-up between the valproate (longer) and lamotrigine/levetiracetm groups (shorter), as observed and already discussed throughout the report. Of note, the lower risk of NDD or the lower probability of being detected or diagnosed with NDD may be due to the shorter follow-up time, which was not long enough to detect enough signs of the disease. It is therefore plausible that the offspring conceived in the latest years did not reach the age required for the diagnosis of NDD to be coded.

In addition, only in Sweden, was the paternal polypharmacy index considered a risk factor, and NDD, including ASD, was 2.5-fold more likely to happen in offspring of fathers with a paternal polypharmacy of 5-10.

Overall, in the current study, the a priori selected confounders and risk factors can be contextualised by previous literature findings listed below:

- Multiple epidemiological studies suggest a relationship between advanced paternal age at conception and adverse neurodevelopmental outcomes in offspring (67,68). This has been particularly noted regarding increased risk for autism, and it was identified as a confounder in our study.

- Children of parents diagnosed with mood disorders including bipolar affective disorder and mania have been shown to present with a higher risk of neurodevelopmental outcomes than those who do not present with these medical conditions. These mood disorders were identified as confounders in our study.

- Maternal epilepsy and maternal exposure to AEDs were considered strong risk factors and were used as exclusion criteria for the comparative, sensitivity, and exploratory analyses. In this report, we can observe that the number of exclusions due to these criteria was low (Denmark: N=64; Sweden N=63; Norway N=55) and did not affect the sample size or the generalizability of results.

- Maternal exposure to drugs other than AEDs - the plausibility of polypharmacy as a confounding variable or risk factor is based on evidence that polypharmacy is associated with harms, including adverse drug effects, drug-to-drug interaction, hospitalisation, and mortality. Furthermore, there is

evidence that psychoactive drugs of other therapeutic class may often be prescribed in combination with AEDs and may be a risk factor for NDD (such as antidepressants [6]). In line with these data, maternal polypharmacy index prior to LMP2 in all study countries, and during pregnancy in Denmark and Norway only, concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 in Denmark and Sweden, and during pregnancy in Denmark and Norway were included as covariates in the multivariate adjusted model. Likewise, concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 and during pregnancy was considered a risk factor in Denmark and Norway.

11.5.2 Descriptive analysis for the secondary outcome for Denmark and Norway

The secondary analysis for CM was conducted in Denmark and Norway. The total number of offspring selected in the Secondary outcome cohort was 8182 (3777 in Denmark and 4676 in Norway). A sensitivity analysis regarding this outcome was conducted in Sweden in a population containing live births only.

Offspring characteristics

Most offspring within the Secondary outcome cohort were born at term (90.4% in Denmark and 89.6 in Norway) and with an adequate weight (95.5% and 95.8% were weighting ≥2500 g in Denmark and Norway, respectively). A slightly higher proportion of the offspring were males (51.8% in Denmark and 52.4% in Norway).

Maternal characteristics

With regards to maternal characteristics for the Secondary outcome cohort, the median (IQR) maternal age distribution in years was 30 (27-34) years in Denmark and 30 (26-34) years in Norway. The most frequent maternal comorbidities diagnosed prior to childbirth were gestational diabetes (4.7%) and obesity (2.1%) in Denmark and diabetes (1.7%) and gestational diabetes (1.5%) in Norway. Overall, 17.1% out of 3722 mothers in Denmark and 9.2% out of 4648 mothers in Norway had a record of smoking during pregnancy. Overall, maternal exposure to AEDs was very low (less than 1.5% for any individual AED) both before LMP2 and during pregnancy in Denmark and Norway. Maternal exposure to medications with teratogenic activity or foetal toxicity prior to LMP2 and during pregnancy was 31.0% and 32.1% in Denmark and 29.2% and 28.9% in Norway. As offspring maternally exposed (3 months prior to conception and/or during pregnancy) to drugs with known teratogenic activity/foetal toxicity are at risk of developing the outcomes of interest for reasons other than valproate, i.e. due to intake of other drugs associated with the CM (69), these offspring were excluded from the comparative, sensitivity and exploratory objective analyses. However, they were not excluded from the descriptive analyses, and this could explain the higher cumulative incidence rate of CM in both groups.

Paternal characteristics

Regarding paternal characteristics, the median (IQR) age of fathers at childbirth was similar in both countries (33 [29, 37] years for Denmark, and 33 [29, 38] for Norway). The proportion of fathers exposed

to valproate was similar in both countries (19.3% in Denmark and 19.8% in Norway). Paternal exposure to medications with teratogenic activity or foetal toxicity prior to LMP2 was 31.0% and 32.1% in Denmark and 29.2% and 28.9% in Norway. Offspring from those exposed fathers were excluded from the comparative, sensitivity ad exploratory analyses. However, they were not excluded from the descriptive analyses, and this could explain the higher cumulative incidence rate of CM in both groups.

Frequency of the outcome of CM

For Denmark, within the Secondary outcome cohort for descriptive analysis, the frequency of CM was 12.5%, major CM was 4.2% while the frequency of minor malformations was 9.2%. For Norway the corresponding numbers were 15.6% for CM, 9.0% for major CM and 8.3% for minor malformations. In Denmark, in the group paternally exposed to valproate, of those offspring for which CM was reported (n=51; 9.3%), the majority had diagnosis of minor CM (6.7%) while 3.5% had a diagnosis of major CM. From 156 (14.1%) offspring with CM in the lamotrigine/levetiracetam paternally exposed group, the majority (10.5%) had a diagnosis of minor CM, while 4.5% had a diagnosis of major CM.I In Norway, in those paternally exposed to valproate, there was a CM report in 107 offspring (16.6%), 9.2% had a diagnosis of a major CM and 9.0% had a minor CM. In the lamotrigine/levetiracetam paternally exposed group, from 209 (15.1%) offspring where a CM was reported, 8.9% had diagnosis of a major CM and 8.0% had a minor CM. It should be noted, however, that major and minor CM categories were not mutually exclusive.

In our study, major malformations were identified by first identifying overall malformations and excluding minor malformations, i.e. non-identification of minor malformations could lead to an overestimation of major malformations. The prevalence of major CM in pregnancies has been estimated at 3.7% of pregnancies among live births (up to 1 year of age) or stillbirths (70), and between 3.9% in 1997 to 5.3% in 2017 in a Danish study (71), and 2.1% in Norway (2006-2007) (72).

Regarding the incidence proportion for the first recorded diagnosis CM with overall study follow-up, the estimate associated with paternal exposure to valproate appeared higher in Norway (16.6% [95% CI: 13.7%,19.5%]) than in Denmark (9.3% [95% CI: 6.9%,11.7%]). Conversely, however, the incidence proportion associated with paternal exposure to lamotrigine or levetiracetam was similar (14.1% [95% CI: 12.1%,16.2%] in Denmark and 15.1 [95% CI: 13.2%,17.2%] in Norway), as was the overall incidence proportion of CM by country (12.5% [95% CI: 10.9%,14.1%] in Denmark and 15.6 [95% CI: 14.0%,17.2%] in Norway). These results may reflect the increasing trends in the detection of and registration of CM in later years, partially explaining the higher overall incidence proportion of CMs by country detected among levetiracetam and lamotrigine-exposed children, as these were exposed on average later in the period of the study. Also, a Danish population-based study found that offspring of fathers exposed to AEDs during the 3 months prior to conception had a higher risk of congenital malformations. Besides, we found that the association was higher for the father exposed to lamotrigine when compared to those exposed to valproic acid. However, more detailed analysis showed that this association was possibly attributed to the underlying indication rather than the effect of AEDs (31).

Risk factors and confounders

No risk factors or confounders were identified for the CM outcome, as none of the variables examined were significantly associated with either the exposure or the outcome in Denmark and Norway.

Some epidemiological studies suggest a relationship between advanced paternal age at conception and CM in offspring (73–75), however this was not shown to be the case in our study. Also, maternal age does not appear to be a risk factor for CM, even if it is supported by several publications (76,77). This might be a result of more frequent testing in older women during early pregnancy for foetal abnormalities, as recommended by some Nordic guidelines (78).

11.5.3 Exploratory analysis discussion

Several exploratory analyses were performed to further investigate the study objectives in specific circumstances (Please see Section 7). Overall, in each country a very low sample size was extracted for each exploratory analysis, specially for the Secondary outcome cohort.

The putative risk factors and frequencies of the outcomes of interest were described in the population of offspring born to fathers exposed to polytherapy of valproate or lamotrigine/levetiracetam and other AEDs, at the time of conception. For this exploratory analysis, 335 (91 in the valproate and 244 in lamotrigine/levetiracetam group) offspring were identified in Denmark, 414 (92 in valproate and 322 in lamotrigine/levetiracetam) in Sweden, and 290 (92 in valproate and 322 in lamotrigine/levetiracetam) in Norway for the Primary outcome cohort. In either monotherapy or polytherapy group, the most common indication for therapy with valproate or lamotrigine/levetiracetam was epilepsy. In Denmark, many of the offspring, maternal, and paternal demographic and clinical characteristics were masked, following the masking rules defined this country, limiting a comparison with the main analyses. As expected the 2 cohorts differed for some characteristics, and consistently across the 3 study countries; a likely consequence of the reduced sample size and the different selected populations. In general, fewer risk factors or confounders were identified in the polytherapy group. As expected, the proportion of NDD, including ASD, was higher in the offspring of fathers exposed to valproate or to lamotrigine/levetiracetam with other AEDs in polytherapy when compared to the main analysis results. However, in Denmark, the cumulative proportion of NDD including ASD was similar in the offspring paternally exposed to valproate polytherapy compared to valproate monotherapy in the main analysis (5.5% vs 5.4%, respectively), though higher in the offspring paternally exposed to lamotrigine/levetiracetam polytherapy compared to lamotrigine/levetiracetam monotherapy. However, the group of fathers in the valproate polytherapy group was very small.

For the analysis of polytherapy in the Secondary outcome cohort (CM), 23 (none in valproate and 23 in lamotrigine/levetiracetam) offspring were identified in Denmark, and 51 (6 in valproate and 45 in lamotrigine/levetiracetam group) in Norway. Due to the small sample size, no conclusion on the putative risk factors or confounders could be drawn.

Risk factors and frequencies of the outcomes of interest were also described in paternal valproate exposure-discordant siblings (at least one offspring with paternal valproate exposure and one offspring without valproate exposure [i.e., at least one offspring with paternal valproate exposure and one offspring exposed to lamotrigine/levetiracetam]). For this analysis, 21 (11 on valproate and 10 on lamotrigine or levetiracetam) offspring were identified in Denmark, 29 (15 on valproate and 14 on lamotrigine or levetiracetam) in Sweden, and 8 (4 on valproate and 4 on lamotrigine or levetiracetam) in Norway for the Primary outcome cohort. Overall, the follow-up length was longer in the valproate group than in the lamotrigine/levetiracetam group. However, no other conclusion could be drawn since none of the

offspring's, father's, or mother's characteristics were considered risk factors or confounders due to the small sample size and lack of observed characteristics, such as maternal and paternal comorbidities.

In the Secondary outcome cohort, no events were observed for Denmark and only one for Norway (in lamotrigine/levetiracetam group), in siblings and their offspring who were paternally and maternally matched exposure-discordant discordant (valproate vs. lamotrigine/levetiracetam monotherapy) at conception. No conclusion could be drawn because most paternal, maternal, and offspring characteristics were not observed due to the small sample size.

12. Other information

None.

13. Conclusions

This comprehensive real-world retrospective study provides the first data on NDD and CM in offspring paternally exposed to valproate during spermatogenesis, compared to those exposed to lamotrigine/levetiracetam. The pooled HR, indicated a moderate risk (HR 1.47, 95% CI: 1.10, 1.96) of NDD including ASD in offspring paternally exposed to valproate compared to those paternally exposed to lamotrigine/levetiracetam.

The pooled risk of congenital malformations suggested no higher risk in offspring paternally exposed to valproate when compared to those exposed to lamotrigine/levetiracetam. Due to the considerable heterogeneity observed, these findings should also be interpreted with caution.

Overall, this retrospective observational study has several limitations, including the difference in follow-up duration between the 2 groups and the different time period of exposure.

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15. Appendix

15.1 Denmark

15.1.1.1 Description of the offspring, maternal and paternal characteristics in the Primary outcome cohort

Characteristics of the offspring, mothers and fathers from the Primary outcome cohort are reported in Table 130-Table 132. Among the 5034 offspring from the Primary outcome cohort, 51.9% were male, 1.4% were diagnosed with epilepsy, and 1.1% were treated with AEDs drugs during the follow-up period (Table 130). Please note that all these offspring were excluded from the comparative analyses, therefore distribution of these characteristics might differ in those analyses (see Figure 9).

Regarding maternal characteristics of this group, the median interquartile range (IQR) age of mothers at childbirth was 30 (27, 34) years. The most frequent maternal comorbidities diagnosed prior to childbirth were neurotic disorders (7.4%), gestational diabetes (4.6%), and affective disorder (4.1%) (Table 131).

Data on smoking prior to LMP2 was missing for 95.5% of mothers.

From a total of 5034 mothers in the Primary outcome cohort, maternal smoking during pregnancy was recorded for 17.6% mothers.

Exposure to AEDs prior to LMP2 and during pregnancy was very low, and the proportion of use of each AED was lower than 2%. These mothers were excluded from the comparative analysis. 44.9% of mothers had at least one prescription of concomitant medications associated with neuropsychiatric adverse events during pregnancy, while prior to LMP2 this percentage was 72.3% (Table 131).

Regarding paternal characteristics of this group, the median (IQR) age of fathers at childbirth was 33 (30, 37) years. The most frequent paternal comorbidities diagnosed prior to childbirth were neurotic disorder (11.6%), affective disorder excluding bipolar affective disorder and mania (7.6%), and bipolar affective disorder (3.1%). With regards to paternal exposure to AEDs, 16.5% of fathers were exposed to valproate in monotherapy, and 23.8% were exposed to lamotrigine/levetiracetam in monotherapy in the 3 months lookback period from LMP2, the remaining ones were exposed to other AEDs. Only 1.0% of conceptions occurred in 2018; this small proportion is due to study period ending in December 2018, which resulted in the inclusion only of those conceptions that occurred in the first months of the year and which resulted in a childbirth in the same year (Table 132).

Table 130 Description of the offspring characteristics in the Primary outcome cohort in Denmark (N=5034)

Neurodevelopmental disorders (NDD) - offspring characteristics		
Number of offspring=5034	N	%
Gestational age (weeks)		
<28 (extremely preterm)	11	0.22

Neurodevelopmental disorders (NDD) - offspring characteristics		
Number of offspring=5034	N	%
28-31 (very preterm)	32	0.64
32-36 (moderate to late preterm)	224	4.45
37-41 (at term)	4509	89.57
≥42 (post-term)	258	5.13
Missing	0	0.00
Birth weight (g)		
<1000 (extremely low)	10	0.20
1000-1499 (very low)	23	0.46
1500-2499 (low)	153	3.04
≥2500	4823	95.81
Missing	25	0.50
Gender [a]		
Male	2613	51.91
Female	2421	48.09
Missing	0	0.00
Comorbidities [b]		
Congenital CMV*	0	0.00
Congenital rubella	0	0.00
Epilepsy	70	1.39
Foetal alcohol syndrome	6	0.12
Fragile X syndrome	0	0.00
Lejeune/cri du chat syndrome	0	0.00
Tuberous sclerosis	***	***
Medication use [b]		
Exposure to AEDs**	53	1.05

*CMV: cytomegalovirus; **AED: antiepileptic drug; g: grams; NDD: neurodevelopmental disorders
*** Masked values indicated that data was calculated but not disclosed due to small number of participants
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics are described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index (childbirth); b) between index and exit date.

Table 131 Description of the maternal characteristics in the Primary outcome cohort in Denmark (N=5034)

Neurodevelopmental disorders (NDD) - maternal characteristics		
Number of offspring=5034	N	%
Mother's age [a]		
≤20 years	90	1.79
21-25	707	14.04
26-30	1725	34.27
31-35	1645	32.68
36-40	738	14.66
>40	129	2.56
Mean (SD)	30.59 (5.00)	
Median (25^{th}-75^{th} percentile)	30.00(27.00, 34.00)	

Neurodevelopmental disorders (NDD) - maternal characteristics		
Number of offspring=5034	N	%
Min, max	***	
Missing	0	0.00
Comorbidities		
Affective disorder [b]	206	4.09
Diabetes [b]	96	1.91
Epilepsy [b]	85	1.69
Neurotic disorder [b]	370	7.35
Schizophrenia, schizotypal and delusional disorders [b]	31	0.62
Obesity [c]	82	1.63
CMV [d]	0	0.00
Gestational diabetes [d]	229	4.55
Rubella [d]	0	0.00
Lifestyle characteristics		
Alcohol abuse prior to LMP2 [c]	15	0.30
Alcohol abuse during pregnancy [d]	10	0.20
Substance abuse prior to LMP2 [c]	5	0.10
Substance abuse during pregnancy [d]	25	0.50
Smoking prior to LMP2 [c]		
Yes	57	1.13
No	171	3.40
Missing	4806	95.47
Smoking during pregnancy [d]		
Yes	884	17.56
No	3874	76.96
Missing	276	5.48
Medication use		
Exposure to AEDs prior to LMP2 [e,f]		
Valproic Acid	9	0.18
Lamotrigine	34	0.68
Levetiracetam	***	***
Barbiturates and derivatives	***	***
Hydantoin derivatives	0	0.00
Oxazolidine derivatives	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	14	0.28
Carboxamide derivatives	13	0.26
Fatty acid derivatives	11	0.22

Neurodevelopmental disorders (NDD) - maternal characteristics		
Number of offspring=5034	**N**	**%**
Other antiepileptics	56	1.11
Exposure to AEDs during pregnancy [d,f]		
Valproic Acid	8	0.16
Lamotrigine	34	0.68
Levetiracetam	***	***
Barbiturates and derivatives	***	***
Hydantoin derivatives	0	0.00
Oxazolidine derivatives	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	19	0.38
Carboxamide derivatives	13	0.26
Fatty acid derivatives	10	0.20
Other antiepileptics	51	1.01
Maternal polypharmacy index prior to LMP2[e]		
0	3128	62.14
1-4	1847	36.69
5-10	***	***
>10	***	***
Mean (SD)	0.66 (1.11)	
Median (25^{th} - 75^{th} percentile)	0.00(0.00, 1.00)	
Min, max	***	
Maternal polypharmacy index during pregnancy [d]		
0	2415	47.97
1-4	2526	50.18
5-10	***	***
>10	***	***
Mean (SD)	0.95 (1.26)	
Median (25^{th} - 75^{th} percentile)	1.00(0.00, 1.00)	
Min, max	***	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [c] - mothers with at least one prescription	455	9.04
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least 1 prescription	265	5.26

Neurodevelopmental disorders (NDD) - maternal characteristics		
Number of offspring=5034	N	%
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [c] -mothers with at least one prescription	3641	72.33
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [d] mothers with at least one prescription	2259	44.87

AED: antiepileptic drug; CMV: cytomegalovirus; LMP2: last menstrual period + 2 weeks; Min: Minimum; Max: Maximum; NDD: neurodevelopmental disorders; SD: standard deviation
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics are described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index (childbirth); b) all available data prior to index date; c) 12 months lookback from LMP2; d) during pregnancy (from LMP2 until index date); e) 3 months lookback from LMP2; f) Oxazolidine derivatives were not marketed in Denmark.

Table 132 Description of the paternal characteristics in the Primary outcome cohort in Denmark (N=5034).

Neurodevelopmental disorders (NDD) - paternal characteristics		
Number of offspring=5034	N	%
Father's age [a]		
≤20 years	21	0.42
21-25	312	6.20
26-30	1236	24.55
31-35	1728	34.33
36-40	1099	21.83
>40	638	12.67
Mean (SD)	33.68 (6.03)	
Median (25th - 75th percentile)	33.00(30.00, 37.00)	
Min, max	***	
Missing	0	0.00
Year of offspring conception [b]		
1996	108	2.15
1997	130	2.58
1998	161	3.20
1999	149	2.96
2000	196	3.89
2001	195	3.87
2002	227	4.51
2003	245	4.87
2004	241	4.79
2005	266	5.28
2006	244	4.85
2007	277	5.50

Neurodevelopmental disorders (NDD) - paternal characteristics		
Number of offspring=5034	N	%
2008	256	5.09
2009	256	5.09
2010	252	5.01
2011	249	4.95
2012	280	5.56
2013	280	5.56
2014	294	5.84
2015	276	5.48
2016	250	4.97
2017	154	3.06
2018	48	0.95
Comorbidities [c]		
Affective disorder excluding bipolar affective disorder and mania	384	7.63
Bipolar affective disorder	158	3.14
Mania	20	0.40
Neurotic disorder	582	11.56
Schizophrenia, schizotypal and delusional disorders	192	3.81
Lifestyle characteristics		
Substance abuse [e]	25	0.50
Medication use		
Exposure to AEDs [f]		
Valproic Acid [g]	1084	21.53
Lamotrigine [g]	1406	27.93
Levetiracetam [g]	268	5.32
Barbiturates and derivatives [g]	124	2.46
Hydantoin derivatives [g]	41	0.81
Oxazolidine derivatives [d,g]	0	0.00
Succinimide derivatives [g]	23	0.46
Benzodiazepine derivatives [g]	304	6.04
Carboxamide derivatives [g]	1386	27.53
Fatty acid derivatives [g]	1127	22.39
Other antiepileptics [g]	2577	51.19
Valproic acid in monotherapy	832	16.53
Lamotrigine in monotherapy	1084	21.53
Levetiracetam in monotherapy	115	2.28
Lamotrigine/levetiracetam in monotherapy	1199	23.82
Paternal polypharmacy index [f]		
0	2674	53.12
1-4	2163	42.97

Neurodevelopmental disorders (NDD) - paternal characteristics		
Number of offspring=5034	N	%
5-10	***	***
>10	***	***
Mean (SD)	1.00 (1.52)	
Median (25th - 75th percentile)	0.00(0.00, 1.00)	
Min, max	***	
Concomitant medications associated with valproate-indicated psychiatric conditions [e] - fathers with at least one prescription	2098	41.68
Concomitant medications associated with neuropsychiatric adverse events [e] - fathers with at least one prescription	3107	61.72
Fathers exposed to AEDs polytherapy prior to LMP2 [f]	652	12.95
Fathers exposed to valproate in combination with other AEDs prior to LMP2 [f]	239	4.75
Fathers switching to/from an AED other than valproate, lamotrigine, levetiracetam prior to LMP2 [f]	323	6.42

AED: antiepileptic drug; LMP2: last menstrual period + 2 weeks; NDD: neurodevelopmental disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum

*** Masked values indicated that data was calculated but not disclosed due to small number of participants.

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics are described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.

a) at index (childbirth); b) at mother's LMP2; c) all available data prior to index date; d) Oxazolidine derivatives were not marketed in Denmark; e) 12 months lookback from LMP2; f) 3 months lookback from LMP2; g) in mono- or polytherapy.

15.1.1.2 Description of the offspring, maternal and paternal characteristics in the Secondary outcome cohort

Characteristics of the offspring, mothers and fathers from the Secondary outcome cohort are reported from Table 133 to Table 135.

Among the 3777 offspring in the Secondary outcome cohort, 51.8% were male, 90.4%, were born at term, 95.5% were weighing ≥2500 g. Most of the comorbidities were present in <5 offspring (masked values) (Table 133).

Regarding maternal characteristics of mothers from the Secondary outcome cohort, the median (IQR) age of mothers at childbirth was 30 (27, 34) years. The most frequent maternal comorbidities prior to childbirth were gestational diabetes (4.7%) and obesity (2.1%). Data on smoking 12 months prior to LMP2 was missing in 95.1% of cases. From a total of 3777 mothers in the Secondary outcome cohort, maternal smoking during pregnancy was reported for 17.1% mothers.

Exposure to other antiepileptics 3 months prior to LMP2 and during pregnancy was observed among 1.4% and 1.3% of mothers, respectively (Table 134).

Regarding characteristics of fathers from the Secondary outcome cohort, the median (IQR) age of fathers at childbirth was 33 (29, 37) years. With regards to exposure to any AEDs,14.5% of fathers were exposed to valproate in monotherapy and 29.3% were exposed to lamotrigine/levetiracetam in monotherapy in the 3 months prior to LMP2, while the remaining patients were exposed to other antiepileptics. Considering the Secondary outcome cohort for descriptive analyses, 63.9% of fathers were exposed to teratogenic activity/foetal toxicity prior to LMP2 (Table 135).

Table 133 Description of the offspring characteristics for the Secondary outcome cohort for descriptive analyses in Denmark (N=3777)

CM - offspring characteristics		
Number of offspring=3777		
	N	%
Gestational age (weeks)		
<28 (extremely preterm)	13	0.34
28-31 (very preterm)	27	0.71
32-36 (moderate to late preterm)	161	4.26
37-41 (at term)	3414	90.39
≥42 (post-term)	162	4.29
Missing	0	0.00
Birth weight (g)		
<1000 (extremely low)	6	0.16
1000-1499 (very low)	17	0.45
1500-2499 (low)	113	2.99
≥2500	3606	95.47
Missing	35	0.93
Gender		
Male	1958	51.84

CM - offspring characteristics		
Number of offspring=3777		
	N	%
Female	1819	48.16
Missing	0	0.00
Comorbidities [a]		
Congenital CMV	0	0.0
Congenital Herpes Simplex	***	***
Congenital rubella	0	0.0
Congenital toxoplasmosis	***	***
Congenital varicella	***	***
Foetal alcohol syndrome	***	***

CM: congenital malformations; CMV: cytomegalovirus
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between 22nd week of gestation in Denmark and exit date.

Table 134 Description of the maternal characteristics for the Secondary outcome cohort for descriptive analyses in Denmark (N=3777)

CM - maternal characteristics		
Number of offspring=3777		
	N	%
Mother's age at index date [a]		
≤20 years	75	1.99
21-25	559	14.80
26-30	1263	33.44
31-35	1244	32.94
36-40	545	14.43
>40	91	2.41
Mean (SD)	30.48 (5.04)	
Median (25th - 75th percentile)	30.00 (27.00, 34.00)	
Min, max	***	
Missing	0	0.00
Comorbidities		
Diabetes [b]	53	1.40
Epilepsy [b]	68	1.80
Obesity [c]	78	2.07
CMV [d]	0	0.00
Folate deficiency [d]	0	0.00
Gestational diabetes [d]	176	4.66
Herpes simplex virus [d]	***	***
Rubella [d]	0	0.00
Toxoplasmosis [d]	***	***
Varicella [d]	***	***
Lifestyle characteristics		
Alcohol abuse prior to LMP2 [c]	***	***
Alcohol abuse during pregnancy [d]	15	0.40
Substance abuse prior to LMP2 [c]	***	***
Substance abuse during pregnancy [d]	16	0.42
Smoking prior to LMP2 [c]		

CM - maternal characteristics		
Number of offspring=3777		
	N	%
Yes	45	1.19
No	142	3.76
Missing	3590	95.05
Smoking during pregnancy [d]		
Yes	644	17.05
No	3067	81.20
Missing	66	1.75
Medication use		
Exposure to AEDs prior to LMP2 [e]		
Valproic Acid	6	0.16
Lamotrigine	31	0.82
Levetiracetam	***	***
Barbiturates and derivatives	0	0.00
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [f]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	11	0.29
Carboxamide derivatives	9	0.24
Fatty acid derivatives	6	0.16
Other antiepileptics	53	1.40
Exposure to AEDs during pregnancy [d]		
Valproic Acid	6	0.16
Lamotrigine	31	0.82
Levetiracetam	***	***
Barbiturates and derivatives	0	0.00
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [f]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	15	0.40
Carboxamide derivatives	8	0.21
Fatty acid derivatives	6	0.16
Other antiepileptics	48	1.27
Maternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [e] - mothers with at least one prescription	1171	31.00
Maternal exposure to teratogenic activity/foetal toxicity during pregnancy [d] - mothers with at least one prescription	1214	32.14

AED: antiepileptic drug; CM: congenital malformations; CMV: cytomegalovirus; LMP2: last menstrual period + 2 weeks
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
SD: standard deviation
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics are described in relation to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index 22nd week of gestation in Denmark b) all available data prior to index date; c) 12 months lookback from LMP2; d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy); e) 3 months lookback from LMP2; f) Oxazolidine derivatives were not marketed in Denmark.

Table 135 Description of the paternal characteristics for the Secondary outcome cohort for descriptive analyses in Denmark (N=3777)

CM - paternal characteristics

Number of offspring=3777	N	%
Father's age [a]		
≤20 years	21	0.56
21-25	244	6.46
26-30	919	24.33
31-35	1274	33.73
36-40	835	22.11
>40	484	12.81
Mean (SD)	33.68 (6.05)	
Median (25th - 75th percentile)	33.00(29.00, 37.00)	
Min, max	***	
Missing	0	0.00
Year of child conception [b]		
2003	157	4.16
2004	244	6.46
2005	265	7.02
2006	243	6.43
2007	276	7.31
2008	256	6.78
2009	255	6.75
2010	253	6.70
2011	244	6.46
2012	279	7.39
2013	281	7.44
2014	295	7.81
2015	278	7.36
2016	250	6.62
2017	154	4.08
2018	47	1.24
Medication use		
Exposure to AEDs		
Valproic Acid [d]	729	19.30
Lamotrigine [d]	1235	32.70
Levetiracetam [d]	255	6.75
Barbiturates and derivatives [d]	55	1.46
Hydantoin derivatives [d]	12	0.32
Oxazolidine derivatives [d,e]	0	0.00
Succinimide derivatives [d]	8	0.21
Benzodiazepine derivatives [d]	213	5.64
Carboxamide derivatives [d]	762	20.17
Fatty acid derivatives [d]	739	19.57
Other antiepileptics [d]	2351	62.25
Valproic acid in monotherapy	549	14.54
Lamotrigine in monotherapy	995	26.34
Levetiracetam in monotherapy	111	2.94
Lamotrigine/levetiracetam in monotherapy	1106	29.28
Fathers exposed to AEDs polytherapy prior to LMP2[c]	468	12.39
Fathers exposed to valproate in combination with other AEDs prior to LMP2 [c]	171	4.53
Fathers switching to/from an AED other than valproate, lamotrigine, levetiracetam prior to LMP2 [c]	250	6.62
Paternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [c,f]	2412	63.86

CM - paternal characteristics		
Number of offspring=3777		
	N	%

AED: antiepileptic drug; CM: congenital malformations; LMP2: last menstrual period + 2 weeks; SD: standard deviation
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. Accordingly, their characteristics were described in relation to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index 22nd week of gestation in Denmark b) at mother's LMP2; c) 3 months lookback from LMP2; d) in mono- or polytherapy; e) Oxazolidine derivatives were not marketed in Denmark; f) Please note, that the list of teratogens include 'All other AEDs'.

15.1.2 Cumulative incidence proportion of NDD by gender

Table 136 Cumulative incidence proportion (risk) of NDD by paternal exposure group for male offspring; Primary outcome cohort for descriptive analyses (N=1061)

		Paternal exposure group				
		Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
0-1 years	N	434	627	565	62	1061
	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
1-2 years	N	***	593	536	57	***
	n	***	0	0	0	***
	n/N*100	***	0.00(0.00,0.00)	0.00(0.00,0.00)	0.00(0.00,0.00)	***
2-3 years	N	417	544	500	44	961
	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
3-4 years	N	402	488	452	36	890
	n	***	***	***	0	7
	n/N*100	***	***	***	0.00(0.00,0.00)	0.79 (0.21, 1.37)
4-5 years	N	376	432	404	28	808
	n	***	***	***	0	6
	n/N*100	***	***	***	0.00(0.00,0.00)	0.74 (0.15, 1.33)
5-6 years	N	357	378	358	20	735
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
6-7 years	N	338	327	***	***	665
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
7-8 years	N	318	288	***	***	606
	n	***	***	***	***	***

		Paternal exposure group				
		Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	n/N*100	***	***	***	***	***
8-9 years	N	305	242	***	***	547
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
9-10 years	N	274	202	192	10	476
	n	5	***	***	***	***
	n/N*100	1.82 (0.24, 3.41)	***	***	***	***
10-11 years	N	241	165	***	***	406
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
11-12 years	N	219	133	***	***	352
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
Overall (0-12 years)	**N**	434	627	565	62	1061
	n	34	31	***	***	65
	n/N*100	7.83 (5.31, 10.36)	4.94 (3.25, 6.64)	***	***	6.13 (4.68, 7.57)

NDD: neurodevelopmental disorders
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) are presented.

Table 137 Cumulative incidence proportion (risk) of NDD by paternal exposure group for female offspring; Primary outcome cohort for descriptive analyses (N=970)

		Paternal exposure group				
		Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period	N	398	572	519	53	970

		Paternal exposure group				
		Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
0-1 years	n	0	***	***	***	***
	n/N*100	0.00(0.00,0.00)	***	***	***	***
1-2 years	N	***	535	491	44	***
	n	***	0	0	0	***
	n/N*100	***	0.00(0.00,0.00)	0.00(0.00,0.00)	0.00(0.00,0.00)	***
2-3 years	N	379	505	467	38	884
	n	***	0	0	0	***
	n/N*100	***	0.00(0.00,0.00)	0.00(0.00,0.00)	0.00(0.00,0.00)	***
3-4 years	N	364	455	425	30	819
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
4-5 years	N	347	403	378	25	750
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
5-6 years	N	328	352	332	20	680
	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
6-7 years	N	314	300	***	***	614
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
7-8 years	N	294	251	***	***	545
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
8-9 years	N	273	209	***	***	482
	n	***	***	***	0	***

		Paternal exposure group				
		Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	n/N*100	***	***	***	0.00(0.00,0.00)	***
9-10 years	N	255	172	164	8	427
	n	0	***	***	0	***
	n/N*100	0.00(0.00,0.00)	***	***	0.00(0.00,0.00)	***
10-11 years	N	240	138	***	***	378
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
11-12 years	N	222	108	***	***	330
	n	***	***	***	0	***
	n/N*100	***	***	***	0.00(0.00,0.00)	***
Overall (0-12 years)	**N**	398	572	519	53	970
	n	21	13	***	***	34
	n/N*100	5.28 (3.08, 7.47)	2.27 (1.05, 3.49)	***	***	3.51 (2.35, 4.66)

NDD: neurodevelopmental disorders
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) are presented.

15.1.3 Cumulative incidence rate and time to NDD diagnosis by gender

Table 138 Cumulative incidence rate of NDD by paternal exposure group for males; Primary outcome cohort for descriptive analysis (N=1036)

	Paternal exposure group				
	Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**

		Paternal exposure group				
		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Follow-up period						
0-1 years	PY	433.20	608.75	549.26	59.49	1041.95
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-2 years	PY	857.88	1180.67	1070.98	109.69	2038.55
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-3 years	PY	1267.28	1698.26	1548.10	150.16	2965.54
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-4 years	PY	1655.78	2158.68	1977.46	181.22	3814.46
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-5 years	PY	2021.19	2562.46	2357.86	204.60	4583.65
	n	***	11	***	***	***
	n/PY*1000	***	4.29 (2.14, 7.68)	***	***	***
0-6 years	PY	2367.51	2914.19	2691.29	222.90	5281.70
	n	12	***	***	***	***
	n/PY*1000	5.07(2.62, 8.85)	***	***	***	***
0-7 years	PY	2693.04	3218.00	2980.77	237.23	5911.04
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-8 years	PY	3006.90	3483.42	3233.32	250.10	6490.32
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	3293.10	3705.85	3444.82	261.04	6998.96

		Paternal exposure group				
		Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
0-9 years	n	25	***	***	***	***
	n/PY*1000	7.59 (4.91, 11.21)	***	***	***	***
0-10 years	PY	3548.20	3891.05	3620.93	270.13	7439.25
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-11 years	PY	3775.72	4040.15	3765.54	274.61	7815.87
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-12 years	**PY**	3982.07	4158.06	3880.45	277.61	8140.13
	n	34	31	***	***	65
	n/PY*1000	8.54 (5.91, 11.93)	7.46 (5.07, 10.58)	***	***	7.99 (6.16, 10.18)

PY: person-year; NDD: neurodevelopmental disorders
*** Masked values indicated that data was calculated but not disclosed
Legend: Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) are presented.

Table 139 Cumulative incidence rate of NDD by paternal exposure group for females; Primary outcome cohort for descriptive analyses (N=937)

Paternal exposure group						
		Valproate	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
0-1 years	PY	394.95	551.09	503.64	47.45	946.04
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-2 years	PY	780.41	1068.26	980.13	88.13	1848.67
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***

Paternal exposure group		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
0-3 years	PY	1152.18	1548.02	1426.81	121.21	2700.2
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-4 years	PY	1507.38	1979.22	1830.56	148.66	3486.6
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-5 years	PY	1844.86	2355.92	2185.35	170.57	4200.78
	n	7	5	***	***	12
	n/PY*1000	3.79 (1.53, 7.82)	2.12 (0.69, 4.95)	***	***	2.86 (1.48, 4.99)
0-6 years	PY	2167.21	2681.09	2493.05	188.04	4848.3
	n	7	***	***	***	***
	n/PY*1000	3.23 (1.30, 6.65)	***	***	***	***
0-7 years	PY	2471.04	2960.27	2757.66	202.61	5431.3
	n	***	***	***	***	20
	n/PY*1000	***	***	***	***	3.68 (2.25, 5.69)
0-8 years	PY	2756.67	3189.51	2975.19	214.32	5946.18
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-9 years	PY	3021.93	3381.43	3158.61	222.82	6403.35
	n	15	***	***	***	25
	n/PY*1000	4.96 (2.78, 8.19)	***	***	***	3.9 (2.53, 5.76)
0-10 years	PY	3270.71	3535.27	3305.8	229.48	6805.99
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-11 years	PY	3499.58	3657.06	3423.98	233.08	7156.64
	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
0-12 years	**PY**	3709.57	3756.02	3521.88	234.14	7465.59
	n	21	13	***	***	34
	n/PY*1000	5.66 (3.50, 8.65)	3.46 (1.84, 5.92)	***	***	4.55 (3.15, 6.36)

Paternal exposure group	Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)

PY: person-year; NDD: neurodevelopmental disorders
*** Masked values indicated that data was calculated but not disclosed
Legend: Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) are presented.

Table 140 Time to NDD by paternal exposure group stratified by offspring gender

Paternal exposure group NDD	Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Male offspring					
Number of events	34	31	***	***	65
Number of censor	400	596	***	***	996
Survival time					
5th percentile	97.90(57.50, -)	92.53(61.33, -)	92.53(61.33, -)	87.53(34.00, -)	97.27(63.80, 126.67)
10th percentile	135.00(104.23, -)	142.57(103.23, -)	145.77(103.93, -)	120.27(87.53, -)	142.57(110.37, -)
25th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
Female offspring					
Number of events	21	13	***	***	34
Number of censor	377	559	***	***	936
Survival time					
5th percentile	122.33(76.50, -)	141.97(105.50, -)	141.97(105.50, -)	127.20(91.90, -)	-(-,-)
10th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
25th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)

NDD: neurodevelopmental disorders
*** Masked values indicated that data was calculated but not disclosed

Legend: some attrition figures below the curve are not provided for data privacy reasons. Due to low number of events the median time-to-event could not be calculated. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event

15.1.4 Variable estimates from propensity score

Table 141. Variable importance metric from random forest propensity score model; Primary outcome cohort in Denmark

NDD	Variable importance
Variable (or interaction)[a]	
Offspring risk factors/confounders	
Gender [b]	-0.02
Foetal alcohol syndrome [c]	0.00
Maternal risk factors/confounders	
Mother's age [b] (categorical)	-0.03
Affective disorder [d]	0.00
Diabetes [d]	0.00
Gestational diabetes [e]	0.00
Neurotic disorder [d]	0.00
Schizophrenia, schizotypal and delusional disorders [d]	0.00
Obesity [f]	0.00
Alcohol abuse prior to LMP2 [f]	0.00
Alcohol abuse during pregnancy [e]	0.00
Substance abuse prior to LMP2 [f]	0.00
Substance abuse during pregnancy [e]	0.00
Smoking during pregnancy [e]	0.00
Maternal polypharmacy index prior to LMP2 [h] (categorical)	0.00
Maternal polypharmacy index during pregnancy [e] (categorical)	-0.01

NDD	Variable importance
Variable (or interaction)[a]	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.00
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.00
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] -mothers with at least one prescription	0.00
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.00
Paternal risk factors/confounders	
Affective disorder [d,g]	0.01
Bipolar affective disorder [d]	0.00
Mania [d]	0.00
Neurotic disorder [d]	0.00
Schizophrenia, schizotypal and delusional disorders [d]	0.00
Substance abuse [f]	0.00
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with atleast one prescription	-0.01
Year of offspring conception [i]	0.06

NDD	Variable importance
Variable (or interaction)[a]	

NDD: neurodevelopmental disorders; LMP2: Last Menstrual Period Date Plus 2 weeks

Legend: Importance metric is represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.

a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. All two-way interactions were considered.

b) at index (childbirth)

c) between index and exit date

d) all available data prior to index date

e) during pregnancy (from LMP2 until index date)

f) 12 months lookback from LMP2

g) excluding bipolar affective disorder and mania

h) 3 months lookback from LMP2

i) at mother's LMP2

Table 142. Variable estimates from logistic regression informed by random forest propensity score model; Primary outcome cohort in Denmark

NDD	Estimate		
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
Offspring risk factors/confounders			
Gender [b]			
Male	Reference	-	-
Female	1.05	0.86 - 1.29	0.6131
Maternal risk factors/confounders			
Mother's age [b] (categorical)			
≤20 years	0.67	0.28 - 1.64	0.3823
21-25	1.19	0.87 - 1.62	0.2710
26-30	Reference	-	-
31-35	1.03	0.81 - 1.31	0.8218
36-40	0.90	0.64 - 1.27	0.5508
>40	0.48	0.20 - 1.18	0.1114
Paternal risk factors/confounders			

Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with atleast one prescription	0.78	0.64 - 0.96	0.0182
Year of offspring conception [i,j]			
1996-2001	Reference	-	-
2002-2007	0.31	0.22 - 0.44	<.0001
2008-2012	0.11	0.08 - 0.15	<.0001
2013-2018	0.06	0.04 - 0.09	<.0001

Legend: NDD: neurodevelopmental disorders, Odds ratios (OR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.
a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.
b) at index (childbirth)
c) between index and exit date
d) all available data prior to index date
f) 12 months lookback from LMP2 (Last Menstrual Period Date Plus 2 weeks)
g) excluding bipolar affective disorder and mania
h) 3 months lookback from LMP2
i) at mother's LMP2
j) calendar years were grouped in each country according to the length of the study period

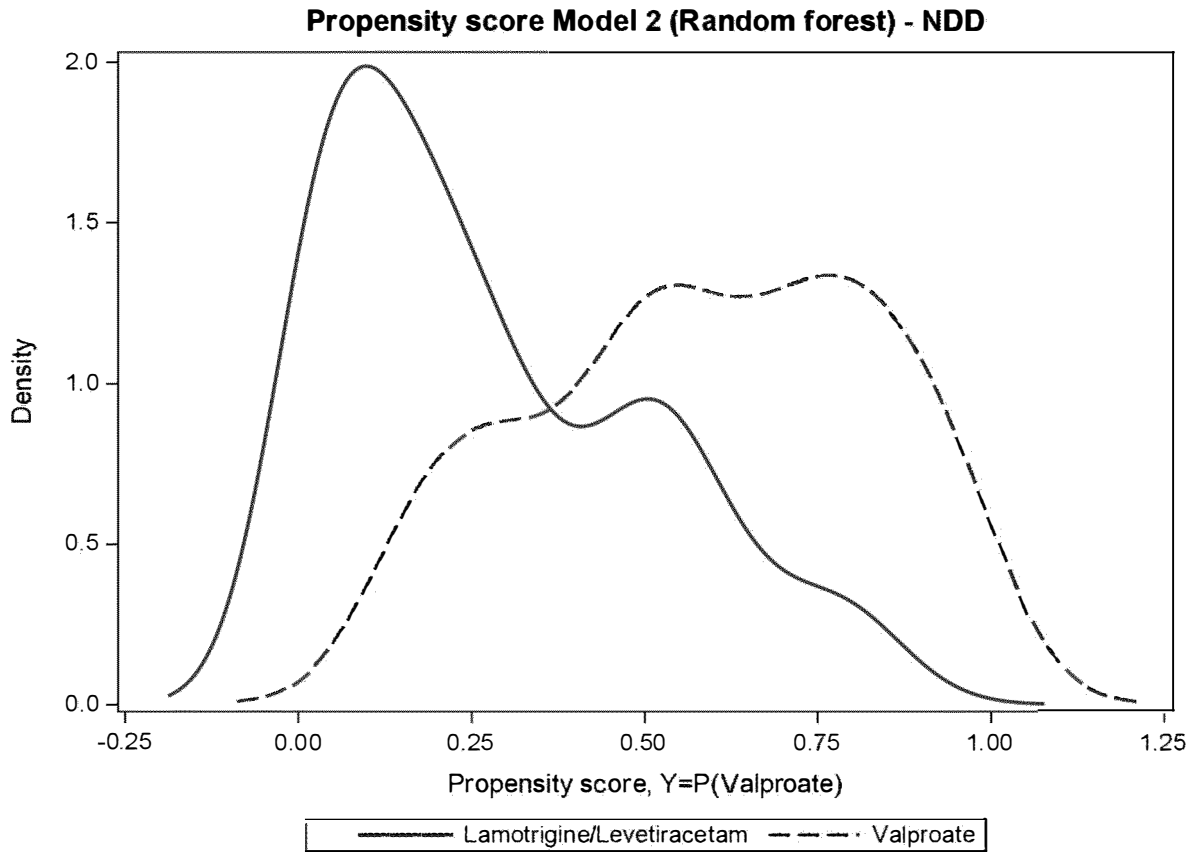
Table 143: Balance of risk factors/confounders after PS weighting (PS scores obtained using logistic regression); primary outcome

NDD	Absolute standardized difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0,00	Yes	0,97	Yes
Congenital CMV [d]	-	- **	-	- ***
Congenital rubella [d]	-	- **	-	- ***
Foetal alcohol syndrome [d]	-	- **	-	- ***
Fragile X syndrome [d]	-	- **	-	- ***
Lejeune/cri du chat syndrome [d]	-	- **	-	- ***
Tuberous sclerosis [d]	-	- **	-	- ***
Maternal risk factors/confounders				
Mother's age [c] (categorical)	0.00*	Yes	0,91	Yes
Affective disorder [e]	0,11	No	0,48	Yes

Diabetes [e]	0,11	No	0,29	Yes
Gestational diabetes [f]	0,06	Yes	0,66	Yes
Neurotic disorder [e]	0,08	Yes	0,71	Yes
Schizophrenia, schizotypal and delusional disorders [e]	0,09	Yes	-	- ***
Obesity [g]	0,05	Yes	0,59	Yes
CMV [g]	-	- **	-	- ***
Rubella [g]	-	- **	-	- ***
Alcohol abuse prior to LMP2 [g]	0,05	Yes	-	- ***
Alcohol abuse during pregnancy [f]	-	- **	-	- ***
Substance abuse prior to LMP2 [g]	0,05	Yes	-	- ***
Substance abuse during pregnancy [f]	0,00	Yes	1,00	Yes
Smoking prior to LMP2 [g]	0,43	No	0,61	Yes
Smoking during pregnancy [f]	0,06	Yes	0,86	Yes
Maternal polypharmacy index prior to LMP2 [i] (categorical)	0.00*	Yes	0,88	Yes
Maternal polypharmacy index during pregnancy [f] (categorical)	0.00*	Yes	0,90	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g] - mothers with at least one prescription	0,07	Yes	0,73	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f] - mothers with at least one prescription	0,11	No	0,52	Yes
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [g] -mothers with at least one prescription	0,01	Yes	0,97	Yes
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [f] -mothers with at least one prescription	0,01	Yes	0,96	Yes
Paternal risk factors/confounders				
Affective disorder [e,h]	0,05	Yes	0,84	Yes
Bipolar affective disorder [e]	0,07	Yes	0,67	Yes
Mania [e]	0,05	Yes	0,40	Yes

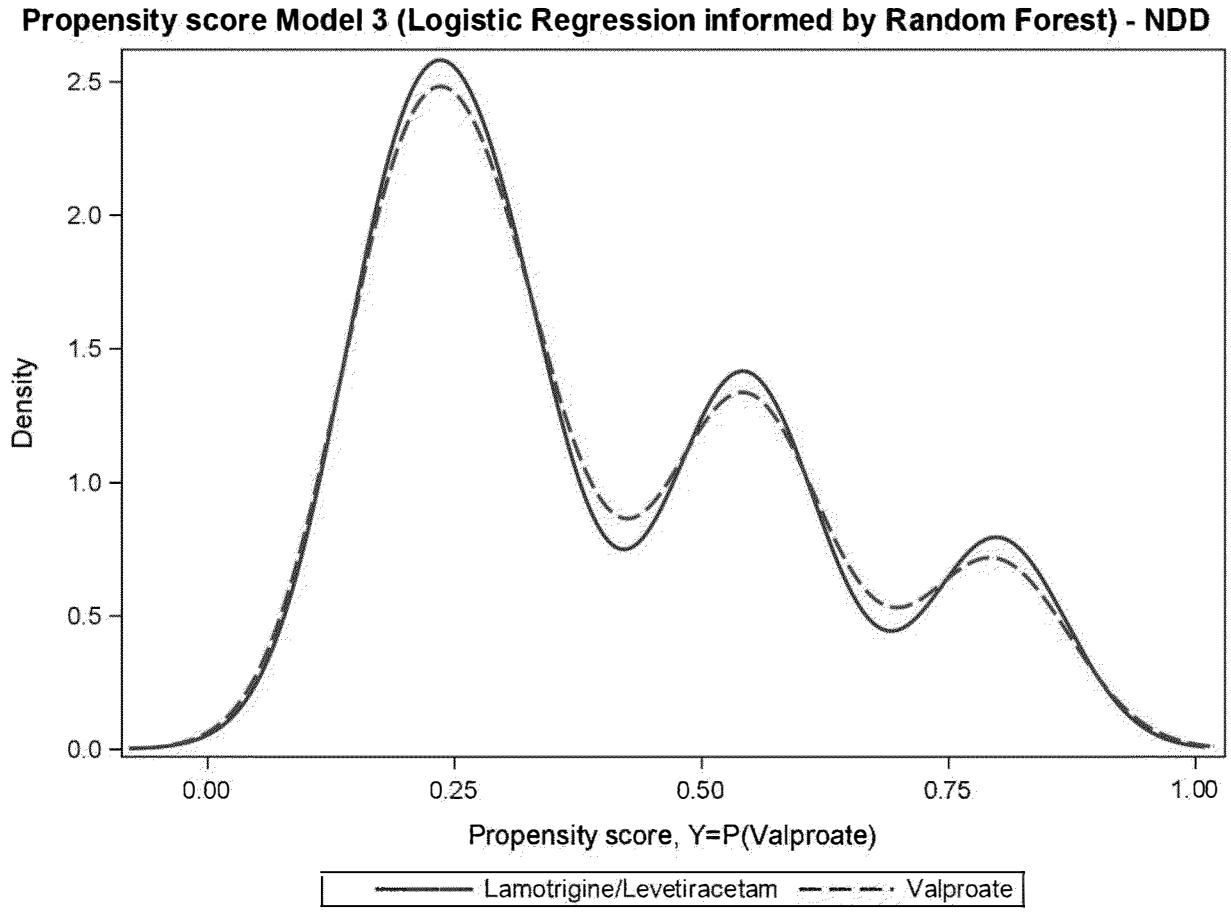
Neurotic disorder [e]	0,04	Yes	1,09	Yes
Schizophrenia, schizotypal and delusional disorders [e]	0,06	Yes	0,55	Yes
Substance abuse [g]	0,07	Yes	-	- ***
Paternal polypharmacy index [i] (categorical)	0.01*	Yes	0,90	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] - fathers with at least one prescription	0,29	No	0,62	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] - fathers with atleast one prescription	0,01	Yes	0,97	Yes
Father's age [c] (categorical)	0.00*	Yes	0,82	Yes
Year of offspring conception [j]	0.00*	Yes	0,92	Yes

a) absolute standardized difference below 0.1
b) variance ratio between 0 and 2
c) at index (childbirth)
d) between index and exit date
e) all available data prior to index date
f) during pregnancy (from LMP2 until index date)
g) 12 months lookback from LMP2
h) excluding bipolar affective disorder and mania
i) 3 months lookback from LMP2
j) at mother's LMP2
* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardized difference is not calculated if a binary variable has only 1 category level in the weighted patient data.
*** The variance ratio is not calculated if a variable has only 1 category level in one of valproate and comparator groups (the denominator of the variance ratio is 0).



NDD: neurodevelopmental disorders

Figure 27.Balance of Model 2 Random Forest Primary outcome cohort in Denmark



NDD: neurodevelopmental disorders

Figure 28 Balance of Model 3 Logistic Regression informed by Random Forest Primary outcome cohort in Denmark

Table 144: Balance of risk factors/confounders between offspring weighted using PS scores obtained with logistic regression; secondary outcome

CM	Absolute standardized difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Congenital CMV [c]	-	-**	-	-***
Congenital Herpes Simplex [c]	-	-**	-	-***
Congenital rubella [c]	-	-**	-	-***
Congenital toxoplasmosis [c]	-	-**	-	-***

Congenital varicella [c]	-	- **	-	- ***
Foetal alcohol syndrome [c]	0,08	Yes	-	- ***
Maternal risk factors/confounders				
Mother's age [d] (categorical)	0.01*	Yes	1,02	Yes
Diabetes [e]	-	- **	-	- ***
Obesity [f]	-	- **	-	- ***
Alcohol abuse prior to LMP2 [f]	0,11	No	-	- ***
Alcohol abuse during pregnancy [g]	0,08	Yes	-	- ***
Substance abuse prior to LMP2 [f]	0,08	Yes	-	- ***
Substance abuse during pregnancy [g]	0,08	Yes	-	- ***
Smoking prior to LMP2 [f]	0,11	No	0,87	Yes
Smoking during pregnancy [g]	0,00	Yes	1,00	Yes
CMV [g]	-	- **	-	- ***
Folate deficiency [g]	-	- **	-	- ***
Gestational diabetes [g]	0,19	No	-	- ***
Herpes simplex virus [g]	-	- **	-	- ***
Rubella [g]	-	- **	-	- ***
Toxoplasmosis [g]	-	- **	-	- ***
Varicella [g]	-	- **	-	- ***
Paternal risk factors/confounders				
Father's age [d] (categorical)	0.00*	Yes	0,93	Yes
Year of offspring conception [h]	0.29*	No	1,04	Yes

a) absolute standardized difference below 0.1

b) variance ratio between 0 and 2

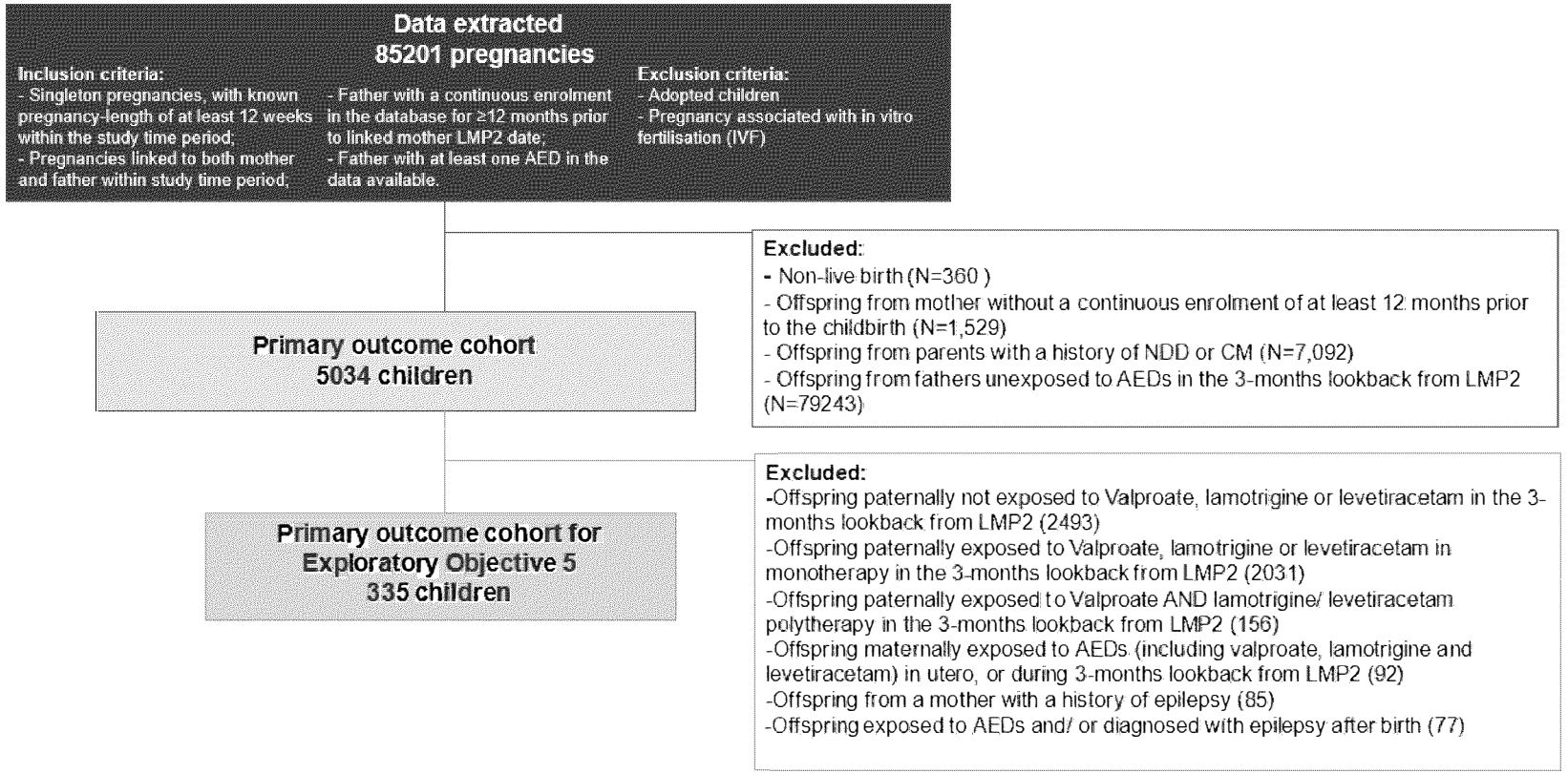
c) between index and exit date

d) at index (12th week of gestation in Norway, 22nd week of gestation in Denmark)

e) all available data prior to index date

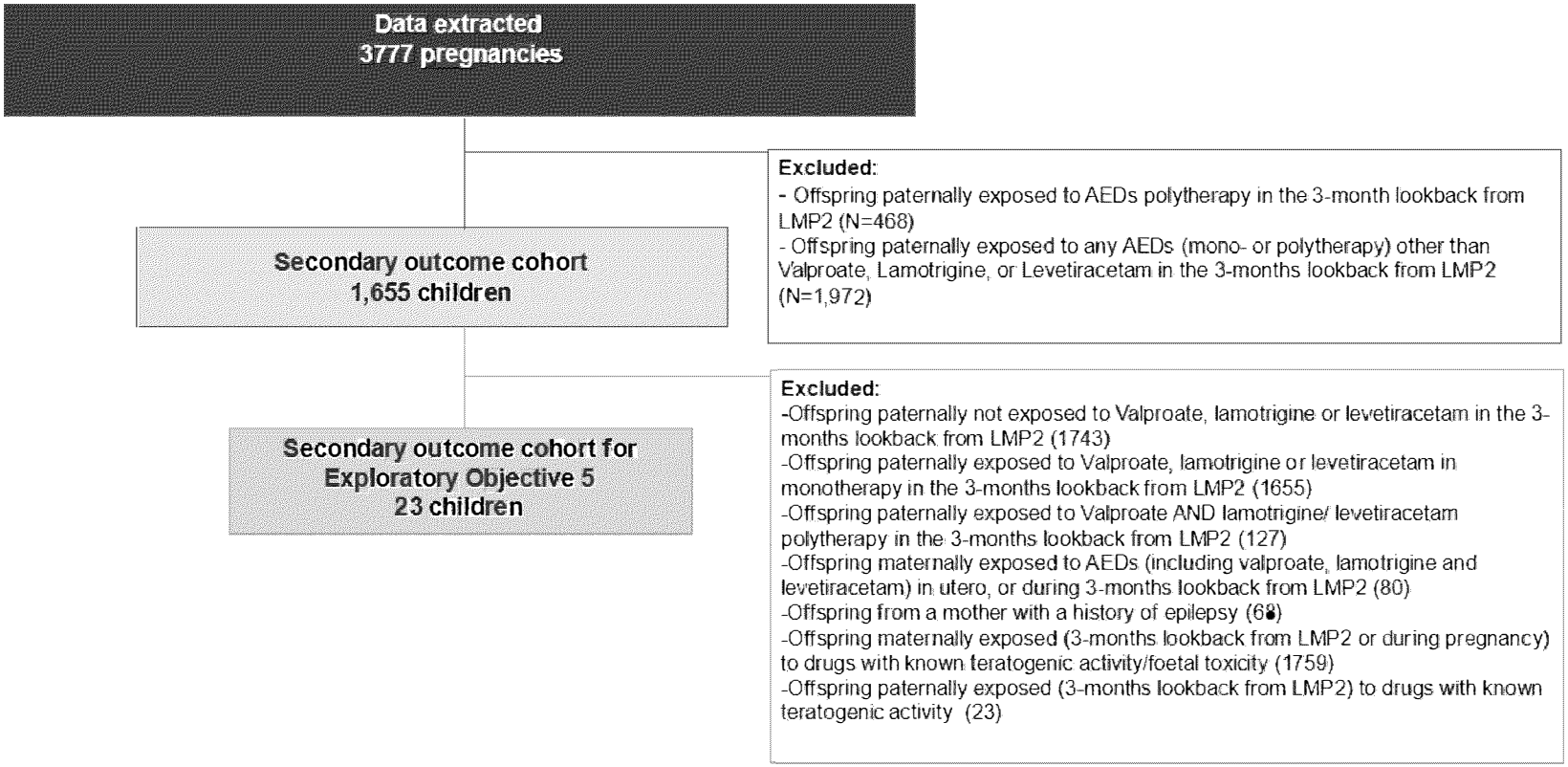
f) 12 months lookback from LMP2
g) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
h) at mother's LMP2
* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardized difference is not calculated if a binary variable has only 1 category level in the weighted patient data.
*** The variance ratio is not calculated if a variable has only 1 category level in one of valproate and comparator groups (the denominator of the variance ratio is 0).

15.1.5 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Exploratory analysis 5 for NDD including ASD)



CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 29 Study population for primary outcome exploratory analysis 5 in Denmark



CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 30 Study population for secondary outcome exploratory analysis 5 in Denmark

Table 145. Offspring demographic characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD **Number of offspring**	**Valproate(polytherapy)** **N=91**		**Lamotrigine/levetiracetam(polytherapy)** **N=244**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	0	0.00
28-31 (very preterm)	0	0.00	***	***
32-36 (moderate to late preterm)	***	***	***	***
37-41 (at term)	81	89.01	220	90.16
≥42 (post-term)	***	***	11	4.51
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	0	0.00
1000-1499 (very low)	0	0.00	***	***
1500-2499 (low)	***	***	***	***
≥2500	85	93.41	230	94.26
Missing	***	***	***	***
Gender [a]				
Male	39	42.86	125	51.23
Female	52	57.14	119	48.77
Missing	0	0.00	0	0.00
Year of birth				
1997	5	5.49	7	2.87
1998	6	6.59	6	2.46
1999	6	6.59	6	2.46
2000	***	***	8	3.28
2001	6	6.59	7	2.87
2002	5	5.49	13	5.33
2003	8	8.79	11	4.51
2004	6	6.59	13	5.33
2005	***	***	10	4.10
2006	7	7.69	10	4.10
2007	***	***	17	6.97
2008	9	9.89	20	8.20
2009	***	***	17	6.97
2010	6	6.59	11	4.51
2011	***	***	10	4.10
2012	***	***	11	4.51
2013	0	0.00	12	4.92

Paternal exposure group				
NDD Number of offspring	**Valproate(polytherapy) N=91**		**Lamotrigine/levetiracetam(polytherapy) N=244**	
	N	**%**	**N**	**%**
2014	***	***	14	5.74
2015	6	6.59	14	5.74
2016	0	0.00	9	3.69
2017	***	***	13	5.33
2018	***	***	5	2.05
Total number of years of follow-up	915.6		2043.56	
Mean follow-up year	10.06		8.38	

NDD: neurodevelopmental disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
***Masked values indicated that data was calculated but not disclosed
a) at index (childbirth)

Table 146. Offspring clinical characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD Number of offspring	**Valproate(polytherapy) N=91**		**Lamotrigine/levetiracetam(polytherapy) N=244**	
	N	**%**	**N**	**%**
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Epilepsy	0	0.00	0	0.00
Foetal alcohol syndrome	0	0.00	0	0.00
Fragile X syndrome	0	0.00	0	0.00
Lejeune/cri du chat syndrome	0	0.00	0	0.00
Tuberous sclerosis	0	0.00	0	0.00
Medication use				
Exposure to AEDs [a]	0	0.00	0	0.00
Outcomes				
ASD (ever, not only as 1st NDD diagnosis)	***	***	6	2.46
ASD (as 1st NDD diagnosis)	***	***	6	2.46
NDD including ASD	5	5.49	***	***
Age at the first diagnosis (years)				
ASD (ever, not only as 1st diagnosis) [b,c]				
0-1	***	***	0	0.00

Paternal exposure group				
NDD **Number of offspring**	**Valproate(polytherapy)** **N=91**		**Lamotrigine/levetiracetam(polytherapy)** **N=244**	
	N	**%**	**N**	**%**
2-3	***	***	***	***
4-5	***	***	***	***
6-7	***	***	0	0.00
8-9	***	***	***	***
10-11	***	***	***	***
Total (offspring with the outcome)	***	***	6	100
NDD including ASD [b,c]				
0-1	***	***	***	***
2-3	***	***	***	***
4-5	0	0.00	***	***
6-7	***	***	0	0.00
8-9	0	0.00	***	***
10-11	***	***	***	***
Total (offspring with the outcome)	5	100	13	100

NDD: neurodevelopmental disorders; CMV: Cytomegalovirus; AED: Antiepileptic Drug; ASD: Autism Spectrum Disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
*** Masked values indicated that data was calculated but not disclosed
a) between index (childbirth) and exit date
b) Categories may be adapted according to the data.
c) Denominator for the percentage is the number of offspring with the outcome.

Table 147. Maternal demographic characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD **Number of offspring**	**Valproate(polytherapy)** **N=91**		**Lamotrigine/levetiracetam(polytherapy)** **N=244**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	***	***	***	***
21-25	***	***	21	8.61
26-30	35	38.46	87	35.66
31-35	25	27.47	89	36.48
36-40	16	17.58	37	15.16
>40	***	***	***	***
Mean (SD)	30.38 (4.67)		31.19 (4.57)	
Median (25th - 75th percentile)	30(26.00, 35.00)		31 (28.00, 34.00)	

Paternal exposure group				
NDD **Number of offspring**	**Valproate(polytherapy)** **N=91**		**Lamotrigine/levetiracetam(polytherapy)** **N=244**	
	N	**%**	**N**	**%**
Min, max	***		***	
Missing	0	0.00	0	0.00

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of pregnancies represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages are calculated over the total number of offspring.
*** Masked values indicated that data was calculated but not disclosed
a) at index (childbirth)

Table 148. Maternal clinical characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD **Number of offspring**	**Valproate(polytherapy)** **N=91**		**Lamotrigine/levetiracetam(polytherapy)** **N=244**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder [a]	***	***	***	***
Diabetes [a]	***	***	6	2.46
Epilepsy [a]	0	0.00	0	0.00
Neurotic disorder [a]	6	6.59	14	5.74
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	***	***
Obesity [b]	0	0.00	***	***
CMV [c]	0	0.00	0	0.00
Gestational diabetes [c]	***	***	8	3.28
Rubella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	0	0.00
Smoking prior to LMP2 [b]				
Yes	0	0.00	***	***
No	***	***	9	3.69
Missing	***	***	***	***
Smoking during pregnancy [c]				
Yes	9	9.89	43	17.62
No	76	83.52	189	77.46

Paternal exposure group				
NDD **Number of offspring**	**Valproate(polytherapy)** **N=91**		**Lamotrigine/levetiracetam(polytherapy)** **N=244**	
	N	**%**	**N**	**%**
Missing	6	6.59	12	4.92
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AED during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K-means cluster prior to LMP2 [d]				
Unexposed	91	100.00	244	100.00
K-means cluster during pregnancy [c]				
Unexposed	91	100.00	244	100.00
Maternal polypharmacy index prior to LMP2 [d]				
0	57	62.64	170	69.67
1-4	***	***	***	***
5-10	***	***	***	***
>10	0	0.00	0	0.00
Mean (SD)	0.67		0.53 (0.98)	

Paternal exposure group				
NDD **Number of offspring**	**Valproate(polytherapy)** **N=91**		**Lamotrigine/levetiracetam(polytherapy)** **N=244**	
	N	**%**	**N**	**%**
	(1.07)			
Median (25th - 75th percentile)	0(0.00, 1.00)		0(0.00, 1.00)	
Min, max	***		***	
Maternal polypharmacy index during pregnancy [c]				
0	51	56.04	135	55.33
1-4	***	***	***	***
5-10	***	***	***	***
>10	0	0.00	0	0.00
Mean (SD)	0.75 (1.06)		0.85 (1.29)	
Median (25th - 75th percentile)	0(0.00, 1.00)		0(0.00, 1.00)	
Min, max	***		***	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	8	8.79	14	5.74
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	***	***	10	4.10
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] -mothers with at least one prescription	64	70.33	159	65.16
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	33	36.26	91	37.30

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; AED: Antiepileptic Drug; SD: Standard deviation

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

*** Masked values indicated that data was calculated but not disclosed

a) all available data prior to index date (childbirth)

b) 12 months lookback from LMP2

c) during pregnancy (from LMP2 until index date)

d) 3 months lookback from LMP2

e) Oxazolidine derivatives were not sold in Denmark during the study period

Table 149. Paternal demographic characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD	**Valproate (polytherapy)**		**Lamotrigine/levetiracetam (polytherapy)**	
Number of offspring	**N=91**		**N=244**	
	N	**%**	**N**	**%**
Father's age [a]				
≤20 years	0	0.00	***	***
21-25	6	6.59	***	***
26-30	20	21.98	60	24.59
31-35	33	36.26	92	37.70
36-40	17	18.68	54	22.13
>40	15	16.48	26	10.66
Mean (SD)	34.51 (6.70)		33.56 (5.33)	
Median (25th - 75th percentile)	33(30.00, 38.00)		33(30.00, 36.00)	
Min, max	***		***	
Missing	-		-	
Year of offspring conception [b]				
1996	***	***	***	***
1997	***	***	6	2.46
1998	8	8.79	5	2.05
1999	5	5.49	9	3.69
2000	6	6.59	5	2.05
2001	5	5.49	12	4.92
2002	6	6.59	13	5.33
2003	8	8.79	12	4.92
2004	***	***	11	4.51
2005	8	8.79	11	4.51
2006	***	***	12	4.92
2007	8	8.79	23	9.43
2008	***	***	16	6.56
2009	6	6.59	10	4.10
2010	***	***	13	5.33
2011	***	***	12	4.92
2012	0	0.00	12	4.92
2013	0	0.00	12	4.92
2014	6	6.59	14	5.74
2015	***	***	9	3.69
2016	***	***	13	5.33
2017	0	0.00	6	2.46
2018	***	***	***	***

	Paternal exposure group			
NDD **Number of offspring**	**Valproate (polytherapy)** **N=91**		**Lamotrigine/levetiracetam (polytherapy)** **N=244**	
	N	**%**	**N**	**%**

NDD: Neurodevelopmental Disorders; SD: Standard deviation; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
*** Masked values indicated that data was calculated but not disclosed
a) at index (childbirth)
b) at mother's LMP2

Table 150. Paternal clinical characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD **Number of offspring**	**Valproate (polytherapy)** **N=91**		**Lamotrigine/levetiracetam (polytherapy)** **N=244**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder excluding bipolar affective disorder and mania [a]	***	***	7	2.87
Bipolar affective disorder [a]	0	0.00	***	***
Mania [a]	0	0.00	0	0.00
Neurotic disorder [a]	***	***	20	8.20
Schizophrenia, schizotypal and delusional disorders [a]	***	***	***	***
Lifestyle characteristics				
Substance abuse [c]	0	0.00	***	***
Medication use				
Exposure to AEDs[d]				
Fatty acid derivatives	***	***	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Barbiturates derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Fatty acid derivatives and other antiepileptics	17	18.68	10	4.10
Carboxamide derivatives and other antiepileptics	0	0.00	99	40.57
Fatty acid derivatives and Carboxamide derivatives	46	50.55	0	0.00
Benzodiazepine derivatives and other antiepileptics	0	0.00	13	5.33

	Paternal exposure group			
NDD **Number of offspring**	**Valproate (polytherapy)** **N=91**		**Lamotrigine/levetiracetam (polytherapy)** **N=244**	
	N	**%**	**N**	**%**
Benzodiazepine derivatives and Fatty acid derivatives	***	***	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives	0	0.00	0	0.00
Succinimide derivatives and other antiepileptics	0	0.00	***	***
Succinimide derivatives and Fatty acid derivatives	8	8.79	0	0.00
Carboxamide derivatives and Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives and Fatty acid derivatives	***	***	0	0.00
Hydantoin derivatives and Carboxamide derivatives	0	0.00	0	0.00
Hydantoin derivatives and other antiepileptics	0	0.00	5	2.05
Hydantoin derivatives and Succinimide derivatives	0	0.00	0	0.00
Barbiturates derivatives and other antiepileptics	0	0.00	***	***
Barbiturates derivatives and Fatty acid derivatives	8	8.79	0	0.00
Barbiturates derivatives and Carboxamide derivatives	0	0.00	0	0.00
Barbiturates derivatives and Benzodiazepine derivatives	0	0.00	0	0.00
Barbiturates derivatives and Hydantoin derivatives	0	0.00	0	0.00
Carboxamide derivatives and Barbiturates derivatives and Hydantoin derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and Fatty acid derivatives and other antiepileptics	***	***	0	0.00
Carboxamide derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	7	2.87
Benzodiazepine derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	***	***
Benzodiazepine derivatives and Succinimide derivatives and Fatty acid derivatives	***	***	0	0.00
Hydantoin derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	***	***
Hydantoin derivatives and Carboxamide derivatives and Fatty acid derivatives	***	***	0	0.00
Barbiturates derivatives and Carboxamide derivatives and Fatty acid derivatives	***	***	0	0.00

	Paternal exposure group			
NDD **Number of offspring**	**Valproate (polytherapy)** **N=91**		**Lamotrigine/levetiracetam (polytherapy)** **N=244**	
	N	**%**	**N**	**%**
Fatty acid derivatives and Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	***	***
Hydantoin derivatives and Succinimide derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
AED indication				
Epilepsy	65	71.43	193	79.10
Bipolar affective disorder and mania	0	0.00	***	***
Other/unknown	26	28.57	***	***
K-means cluster [d]				
Cluster A	65	71.43	111	45.49
Cluster B	26	28.57	133	54.51
Paternal polypharmacy index [d]				
0	58	63.74	136	55.74
1-4	33	36.26	99	40.57
5-10	0	0.00	9	3.69
>10	0	0.00	0	0.00
Mean (SD)	0.65 (1.00)		0.89 (1.43)	
Median (25^{th} - 75^{th} percentile)	0(0.00, 1.00)		0(0.00, 1.00)	
Min, max	***		***	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	37	40.66	91	37.30
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	51	56.04	156	63.93

Cluster A: constant high exposure; Cluster B: constant low exposure
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring. AED: Antiepileptic Drug, NDD: Neurodevelopmental Disorders, SD: Standard Deviation
a) all available data prior to index date (childbirth)

NDD Number of offspring	Paternal exposure group Valproate (polytherapy) N=91		Lamotrigine/levetiracetam (polytherapy) N=244	
	N	%	N	%

c) 12 months lookback from LMP2
d) 3 months lookback from LMP2

Table 151. Association between potential offspring risk factors/confounders for NDD by paternal exposure group; primary outcome

NDD Number of offspring	Paternal exposure group Valproate (polytherapy) N=91		Lamotrigine/levetiracetam (polytherapy) N=244		Comparison * Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -
	N	%	N	%	
Offspring risk factors/confounders **Gender** [a]					
Male	39	42.86	125	51.23	-
Female	52	57.14	119	48.77	-
Missing	0	0.00	0	0.00	-
Test statistics	-	-	-	-	1.86 (0.1727)
Congenital CMV [b]	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	-
Foetal alcohol syndrome [b]	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	0	0.00	-

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) between index and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 152. Association between potential maternal risk factors/confounders for NDD by paternal exposure group; primary outcome

Paternal exposure group					**Comparison**
NDD Number of offspring	**Valproate(polytherapy) N=91**		**Lamotrigine/levetiracetam (polytherapy) N=244**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
Maternal risk factors/confounders					
Mother's age [a] (categorical)					
≤20 years	***	***	***	***	-
21-25	***	***	21	8.61	-
26-30	35	38.46	87	35.66	-
31-35	25	27.47	89	36.48	-
36-40	16	17.58	37	15.16	-
>40	***	***	***	***	-
Test statistics	-	-	-	-	4.95 (0.4217)
Mother's age [a] (continuous)					
Mean (SD)	30.38 (4.67)		31.19 (4.57)		14064.50 (0.1201)*
Median (25^{th} - 75^{th} percentile)	30(26.00, 35.00)		31(28.00, 34.00)		-
Min, max	***		***		-
Missing	0	0.00	0	0.00	-
Affective disorder [b]	***	***	***	***	0.02 (0.0205)*
Diabetes [b]	***	***	6	2.46	0.67 (0.6789)*
Gestational diabetes [c]	***	***	8	3.28	1.00 (1.0000)*
Neurotic disorder [b]	6	6.59	14	5.74	0.09 (0.7687)
Schizophrenia, schizotypal and delusional disorders [b]	0	0.00	***	***	1.00 (1.0000)*
Obesity [d]	0	0.00	***	***	0.56 (0.5656)*
CMV [c]	0	0.00	0	0.00	-
Rubella [c]	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [d]	0	0.00	0	0.00	-
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [d]	0	0.00	0	0.00	-
Substance abuse during pregnancy [c]	0	0.00	0	0.00	-
Smoking prior to LMP2 [d]					
Yes	0	0.00	***	***	-

Paternal exposure group					Comparison
NDD Number of offspring	**Valproate(polytherapy) N=91**		**Lamotrigine/levetiracetam (polytherapy) N=244**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
No	***	***	9	3.69	-
Missing	***	***	***	***	-
Test statistics without 'Missing' category	-	-	-	-	1.00 (1.0000)*
Smoking during pregnancy [c]					
Yes	9	9.89	43	17.62	-
No	76	83.52	189	77.46	-
Missing	6	6.59	12	4.92	-
Test statistics without 'Missing' category	-	-	-	-	2.86 (0.0906)
Maternal polypharmacy index prior to LMP2 [e](categorical)					
0	57	62.64	170	69.67	-
1-4	***	***	***	***	-
5-10	***	***	***	***	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	1.85 (0.3956)
Maternal polypharmacy index prior to LMP2 [e] (continuous)					
Mean (SD)	0.67 (1.07)		0.53 (0.98)		16121.50 (0.2012)*
Median (25th - 75th percentile)	0(0.00, 1.00)		0(0.00, 1.00)		-
Min, max	***		***		-
Maternal polypharmacy index during pregnancy [c](categorical)					
0	51	56.04	135	55.33	-
1-4	***	***	***	***	-
5-10	***	***	***	***	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.14 (0.9341)
Maternal polypharmacy index during pregnancy[c] (continuous)					
Mean (SD)	0.75 (1.06)		0.85 (1.29)		15075.00 (0.7652)*
Median (25th - 75th	0(0.00, 1.00)		0(0.00, 1.00)		-

Paternal exposure group					Comparison
NDD Number of offspring	**Valproate(polytherapy) N=91**		**Lamotrigine/levetiracetam (polytherapy) N=244**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
percentile)					
Min, max	***		***		-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	8	8.79	14	5.74	1.01 (0.3156)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	***	***	10	4.10	1.00 (1.0000)*
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription	64	70.33	159	65.16	0.79 (0.3727)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	33	36.26	91	37.30	0.03 (0.8619)

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum; LMP2: Last Menstrual Period Date Plus 2 weeks; CMV: Cytomegalovirus

*** Masked values indicated that data was calculated but not disclosed

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) at index (childbirth)

b) all available data prior to index date

c) during pregnancy (from LMP2 until index date)

d) 12 months lookback from LMP2

e) 3 months lookback from LMP2

Table 153. Association between potential paternal risk factors/confounders for NDD by paternal exposure group; primary outcome

Paternal exposure group					Comparison
NDD Number of offspring	**Valproate(polytherapy) N=91**		**Lamotrigine/levetiracetam(polytherapy) N=244**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
Paternal risk factors/confounders					
Affective disorder excluding bipolar affective disorder and mania [a]	***	***	7	2.87	1.00 (1.0000)*
Bipolar affective disorder [a]	0	0.00	***	***	0.57 (0.5778)*
Mania [a]	0	0.00	0	0.00	-
Neurotic disorder [a]	***	***	20	8.20	0.34 (0.3403)*
Schizophrenia, schizotypal and delusional disorders [a]	***	***	***	***	0.35 (0.3502)*
Substance abuse [c]	0	0.00	***	***	1.00 (1.0000)*
Paternal polypharmacy index [d] (categorical)					
0	58	63.74	136	55.74	-
1-4	33	36.26	99	40.57	-
5-10	0	0.00	9	3.69	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	4.40 (0.1107)
Paternal polypharmacy index [d] (continuous)					
Mean (SD)	0.65 (1.00)		0.89 (1.43)		14446.00 (0.2311)*
Median (25^{th} - 75^{th} percentile)	0(0.00, 1.00)		0(0.00, 1.00)		-
Min, max	***		***		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	37	40.66	91	37.30	0.32 (0.5730)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	51	56.04	156	63.93	1.75 (0.1861)
Father's age [e] (categorical)					
≤20 years	0	0.00	***	***	-
21-25	6	6.59	***	***	-

Paternal exposure group					Comparison
NDD Number of offspring	**Valproate(polytherapy) N=91**		**Lamotrigine/levetiracetam(polytherapy) N=244**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
26-30	20	21.98	60	24.59	-
31-35	33	36.26	92	37.70	-
36-40	17	18.68	54	22.13	-
>40	15	16.48	26	10.66	-
Test statistics	-	-	-	-	3.38 (0.6418)
Father's age [e] (continuous)					
Mean (SD)	34.51 (6.70)		33.56 (5.33)		15807.00 (0.5100)*
Median (25th - 75th percentile)	33(30.00, 38.00)		33(30.00, 36.00)		-
Min, max	***		***		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [f,g]					
1996-2001	31	34.07	42	17.21	-
2002-2007	37	40.66	82	33.61	-
2008-2012	14	15.38	63	25.82	-
2013-2018	9	9.89	57	23.36	-
Test statistics	-	-	-	-	18.81 (0.0003)

NDD: Neurodevelopmental Disorders; SD: Standard deviation; Min: Minimum; Max: Maximum; LMP2 Last Menstrual Period Date Plus 2 weeks

*** Masked values indicated that data was calculated but not disclosed

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) all available data prior to index date (childbirth)

c) 12 months lookback from LMP2

d) 3 months lookback from LMP2

e) at index

f) at mother's LMP2

g) calendar years were grouped in each country according to the length of the study period

Table 154. Association between potential offspring risk factors/confounders and NDD; primary outcome

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Offspring risk factors/confounders								
Gender [a]								
Male	164	48.96	11	6.71	153	93.29	Reference	-
Female	171	51.04	7	4.09	164	95.91	0.59(0.22, 1.57)	-
Missing	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	1.10,0.2935
Congenital CMV [b]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital rubella [b]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Foetal alcohol syndrome [b]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Fragile X syndrome [b]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Lejeune/cri du chat syndrome [b]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Tuberous sclerosis [b]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; OR: Odds ratio; CI: Confidence interval; SD: Standard deviation
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage is calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at index (childbirth)
b) between index and exit date

Table 155. Association between potential maternal risk factors/confounders and NDD; primary outcome

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Maternal risk factors/confounders								
Mother's age [a] (categorical)								
≤20 years	***	***	***	***	***	***	6.45 (0.58, 71.57)	-
21-25	34	10.15	***	***	***	***	1.87 (0.44, 7.91)	-
26-30	122	36.42	6	4.92	116	95.08	Reference	-
31-35	114	34.03	6	5.26	108	94.74	1.07 (0.34, 3.43)	-
36-40	53	15.82	***	***	***	***	0.37 (0.04, 3.17)	-
>40	***	***	***	***	***	***	2.76 (0.29, 26.21)	-
Wald test	-	-	-	-	-	-	-	4.87,0.4325
Affective disorder [b]								
No	330	98.51	18	5.45	312	94.55	Reference	-
Yes	5	1.49	0	0.00	5	100.00	0.00(0.00, I)	0.00,0.9878
Diabetes [b]								

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
No	328	97.91	18	5.49	310	94.51	Reference	-
Yes	7	2.09	0	0.00	7	100.00	0.00(0.00, I)	0.00,0.9855
Gestational diabetes [c]								
No	324	96.72	18	5.56	306	94.44	Reference	-
Yes	11	3.28	0	0.00	11	100.00	0.00(0.00, I)	0.00,0.9819
Neurotic disorder [b]								
No	315	94.03	***	***	***	***	Reference	-
Yes	20	5.97	***	***	***	***	5.38 (1.59, 18.20)	7.30,0.0069
Schizophrenia, schizotypal and delusional disorders [b]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00(0.00,I)	0.00,0.9945
Obesity [d]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	9.26 (0.80, 107.32)	3.17,0.0749
CMV [c]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Rubella [c]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse prior to LMP2 [d]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse during pregnancy [c]								

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Substance abuse prior to LMP2 [d]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Substance abuse during pregnancy [c]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Smoking prior to LMP2 [d]								
Yes	***	***	***	***	***	***	0.00 (0.00, 1.3154E165)	-
No	***	***	***	***	***	***	Reference	-
Missing	321	95.82	17	5.30	304	94.70	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	0.00,0.9624
Smoking during pregnancy [c]								
Yes	52	15.52	7	13.46	45	86.54	3.59 (1.32, 9.76)	-
No	265	79.10	11	4.15	254	95.85	Reference	-
Missing	18	5.37	0	0.00	18	100.00	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	6.29,0.0121
Maternal polypharmacy index prior to LMP2 [e](categorical)								
0	227	67.76	12	5.29	215	94.71	Reference	-
1-4	***	***	***	***	***	***	0.89 (0.30, 2.59)	-
5-10	***	***	***	***	***	***	17.92 (1.06, 304.25)	-
>10	0	0.00	0	0.00	0	0.00	-	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Wald test	-	-	-	-	-	-	-	4.19,0.1233
Maternal polypharmacy index during pregnancy [c](categorical)								
0	186	55.52	9	4.84	177	95.16	Reference	-
1-4	144	42.99	9	6.25	135	93.75	1.31(0.51, 3.39)	-
5-10	5	1.49	0	0.00	5	100.00	0.00(0.00,I)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	0.31,0.8555
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription								
No	313	93.43	18	5.75	295	94.25	Reference	-
Yes	22	6.57	0	0.00	22	100.00	0.00(0.00,I)	0.00,0.9743
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription								
No	321	95.82	18	5.61	303	94.39	Reference	-
Yes	14	4.18	0	0.00	14	100.00	0.00(0.00,I)	0.00,0.9795
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] -								

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
mothers with at least one prescription								
No	112	33.43	***	***	***	***	Reference	-
Yes	223	66.57	***	***	***	***	2.62 (0.74, 9.25)	2.24,0.1344
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription								
No	211	62.99	9	4.27	202	95.73	Reference	-
Yes	124	37.01	9	7.26	115	92.74	1.76 (0.68, 4.55)	1.35,0.2461

NDD: Neurodevelopmental Disorders; OR: Odds ratio; CI: Confidence interval; LMP2: Last Menstrual Period Date Plus 2 weeks; CMV: cytomegalovirus
*** Masked values indicated that data was calculated but not disclosed
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2

Table 156. Association between potential paternal risk factors/confounders and NDD; primary outcome

NDD	Overall	Event	Non-event	Association

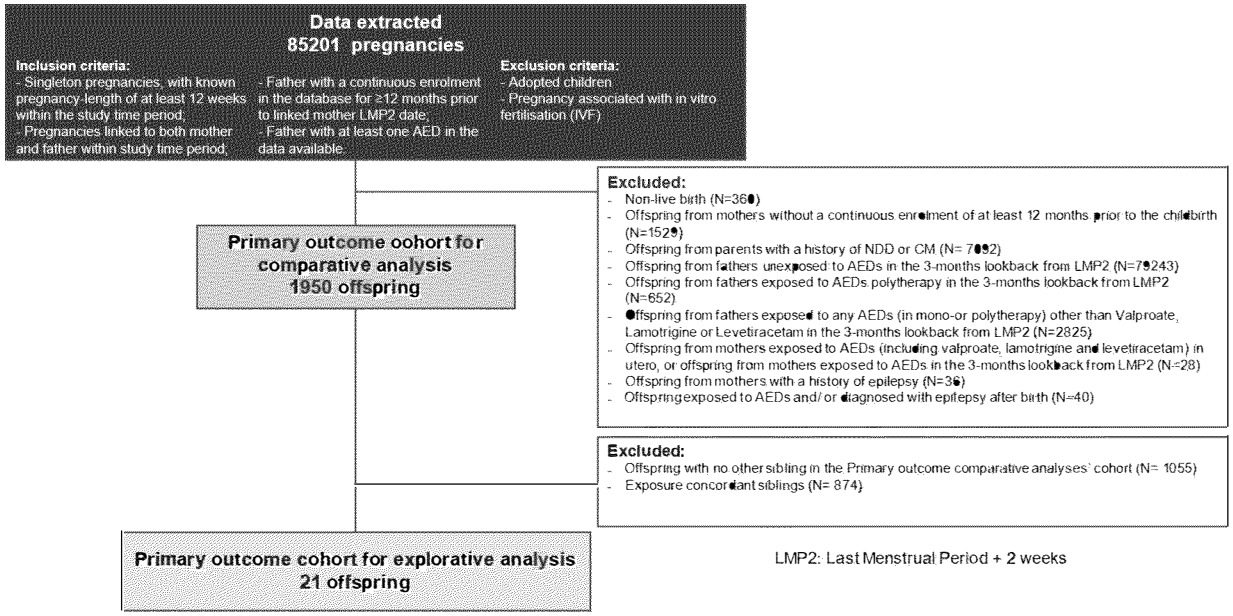
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Paternal risk factors/confounders								
Affective disorder excluding bipolar affective disorder and mania [a]								
No	326	97.31	***	***	***	***	Reference	-
Yes	9	2.69	***	***	***	***	2.27 (0.27, 19.23)	0.57, 0.4509
Bipolar affective disorder [a]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00, I)	0.00, 0.9891
Mania [a]								
No	335	100.00	18	5.37	317	94.63	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Neurotic disorder [a]								
No	311	92.84	***	***	***	***	Reference	-
Yes	24	7.16	***	***	***	***	2.82 (0.76, 10.51)	2.38, 0.1228
Schizophrenia, schizotypal and delusional disorders [a]								
No	329	98.21	18	5.47	311	94.53	Reference	-
Yes	6	1.79	0	0.00	6	100.00	0.00 (0.00, I)	0.00, 0.9866
Substance abuse [c]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	[1]	0.00,0.9964
Paternal polypharmacy index [d] (categorical)								
0	194	57.91	***	***	***	***	Reference	-
1-4	132	39.40	9	6.82	123	93.18	1.70 (0.64, 4.53)	-
5-10	9	2.69	***	***	***	***	2.91 (0.32, 26.13)	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	1.66,0.4367
Concomitant medications associated with valproate-indicated psychiatric conditions [c] -fathers with at least one prescription								
No	207	61.79	8	3.86	199	96.14	Reference	-
Yes	128	38.21	10	7.81	118	92.19	2.11 (0.81, 5.49)	2.33,0.1267
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription								
No	128	38.21	7	5.47	121	94.53	Reference	-
Yes	207	61.79	11	5.31	196	94.69	0.97 (0.37, 2.57)	0.00,0.9512
Father's age [e] (categorical)								
≤20 years	***	***	***	***	***	***	0.00(0.00,I)	-
21-25	***	***	***	***	***	***	4.03 (0.68, 23.92)	-
26-30	80	23.88	***	***	***	***	1.59 (0.39, 6.56)	-
31-35	125	37.31	***	***	***	***	Reference	-
36-40	71	21.19	***	***	***	***	1.81 (0.44, 7.45)	-
>40	41	12.24	***	***	***	***	3.27 (0.78, 13.72)	-
Wald test	-	-	-	-	-	-	-	3.79, 0.5804
Year of offspring conception [f,g]								
1996-2001	73	21.79	***	***	***	***	Reference	-
2002-2007	119	35.52	12	10.08	107	89.92	3.98 (0.86, 18.33)	-
2008-2012	77	22.99	***	***	***	***	1.95 (0.35, 10.96)	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
2013-2018	66	19.70	0	0.00	66	100.00	-	-
Wald test	-	-	-	-	-	-	-	3.90, 0.2730

NDD: Neurodevelopmental Disorders; OR: Odds ratio; CI: Confidence interval
*** Masked values indicated that data was calculated but not disclosed
[1]: no event in Lamotrigine group was recorded, resulted in quasi-separation, hence the computed HR observed was not an interpretable
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index (date of childbirth)
f) at month's LMP2
g) calendar years were grouped in each country according to the length of the study period

15.1.6 Exposure to valproate or lamotrigine/levetiracetam in paternally and maternally matched siblings (Exploratory analysis 6 for NDD including ASD)



CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 31 Study population for primary outcome exploratory analysis 6 in Denmark

Table 157. Offspring demographic characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD	**Valproate**		**Lamotrigine/levetiracetam(composite)**	
Number of offspring	**N=11**		**N=10**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	0	0.00
28-31 (very preterm)	0	0.00	0	0.00
32-36 (moderate to late preterm)	***	***	0	0.00
37-41 (at term)	***	***	10	100.00
≥42 (post-term)	0	0.00	0	0.00

Paternal exposure group				
NDD	**Valproate**		**Lamotrigine/levetiracetam(composite)**	
Number of offspring	**N=11**		**N=10**	
	N	**%**	**N**	**%**
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	0	0.00
1000-1499 (very low)	0	0.00	0	0.00
1500-2499 (low)	0	0.00	0	0.00
≥2500	11	100.00	10	100.00
Missing	0	0.00	0	0.00
Gender [a]				
Male	***	***	***	***
Female	***	***	***	***
Missing	0	0.00	0	0.00
Year of birth				
1997	***	***	0	0.00
1998	0	0.00	0	0.00
1999	0	0.00	0	0.00
2000	0	0.00	0	0.00
2001	***	***	***	***
2002	***	***	0	0.00
2003	0	0.00	0	0.00
2004	***	***	0	0.00
2005	***	***	***	***
2006	***	***	***	***
2007	0	0.00	***	***
2008	0	0.00	***	***
2009	0	0.00	***	***
2010	0	0.00	0	0.00
2011	***	***	0	0.00
2012	0	0.00	0	0.00
2013	0	0.00	0	0.00
2014	0	0.00	0	0.00
2015	0	0.00	0	0.00
2016	0	0.00	***	***
2017	0	0.00	0	0.00
2018	0	0.00	0	0.00
Total number of years of follow-up	119.87		96.96	
Mean follow-up year	10.9		9.7	

NDD: Neurodevelopmental Disorders
***: Masked values indicated that data was calculated but not disclosed
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam(composite) N=10	
	N	%	N	%

a) at index (childbirth)

Table 158. Offspring clinical characteristics by paternal exposure group; primary outcome

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10	
	N	%	N	%
Comorbidities				
Congenital CMV [a]	0	0.00	0	0.00
Congenital rubella [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00
Foetal alcohol syndrome [a]	0	0.00	0	0.00
Fragile X syndrome [a]	0	0.00	0	0.00
Lejeune/cri du chat syndrome [a]	0	0.00	0	0.00
Tuberous sclerosis [a]	0	0.00	0	0.00
Medication use				
Exposure to AEDs [a]	0	0.00	0	0.00
Outcomes				
ASD (ever, not only as 1st diagnosis)	0	0.00	0	0.00
ASD (as 1st diagnosis)	0	0.00	0	0.00
NDD including ASD	0	0.00	0	0.00
Age at the first diagnosis (years)				
ASD (ever, not only as 1st diagnosis) [b,c]				
0-1	0	0.00	0	0.00
2-3	0	0.00	0	0.00
4-5	0	0.00	0	0.00
6-7	0	0.00	0	0.00
8-9	0	0.00	0	0.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	0	0.00	0	0.00
NDD including ASD [b,c]				
0-1	0	0.00	0	0.00
2-3	0	0.00	0	0.00
4-5	0	0.00	0	0.00
6-7	0	0.00	0	0.00
8-9	0	0.00	0	0.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	0	0.00	0	0.00

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10	
	N	%	N	%

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; AED: Antiepileptic Drug; ASD: Autism Spectrum Disorders
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages are calculated over the total number of offspring.
a) between index (childbirth) and exit date
b) Categories may be adapted according to the data.
c) Denominator for the percentage is the number of offspring with the outcome.

Table 159. Maternal demographic characteristics by paternal exposure group; primary outcome

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10	
	N	%	N	%
Mother's age [a]				
≤20 years	0	0.00	0	0.00
21-25	5	45.45	0	0.00
26-30	***	***	5	50.00
31-35	***	***	5	50.00
36-40	0	0.00	0	0.00
>40	0	0.00	0	0.00
Mean (SD)	26.18 (3.46)		29.70 (3.09)	
Median (25^{th} - 75^{th} percentile)	26(23.00, 29.00)		29.5 (27.00, 32.00)	
Min, max	***		***	
Missing	0	0.00	0	0.00

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum;
*** Masked values indicated that data was calculated but not disclosed
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages are calculated over the total number of offspring.

Table 160. Maternal clinical characteristics by paternal exposure group; primary outcome

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10	
	N	%	N	%
Comorbidities				
Affective disorder [a]	0	0.00	0	0.00
Diabetes [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00
Neurotic disorder [a]	***	***	***	***

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10	
	N	%	N	%
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Obesity [b]	0	0.00	0	0.00
CMV [c]	0	0.00	0	0.00
Gestational diabetes [c]	0	0.00	***	***
Rubella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	0	0.00
Smoking prior to LMP2 [b]				
Yes	0	0.00	0	0.00
No	***	***	***	***
Missing	***	***	***	***
Smoking during pregnancy [c]				
Yes	0	0.00	***	***
No	***	***	***	***
Missing	***	***	0	0.00
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AED during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10	
	N	%	N	%
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K-means cluster prior to LMP2 [d]				
Unexposed	11	100.00	10	100.00
K-means cluster during pregnancy [c]				
Unexposed	11	100.00	10	100.00
Maternal polypharmacy index prior to LMP2 [d]				
0	***	***	***	***
1-4	***	***	***	***
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.36 (0.50)		0.80 (1.03)	
Median (25^{th} - 75^{th} percentile)	0 (0.00, 1.00)		0 (0.00, 2.00)	
Min, max	***		***	
Maternal polypharmacy index during pregnancy [c]				
0	***	***	***	***
1-4	***	***	***	***
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	1.00 (0.77)		0.60 (1.07)	
Median (25^{th} - 75^{th} percentile)	1 (0.00, 2.00)		0(0.00, 1.00)	
Min, max	***		***	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	0	0.00	0	0.00
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	0	0.00	0	0.00
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] -mothers with at least one prescription	8	72.73	7	70.00
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	7	63.64	***	***

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10	
	N	%	N	%

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; AED: Antiepileptic Drug; SD: Standard Deviation; Min: Minimum; Max: Maximum
***Masked values indicated that data was calculated but not disclosed
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until index date)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Denmark during the study period

Table 161. Paternal demographic characteristics by paternal exposure group; primary outcome

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10	
	N	%	N	%
Father's age [a]				
≤20 years	0	0.00	***	***
21-25	***	***	0	0.00
26-30	***	***	***	***
31-35	***	***	***	***
36-40	0	0.00	***	***
>40	***	***	***	***
Mean (SD)	31.00 (6.65)		33.10 (6.85)	
Median (25th - 75th percentile)	29 (25.00, 33.00)		33.5 (31.00, 35.00)	
Min, max	***		***	
Missing	-		-	
Year of offspring conception [b]				
1996	***	***	0	0.00
1997	0	0.00	0	0.00
1998	0	0.00	0	0.00
1999	0	0.00	0	0.00
2000	***	***	***	***
2001	***	***	0	0.00
2002	0	0.00	0	0.00
2003	0	0.00	0	0.00
2004	***	***	***	***
2005	***	***	***	***
2006	***	***	***	***
2007	0	0.00	***	***

Paternal exposure group				
NDD **Number of offspring**	**Valproate** **N=11**		**Lamotrigine/levetiracetam (composite)** **N=10**	
	N	**%**	**N**	**%**
2008	0	0.00	***	***
2009	0	0.00	0	0.00
2010	***	***	0	0.00
2011	0	0.00	0	0.00
2012	0	0.00	0	0.00
2013	0	0.00	0	0.00
2014	0	0.00	0	0.00
2015	0	0.00	***	***
2016	0	0.00	0	0.00
2017	0	0.00	0	0.00
2018	0	0.00	0	0.00

NDD: Neurodevelopmental Disorders; Min: Minimum; Max: Maximum; SD: Standard Deviation
***Masked values indicated that data was calculated but not disclosed
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index (childbirth)
b) at mother's LMP2

Table 162. Paternal clinical characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD **Number of offspring**	**Valproate** **N=11**		**Lamotrigine/levetiracetam (composite)** **N=10**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder excluding bipolar affective disorder and mania [a]	0	0.00	0	0.00
Bipolar affective disorder [a]	0	0.00	0	0.00
Mania [a]	0	0.00	0	0.00
Neurotic disorder [a]	0	0.00	***	***
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Lifestyle characteristics				
Substance abuse [c]	0	0.00	0	0.00
Medication use				
AED indication				
Epilepsy	11	100.00	10	100.00
Bipolar affective disorder and mania	0	0.00	0	0.00
Other/unknown	0	0.00	0	0.00

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10	
	N	%	N	%
K-means cluster [d]				
Cluster A	***	***	***	***
Cluster B	***	***	***	***
Paternal polypharmacy index [d]				
0	***	***	***	***
1-4	***	***	***	***
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.45 (0.69)		0.90 (1.20)	
Median (25^{th} - 75^{th} percentile)	0 (0.00, 1.00)		1 (0.00, 1.00)	
Min, max	***		***	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	0	0.00	***	***
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	6	54.55	***	***

NDD: Neurodevelopmental Disorders, AED: Antiepileptic Drug; SD: Standard Deviation; Min: Minimum; Max: Maximum
***Masked values indicated that data was calculated but not disclosed Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
A: constant high exposure; Cluster B: constant low exposure

Table 163. Association between potential offspring risk factors/confounders for NDD by paternal exposure group; primary outcome

NDD Number of offspring	Paternal exposure group Valproate N=11		Lamotrigine/levetiracetam (composite) N=10		Comparison Valproatevs Lamotrigine /levetiracetam
	N	%	N	%	
Offspring risk factors/confounders					
Male	***	***	***	***	-
Female	***	***	***	***	-
Missing	0	0.00	0	0.00	-
Test statistics	-	-	-	-	1.00 (1.0000)*
Congenital CMV [b]	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	-

Foetal alcohol syndrome [b]	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	0	0.00	-

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of pregnancies represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
b) between index and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 164. Association between potential maternal risk factors/confounders for NDD by paternal exposure group; primary outcome

Paternal exposure group					**Comparison**
NDD Number of offspring	**Valproate N=11**		**Lamotrigine/levetiracetam (composite) N=10**		**Valproatevs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	
Maternal risk factors/confounders					
Mother's age [a] (categorical)					
≤20 years	0	0	0	0	-
21-25	5	45, 45	0	0	-
26-30	***	***	5	50	-
31-35	***	***	5	50	-
36-40	0	0	0	0	-
>40	0	0	0	0	-
Test statistics	-	-	-	-	7.64 (0.0220)
Mother's age [a] (continuous)					
Mean (SD)	26.18 (3.46)		29.70 (3.09)		-2.46 (0.0236)
Median (25th - 75th percentile)	26 (23.00, 29.00)		29.5 (27.00, 32.00)		-
Min, max	***		***		-
Missing	0	0	0	0	-
Affective disorder [b]	0	0	0	0	-
Diabetes [b]	0	0	0	0	-
Gestational diabetes [c]	0	0	***	***	0.47 (0.4762)*
Neurotic disorder [b]	***	***	***	***	1.00 (1.0000)*
Schizophrenia, schizotypal and delusional disorders [b]	0	0	0	0	-
Obesity [d]	0	0	0	0	-
CMV [c]	0	0	0	0	-
Rubella [c]	0	0	0	0	-
Alcohol abuse prior to LMP2 [d]	0	0	0	0	-

Paternal exposure group **NDD** **Number of offspring**	**Valproate** **N=11**		**Lamotrigine/levetiracetam (composite)** **N=10**		**Comparison** **Valproatevs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	
Alcohol abuse during pregnancy [c]	0	0	0	0	-
Substance abuse prior to LMP2 [d]	0	0	0	0	-
Substance abuse during pregnancy [c]	0	0	0	0	-
Smoking prior to LMP2 [d]					
Yes	0	0	0	0	-
No	***	***	***	***	-
Missing	***	***	***	***	-
Test statistics without 'Missing' category	-	-	-	-	-
Smoking during pregnancy [c]					
Yes	0	0	***	***	-
No	***	***	***	***	-
Missing	***	***	0	0	-
Test statistics without 'Missing' category	-	-	-	-	1.00 (1.0000)*
Maternal polypharmacy index prior to LMP2 [e](categorical)					
0	***	***	***	***	-
1-4	***	***	***	***	-
5-10	0	0	0	0	-
>10	0	0	0	0	-
Test statistics	-	-	-	-	1.00 (1.0000)*
Maternal polypharmacy index prior to LMP2 [e] (continuous)					
Mean (SD)	0.36 (0.50)		0.80 (1.03)		120.00 (0.4400)*
Median (25th - 75th percentile)	0(0.00, 1.00)		0(0.00, 2.00)		-

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10		Comparison Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Min, max	***		***		-
Maternal polypharmacy index during pregnancy [c](categorical)					
0	***	***	***	***	-
1-4	***	***	***	***	-
5-10	0	0	0	0	-
>10	0	0	0	0	-
Test statistics	-	-	-	-	0.08 (0.0861)*
Maternal polypharmacy index during pregnancy[c] (continuous)					
Mean (SD)	1.00 (0.77)		0.60 (1.07)		91.50 (0.1726)*
Median (25th - 75th percentile)	1 (0.00, 2.00)		0 (0.00, 1.00)		-
Min, max	***		***		-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	0	0	0	0	-
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	0	0	0	0	-
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription	8	72.73	7	70	1.00 (1.0000)*

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10		Comparison Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	7	63.64	***	***	0.08 (0.0805)*

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum; LMP2: Last Menstrual Period Date Plus 2 weeks
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 165. Association between potential paternal risk factors/confounders for NDD by paternal exposure group; primary outcome

Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10		Comparison Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Paternal risk factors/confounders					
Affective disorder [a,b]	0	0.00	0	0.00	-
Bipolar affective disorder [a]	0	0.00	0	0.00	-

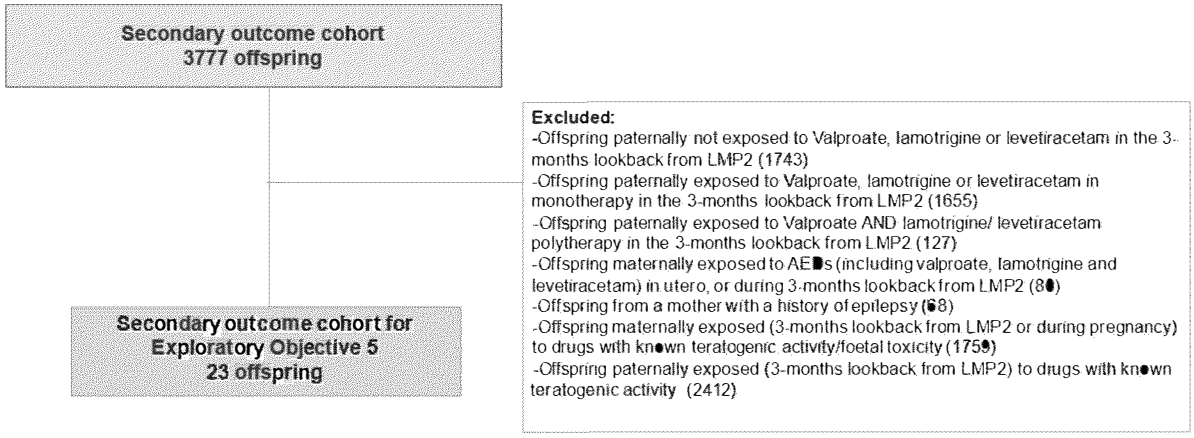
Paternal exposure group NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10		Comparison Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Mania [a]	0	0.00	0	0.00	-
Neurotic disorder [a]	0	0.00	***	***	1.16 (0.2825)
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00	-
Substance abuse [c]	0	0.00	0	0.00	-
Paternal polypharmacy index [d] (categorical)					
0	***	***	***	***	-
1-4	***	***	***	***	-
5-10	0	0.00	0	0.00	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	1.17 (0.2787)
Paternal polypharmacy index [d] (continuous)					
Mean (SD)	0.45 (0.69)		0.90 (1.20)		122.50 (0.3456)*
Median (25th - 75th percentile)	0 (0.00, 1.00)		1 (0.00, 1.00)		-
Min, max	***		***		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	0	0.00	***	***	2.43 (0.1189)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	6	54.55	***	***	0.44 (0.5051)
Father's age [e] (categorical)					
≤20 years	0	0.00	***	***	-
21-25	***	***	0	0.00	-

Paternal exposure group **NDD** **Number of offspring**	**Valproate** **N=11**		**Lamotrigine/levetiracetam (composite)** **N=10**		**Comparison** **Valproatevs Lamotrigine /levetiracetam** **-**
	N	**%**	**N**	**%**	
26-30	***	***	***	***	-
31-35	***	***	***	***	-
36-40	0	0.00	***	***	-
>40	***	***	***	***	-
Test statistics	-	-	-	-	7.30 (0.1991)
Father's age [e] (continuous)					
Mean (SD)	31.00 (6.65)		33.10 (6.85)		-0.71 (0.4857)
Median (25^{th} - 75^{th} percentile)	29 (25.00, 33.00)		33.5(31.00, 35.00)		-
Min, max	***		***		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [f,g]					
1996-2001	5	45.45	***	***	-
2002-2007	***	***	***	***	-
2008-2012	***	***	***	***	-
2013-2018	0	0.00	***	***	-
Test statistics	-	-	-	-	3.96 (0.2657)

Paternal exposure group					Comparison
NDD Number of offspring	Valproate N=11		Lamotrigine/levetiracetam (composite) N=10		Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) all available data prior to index date (childbirth)
b) excluding bipolar affective disorder and mania
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

15.1.7 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Explorative analysis 5 CM)



CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 32. Study population for secondary outcome explorative analysis 5 in Denmark

Table 166. Offspring demographic characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM **Number of offspring**	**Valproate(polytherapy)** **N=0**		**Lamotrigine/levetiracetam(polytherapy)** **N=23**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	0	0.00
28-31 (very preterm)	0	0.00	0	0.00
32-36 (moderate to late preterm)	0	0.00	***	***
37-41 (at term)	0	0.00	***	***
≥42 (post-term)	0	0.00	***	***
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	0	0.00
1000-1499 (very low)	0	0.00	0	0.00
1500-2499 (low)	0	0.00	***	***
≥2500	0	0.00	***	***
Missing	0	0.00	0	0.00
Gender [a]				
Male	0	0.00	13	56.52
Female	0	0.00	10	43.48
Missing	0	0.00	0	0.00
Year of birth				
1997	0	0.00	0	0.00
1998	0	0.00	0	0.00
1999	0	0.00	0	0.00
2000	0	0.00	0	0.00
2001	0	0.00	0	0.00
2002	0	0.00	0	0.00
2003	0	0.00	0	0.00
2004	0	0.00	0	0.00
2005	0	0.00	***	***
2006	0	0.00	***	***
2007	0	0.00	***	***
2008	0	0.00	***	***
2009	0	0.00	***	***
2010	0	0.00	0	0.00
2011	0	0.00	0	0.00
2012	0	0.00	***	***
2013	0	0.00	***	***
2014	0	0.00	***	***
2015	0	0.00	***	***

	Paternal exposure group			
CM Number of offspring	**Valproate(polytherapy) N=0**		**Lamotrigine/levetiracetam(polytherapy) N=23**	
	N	**%**	**N**	**%**
2016	0	0.00	***	***
2017	0	0.00	***	***
2018	0	0.00	0	0.00

CM: Congenital Malformations
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index (childbirth)

Table 167. Offspring clinical characteristics paternal exposure group; secondary outcome

	Paternal exposure group			
CM Number of offspring	**Valproate(polytherapy) N=0**		**Lamotrigine/levetiracetam (polytherapy) N=23**	
	N	**%**	**N**	**%**
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital Herpes Simplex	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00
Congenital varicella	0	0.00	0	0.00
Foetal alcohol syndrome	0	0.00	0	0.00
Outcomes				
CM	0	0.00	***	***
Major CM (at any time)	0	0.00	***	***
Minor CM (at any time)	0	0.00	***	***
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]				
Stillbirth	0	0.00	0	0.00
Spontaneous abortion [c]	NA	NA	NA	NA
Intrauterine growth retardation	0	0.00	***	***
Perinatal mortality	0	0.00	0	0.00

CM: Congenital Malformations; CMV: Cytomegalovirus; NA: not available
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date
b) Denominator for the percentage is the number of offspring with CM.
c) Information on spontaneous abortion is not available in Denmark.

Table 168. Maternal demographic characteristics by paternal exposure group; secondary outcome

CM **Number of offspring**	**Valproate(polytherapy)** **N=0**		**Lamotrigine/levetiracetam(polytherapy)** **N=23**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	0	0.00	0	0.00
21-25	0	0.00	***	***
26-30	0	0.00	8	34.78
31-35	0	0.00	8	34.78
36-40	0	0.00	***	***
>40	0	0.00	0	0.00
Mean (SD)	-		31.04 (3.62)	
Median (25^{th} - 75^{th} percentile)	-		31 (28.00, 34.00)	
Min, max	-		***	
Missing	0	0.00	0	0.00

CM: Congenital Malformations, SD: Standard Deviation, Min: Minimum, Max: Maximum
*** Masked values indicated that data was calculated but not disclosed
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 169. Maternal clinical characteristics by paternal exposure group; secondary outcome

CM **Number of offspring**	**Valproate(polytherapy)** **N=0**	**Lamotrigine/levetiracetam(polytherapy)** **N=23**

	N	%	N	%
Diabetes [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00
Obesity [b]	0	0.00	0	0.00
CMV [c]	0	0.00	0	0.00
Folate deficiency [c]	0	0.00	0	0.00
Gestational diabetes [c]	0	0.00	0	0.00
Herpes simplex virus [c]	0	0.00	0	0.00
Rubella [c]	0	0.00	0	0.00
Toxoplasmosis [c]	0	0.00	0	0.00
Varicella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	0	0.00
Smoking prior to LMP2 [b]				
Yes	0	0.00	0	0.00
No	0	0.00	***	***
Missing	0	0.00	***	***
Smoking during pregnancy [c]				
Yes	0	0.00	***	***
No	0	0.00	***	***
Missing	0	0.00	0	0.00
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AEDs during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00

CM Number of offspring	Valproate(polytherapy) N=0		Lamotrigine/levetiracetam(polytherapy) N=23	
	N	**%**	**N**	**%**
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K-means cluster prior to LMP2 [d]				
Unexposed	0	0.00	23	100.00
K-means cluster during pregnancy [c]				
Unexposed	0	0.00	23	100.00
Maternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [d] - mothers with at least one prescription	0	0.00	0	0.00
Maternal exposure to teratogenic activity/foetal toxicity during pregnancy [c] - mothers with atleast one prescription	0	0.00	0	0.00

AED: Antiepileptic Drug; CM: Congenital Malformations; LMP2: Last Menstrual Period Date Plus 2 weeks; SD: Standard Deviation; CMV: Cytomegalovirus
Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) all available data prior to index date (12th week of gestation in Norway, 22nd week of gestation in Denmark)
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Denmark during the study period

Table 170. Paternal demographic characteristics by paternal exposure group; secondary outcome

CM Number of offspring	Paternal exposure group Valproate (polytherapy) N=0		Lamotrigine/levetiracetam (polytherapy) N=23	
	N	**%**	**N**	**%**
Father's age [a]				
≤20 years	0	0.00	0	0.00
21-25	0	0.00	0	0.00
26-30	0	0.00	6	26.09
31-35	0	0.00	11	47.83

CM Number of offspring	Paternal exposure group Valproate (polytherapy) N=0		Lamotrigine/levetiracetam (polytherapy) N=23	
	N	**%**	**N**	**%**
36-40	0	0.00	***	***
>40	0	0.00	***	***
Mean (SD)	-	-	33.70 (4.85)	-
Median (25th - 75th percentile)	-	-	34 (29.00, 36.00)	-
Min, max	-	-	***	-
Year of offspring conception [b]				
1996	0	0.00	0	0.00
1997	0	0.00	0	0.00
1998	0	0.00	0	0.00
1999	0	0.00	0	0.00
2000	0	0.00	0	0.00
2001	0	0.00	0	0.00
2002	0	0.00	0	0.00
2003	0	0.00	0	0.00
2004	0	0.00	***	***
2005	0	0.00	***	***
2006	0	0.00	***	***
2007	0	0.00	***	***
2008	0	0.00	***	***
2009	0	0.00	***	***
2010	0	0.00	0	0.00
2011	0	0.00	***	***
2012	0	0.00	***	***
2013	0	0.00	***	***
2014	0	0.00	***	***
2015	0	0.00	***	***
2016	0	0.00	***	***
2017	0	0.00	0	0.00
2018	0	0.00	0	0.00

Legend: CM: Congenital Malformations, LMP2: Last Menstrual Period Date Plus 2 weeks, Min: Minimum; Max: Maximum; SD: Standard Deviation
*** Masked values indicated that data was calculated but not disclosed
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) at mother's LMP2

Table 171. Paternal clinical characteristics by paternal exposure group; secondary outcome

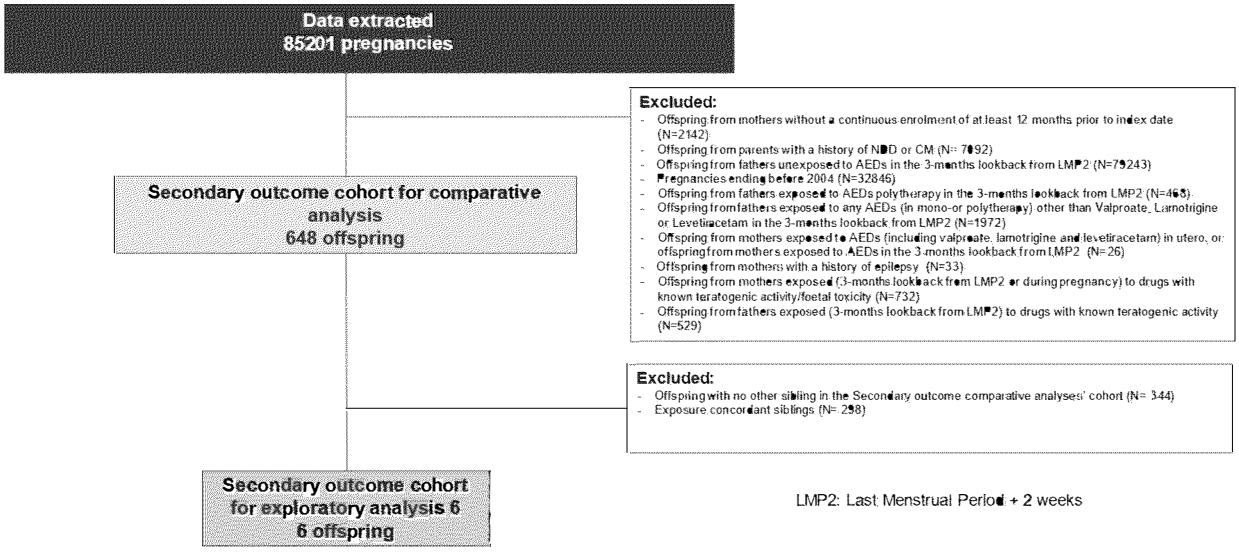
	Paternal exposure group

CM Number of offspring	Valproate (polytherapy) N=0		Lamotrigine/levetiracetam (polytherapy) N=23	
	N	%	N	%
Medication use				
Exposure to AEDs[a, b]				
Fatty acid derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Barbiturates derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	18	78.26
Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Carboxamide derivatives and other antiepileptics	0	0.00	5	21.74
Fatty acid derivatives and Carboxamide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and other antiepileptics	0	0.00	0	0.00
Benzodiazepine derivatives and Fatty acid derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives	0	0.00	0	0.00
Succinimide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Hydantoin derivatives and Carboxamide derivatives	0	0.00	0	0.00
Hydantoin derivatives and other antiepileptics	0	0.00	0	0.00
Hydantoin derivatives and Succinimide derivatives	0	0.00	0	0.00
Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Fatty acid derivatives	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives	0	0.00	0	0.00
Barbiturates derivatives and Benzodiazepine derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Carboxamide derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	0	0.00
Benzodiazepine derivatives and Succinimide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Fatty acid derivatives and Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	0	0.00
AED indication				
Epilepsy	0	0.00	***	***
Bipolar affective disorder and mania	0	0.00	***	***

CM Number of offspring	Paternal exposure group Valproate (polytherapy) N=0		Lamotrigine/levetiracetam (polytherapy) N=23	
	N	%	N	%
Other/unknown	0	0.00	***	***
K-means cluster [a]				
Cluster A	0	0.00	***	***
Cluster B	0	0.00	***	***
Paternal exposure to teratogenic activity/foetal toxicity [a]	0	0.00	0	0.00

AED: Antiepileptic Drug; CM: Congenital Malformations
*** Masked values indicated that data was calculated but not disclosed. Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
Cluster A: constant high exposure; Cluster B: constant low exposure
a) 3 months lookback from LMP2
b) Valproate or lamotrigine/levetiracetam in combination with other AED(s). Each combination found in the data were listed here.

15.1.8 Exposure to valproate or lamotrigine/levetiracetam in paternally and maternally matched siblings (Exploratory analysis 6 CM)



CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 33 Study population for secondary outcome exploratory analysis 6 in Denmark

Table 172. Offspring demographic characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM **Number of offspring**	**Valproate** **N<5**		**Lamotrigine/levetiracetam (composite)** **N<5**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	***	***	***	***
28-31 (very preterm)	***	***	***	***
32-36 (moderate to late preterm)	***	***	***	***
37-41 (at term)	***	***	***	***
≥42 (post-term)	***	***	***	***
Missing	***	***	***	***
Birth weight (g)				
<1000 (extremely low)	***	***	***	***
1000-1499 (very low)	***	***	***	***
1500-2499 (low)	***	***	***	***
≥2500	***	***	***	***
Missing	***	***	***	***
Gender [a]				
Male	***	***	***	***
Female	***	***	***	***
Missing	***	***	***	***
Year of birth				
1997	***	***	***	***
1998	***	***	***	***
1999	***	***	***	***
2000	***	***	***	***
2001	***	***	***	***
2002	***	***	***	***
2003	***	***	***	***
2004	***	***	***	***
2005	***	***	***	***
2006	***	***	***	***
2007	***	***	***	***
2008	***	***	***	***
2009	***	***	***	***
2010	***	***	***	***
2011	***	***	***	***
2012	***	***	***	***
2013	***	***	***	***
2014	***	***	***	***
2015	***	***	***	***
2016	***	***	***	***

	Paternal exposure group			
CM Number of offspring	**Valproate N<5**		**Lamotrigine/levetiracetam (composite) N<5**	
	N	**%**	**N**	**%**
2017	***	***	***	***
2018	***	***	***	***

CM: Congenital Malformations
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 173. Offspring clinical characteristics paternal exposure group; secondary outcome

Paternal exposure group				
CM Number of offspring	**Valproate N<5**		**Lamotrigine/levetiracetam (composite) N<5**	
	N	**%**	**N**	**%**
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital Herpes Simplex	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00
Congenital varicella	0	0.00	0	0.00
Foetal alcohol syndrome	0	0.00	0	0.00
Outcomes				
CM	0	0.00	0	0.00
Major CM (at any time)	0	0.00	0	0.00
Minor CM (at any time)	0	0.00	0	0.00
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]				
Stillbirth	0	0.00	0	0.00
Spontaneous abortion [c]	NA	NA	NA	NA
Intrauterine growth retardation	0	0.00	0	0.00
Perinatal mortality	0	0.00	0	0.00

CM: Congenital Malformations; CMV: Cytomegalovirus
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date
b) Denominator for the percentage is the number of offspring with CM.
c) Information on spontaneous abortion is not available in Denmark.

Table 174. Maternal demographic characteristics by paternal exposure group; secondary outcome

Paternal exposure group				
CM Number of offspring	**Valproate N<5**		**Lamotrigine/levetiracetam (composite) N<5**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	***	***	***	***
21-25	***	***	***	***
26-30	***	***	***	***
31-35	***	***	***	***
36-40	***	***	***	***
>40	***	***	***	***
Mean (SD)	***		***	
Median (25^{th} - 75^{th} percentile)	***		***	
Min, max	***		***	
Missing	0	0.00	0	0.00

SD: Standard Deviation; CM: Congenital Malformations; Min: Minimum; Max: Maximum
*** Masked values indicated that data was calculated but not disclosed
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 175. Maternal clinical characteristics by paternal exposure group; secondary outcome

Paternal exposure group				
CM Number of offspring	**Valproate N<5**		**Lamotrigine/levetiracetam (composite) N<5**	
	N	**%**	**N**	**%**
Comorbidities				
Diabetes [a]	***	***	***	***
Epilepsy [a]	***	***	***	***
Obesity [b]	***	***	***	***
CMV [c]	***	***	***	***
Folate deficiency [c]	***	***	***	***
Gestational diabetes [c]	***	***	***	***
Herpes simplex virus [c]	***	***	***	***
Rubella [c]	***	***	***	***
Toxoplasmosis [c]	***	***	***	***
Varicella [c]	***	***	***	***
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	***	***	***	***

	Paternal exposure group			
CM **Number of offspring**	**Valproate** **N<5**		**Lamotrigine/levetiracetam (composite)** **N<5**	
	N	**%**	**N**	**%**
Alcohol abuse during pregnancy [c]	***	***	***	***
Substance abuse prior to LMP2 [b]	***	***	***	***
Substance abuse during pregnancy [c]	***	***	***	***
Smoking prior to LMP2 [b]				
Yes	***	***	***	***
No	***	***	***	***
Missing	***	***	***	***
Smoking during pregnancy [c]				
Yes	***	***	***	***
No	***	***	***	***
Missing	***	***	***	***
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	***	***	***	***
Lamotrigine	***	***	***	***
Levetiracetam	***	***	***	***
Barbiturates and derivatives	***	***	***	***
Hydantoin derivatives	***	***	***	***
Oxazolidine derivatives [e]	***	***	***	***
Succinimide derivatives	***	***	***	***
Benzodiazepine derivatives	***	***	***	***
Carboxamide derivatives	***	***	***	***
Fatty acid derivatives	***	***	***	***
Other antiepileptics	***	***	***	***
Exposure to AEDs during pregnancy [c]				
Valproate	***	***	***	***
Lamotrigine	***	***	***	***
Levetiracetam	***	***	***	***
Barbiturates and derivatives	***	***	***	***
Hydantoin derivatives	***	***	***	***
Oxazolidine derivatives [e]	***	***	***	***
Succinimide derivatives	***	***	***	***
Benzodiazepine derivatives	***	***	***	***
Carboxamide derivatives	***	***	***	***
Fatty acid derivatives	***	***	***	***
Other antiepileptics	***	***	***	***
K-means cluster prior to LMP2 [d]				
Unexposed	***	***	***	***
K-means cluster during pregnancy [c]				

	Paternal exposure group			
CM **Number of offspring**	**Valproate** **N<5**		**Lamotrigine/levetiracetam (composite)** **N<5**	
	N	**%**	**N**	**%**
Unexposed	***	***	***	***
Maternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [d] - mothers with at least one prescription	***	***	***	***
Maternal exposure to teratogenic activity/foetal toxicity during pregnancy [c] - mothers with atleast one prescription	***	***	***	***

AED: Antiepileptic Drug; CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks;
*** Masked values indicated that data was calculated but not disclosed
Legend:
Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (12th week of gestation in Norway, 22nd week of gestation in Denmark)
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Denmark during the study period

Table 176. Paternal demographic characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM **Number of offspring**	**Valproate** **N<5**		**Lamotrigine/levetiracetam (composite)** **N=<5**	
	N	**%**	**N**	**%**
Father's age [a]				
≤20 years	***	***	***	***
21-25	***	***	***	***
26-30	***	***	***	***
31-35	***	***	***	***
36-40	***	***	***	***
>40	***	***	***	***
Mean (SD)	***		***	
Median (25th - 75th percentile)	***		***	
Min, max	***		***	
Year of offspring conception [b]				
1996	***	***	***	***
1997	***	***	***	***

	Paternal exposure group			
CM Number of offspring	**Valproate N<5**		**Lamotrigine/levetiracetam (composite) N=<5**	
	N	**%**	**N**	**%**
1998	***	***	***	***
1999	***	***	***	***
2000	***	***	***	***
2001	***	***	***	***
2002	***	***	***	***
2003	***	***	***	***
2004	***	***	***	***
2005	***	***	***	***
2006	***	***	***	***
2007	***	***	***	***
2008	***	***	***	***
2009	***	***	***	***
2010	***	***	***	***
2011	***	***	***	***
2012	***	***	***	***
2013	***	***	***	***
2014	***	***	***	***
2015	***	***	***	***
2016	***	***	***	***
2017	***	***	***	***
2018	***	***	***	***

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) at mother's LMP2

Table 177. Paternal clinical characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM Number of offspring	**Valproate N<5**		**Lamotrigine/levetiracetam (composite) N<5**	
	N	**%**	**N**	**%**
Medication use				
AED indication				
Epilepsy	***	***	***	***
Bipolar affective disorder and mania	***	***	***	***

Other/unknown	***	***	***	***
K-means cluster [a]				
Group A	***	***	***	***
Group B	***	***	***	***
Paternal exposure to teratogenic activity/foetal toxicity [a]	***	***	***	***

CM: Congenital Malformations
*** Masked values indicated that data was calculated but not disclosed
Legend:
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) 3 months lookback from LMP2

Table 178.Association between potential offspring risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				**Comparison ***
CM Number of offspring	**Valproate N<5**		**Lamotrigine/levetiracetam (composite) N<5**		**Valproatevs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	
Offspring risk factors/confounders[a]					
Congenital CMV	***	***	***	***	-
Congenital Herpes Simplex	***	***	***	***	-
Congenital rubella	***	***	***	***	-
Congenital toxoplasmosis	***	***	***	***	-
Congenital varicella	***	***	***	***	-
Foetal alcohol syndrome	***	***	***	***	-

CM; Congenital Malformations; CMV: Cytomegalovirus
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 179. Association between potential maternal risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group	**Comparison ***

CM Number of offspring	Valproate N<5		Lamotrigine/levetiracetam (composite) N<5		Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Maternal risk factors/confounders **Mother´s age [a](categorical)**					
≤20 years	***	***	***	***	-
21-25	***	***	***	***	-
26-30	***	***	***	***	-
31-35	***	***	***	***	-
36-40	***	***	***	***	-
>40	***	***	***	***	-
Test statistics	-	-	-	-	3.00 (0.2231)
Mother´s age [a](continuous)					
Mean (SD)	***		***		-0.46 (0.7076)
Median (25^{th} - 75^{th} percentile)	***		***		-
Min, max	***		***		-
Missing	-		-		-
Diabetes [b]	***	***	***	***	-
Obesity [c]	***	***	***	***	-
Alcohol abuse prior to LMP2 [c]	***	***	***	***	-
Alcohol abuse during pregnancy [d]	***	***	***	***	-
Substance abuse prior to LMP2 [c]	***	***	***	***	-
Substance abuse during pregnancy [d]	***	***	***	***	-
Smoking prior to LMP2 [c]					
No	***	***	***	***	-
Yes	***	***	***	***	-
Missing	***	***	***	***	-
Test statistics without 'Missing' category	-	-	-	-	-
Smoking during pregnancy [d]					
No	***	***	***	***	-
Yes	***	***	***	***	-
Missing	***	***	***	***	-
Test statistics without 'Missing' category	-	-	-	-	-
CMV [d]	***	***	***	***	-
Folate deficiency [d]	***	***	***	***	-
Gestational diabetes [d]	***	***	***	***	1.00 (1.0000)*
Herpes simplex virus [d]	***	***	***	***	-
Rubella [d]	***	***	***	***	-
Toxoplasmosis [d]	***	***	***	***	-
Varicella [d]	***	***	***	***	-

	Paternal exposure group				Comparison *
CM **Number of offspring**	**Valproate** **N<5**		**Lamotrigine/levetiracetam (composite)** **N<5**		**Valproatevs Lamotrigine /levetiracetam** **-**
	N	**%**	**N**	**%**	

CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; Min: Minimum; Max: Maximum; SD: Standard Deviation
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (12th week of gestation in Norway, 22nd week of gestation in Denmark)
b) all available data prior to index date
c) 12 months lookback from LMP2
d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 180. Association between potential paternal risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				Comparison *
CM **Number of offspring**	**Valproate** **N<5**		**Lamotrigine/levetiracetam (composite)** **N<5**		**Valproatevs Lamotrigine /levetiracetam** **-**
	N	**%**	**N**	**%**	
Paternal risk factors/confounders **Father´s age [a](categorical)**					
≤20 years	***	***	***	***	-
21-25	***	***	***	***	-
26-30	***	***	***	***	-
31-35	***	***	***	***	-
36-40	***	***	***	***	-
>40	***	***	***	***	-
Test statistics	-	-	-	-	2.63 (0.2691)
Father´s age [a] (continuous)					
Mean (SD)	***		***		-2.05 (0.2482)
Median (25th - 75th percentile)	***		***		-
Min, max	***		***		-
Missing	***	***	***	***	-
Year of offspring conception [b,c]					

2003-2007	***	***	***	***	-
2008-2012	***	***	***	***	-
2013-2018	***	***	***	***	-
Test statistics	-	-	-	-	0.60 (0.4386)

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum
*** Masked values indicated that data was calculated but not disclosed
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (12th week of gestation in Norway, 22nd week of gestation in Denmark)
b) at mother's LMP2
c) calendar years were grouped in each country according to the length of the study period
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

15.2 Sweden

15.2.1.1 Description of the offspring, maternal and paternal characteristics in the Primary outcome cohort

Characteristics of the offspring, mothers and fathers from the Primary outcome cohort are reported in Table 181 to Table 183. Of the 6664 offspring from the Primary outcome cohort, 51.0% were male, 1.2% were diagnosed with epilepsy, and 1.3% were exposed to AEDs drugs during the period they were followed-up (Table 181).

Regarding maternal characteristics of this group, the median (IQR) age of mothers at childbirth was 31 (27, 35) years. The most frequent maternal comorbidities diagnosed prior to childbirth were neurotic disorders (12.7%), affective disorder (9.4%) and gestational diabetes (3.6%), smoking prior to LMP2 was observed in 17.1% from a total of 6,664 mothers from the entire cohort (including 4.8% missing values). Smoking during pregnancy was observed in 8.8% mothers from the entire cohort (including 2.9% missing values) (Table 182).

The median (IQR) of maternal polypharmacy index during pregnancy was 1.0 (0.0, 2.0), and 45.8% of mothers had at least one prescription of concomitant medications associated with neuropsychiatric adverse events during pregnancy (Table 182).

Regarding paternal characteristics of fathers from the Primary outcome cohort, the median (IQR) age of fathers at childbirth was 34 (30-39) years Table 183.

The most frequent paternal comorbidities diagnosed prior to childbirth were neurotic disorders (23.5%), affective disorder excluding bipolar affective disorder and mania (17.9%) and bipolar affective disorder (10.5%). With regards to paternal exposure to AEDs, 14.5% of fathers were exposed to valproate in monotherapy and 22.3% were exposed to lamotrigine/levetiracetam in monotherapy in the 3 months lookback period from LMP2, while 62.9% were exposed to other antiepileptics. The distribution of the year of offspring conception is presented, with only 2.1% of conceptions occurring in 2019. The small proportion is attributed to the end of the study period in December 2019 (Table 183).

Table 181 Description of the offspring characteristics in the Primary outcome cohort in Sweden (N=6664)

NDD - offspring characteristics		
Number of offspring=6,664	**N**	**%**
Gestational age (weeks)		
<28 (extremely preterm)	18	0.27
28-31 (very preterm)	37	0.56
32-36 (moderate to late preterm)	305	4.58
37-41 (at term)	5887	88.34
≥42 (post-term)	417	6.26
Missing	0	0.00

NDD - offspring characteristics		
Birth weight (g)		
<1000 (extremely low)	19	0.29%
1000-1499 (very low)	23	0.35%
1500-2499 (low)	205	3.08%
≥2500	6407	96.14%
Missing	10	0.15%
Gender [a]		
Male	3399	51.01%
Female	3265	48.99%
Missing	0	0.00%
Comorbidities [b]		
Congenital CMV	1	0.02%
Congenital rubella	0	0.00%
Epilepsy	82	1.23%
Foetal alcohol syndrome	0	0.00%
Fragile X syndrome	0	0.00%
Lejeune/cri du chat syndrome	0	0.00%
Tuberous sclerosis	4	0.06%
Medication use [b]		
Exposure to AEDs	84	1.26%

AED: antiepileptic drug; CMV: cytomegalovirus; NDD: neurodevelopmental disorders; g: grams
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth); b) between index and exit date; b) between index and exit date.

Table 182 Description of the maternal characteristics in the Primary outcome cohort in Sweden (N=6664)

NDD - maternal characteristics		
Number of offspring=6664	**N**	**%**
Mother's age[a]		
≤20 years	120	1.80
21-25	907	13.61
26-30	2018	30.28
31-35	2167	32.52
36-40	1234	18.52
>40	218	3.27
Mean (SD)	31.11 (5.28)	
Median (25^{th} - 75^{th} percentile)	31.00 (27.00, 35.00)	
Min, max	16.00, 53.00	
Missing	0	0.00
Comorbidities		
Affective disorder[b]	624	9.36
Diabetes[b]	87	1.31

NDD - maternal characteristics		
Number of offspring=6664		
	N	**%**
Epilepsy[b]	55	0.83
Neurotic disorder[b]	846	12.70
Schizophrenia, schizotypal and delusional disorders[b]	26	0.39
Obesity[c]	92	1.38
CMV[d]	2	0.03
Gestational diabetes[d]	237	3.56
Rubella[d]	0	0.00
Lifestyle characteristics		
Alcohol abuse prior to LMP2[c]	31	0.47
Alcohol abuse during pregnancy[d]	14	0.21
Substance abuse prior to LMP2[c]	32	0.48
Substance abuse during pregnancy[d]	35	0.53
Smoking prior to LMP2[e]		
Yes	1136	17.05
No	5208	78.15
Missing	320	4.80
Smoking during pregnancy[d]		
Yes	586	8.79
No	5884	88.30
Missing	194	2.91
Medication use		
Exposure to AEDs prior to LMP2[e]		
Valproic Acid	6	0.09
Lamotrigine	62	0.93
Levetiracetam	3	0.05
Barbiturates and derivatives	2	0.03
Hydantoin derivatives	0	0.00
Oxazolidine derivatives[f]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	13	0.20
Carboxamide derivatives	11	0.17
Fatty acid derivatives	6	0.09
Other antiepileptics	119	1.79
Exposure to AEDs during pregnancy[d]		
Valproic Acid	8	0.12
Lamotrigine	52	0.78
Levetiracetam	2	0.03
Barbiturates and derivatives	1	0.02
Hydantoin derivatives	0	0.00
Oxazolidine derivatives[f]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	10	0.15
Carboxamide derivatives	10	0.15

NDD - maternal characteristics		
Number of offspring=6664	**N**	**%**
Fatty acid derivatives	8	0.12
Other antiepileptics	101	1.52
Maternal polypharmacy index prior to LMP2[e]		
0	4382	65.76
1-4	2113	31.71
5-10	164	2.46
>10	5	0.08
Mean (SD)	0.71 (1.33)	
Median (25^{th} - 75^{th} percentile)	0.00(0.00, 1.00)	
Min, max	0.00, 13.00	
Maternal polypharmacy index during pregnancy[d]		
0	3256	48.86
1-4	3137	47.07
5-10	261	3.92
>10	10	0.15
Mean (SD)	1.08 (1.55)	
Median (25^{th} - 75^{th} percentile)	1.00(0.00, 2.00)	
Min, max	0.00, 15.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior toLMP2[c]- mothers with at least one prescription	915	13.73
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy[d]- mothers with at least 1 prescription	574	8.61
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2[c]-mothers with at least one prescription	4147	62.23
Concomitant medications associated with neuropsychiatric adverse events during pregnancy[d]-mothers with at least one prescription	3055	45.84

AED: antiepileptic drug; CMV: cytomegalovirus; LMP2: last menstrual period + 2 weeks; NDD: neurodevelopmental disorders; SD: standard deviation

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at index (childbirth); b) all available data prior to index date; c) 12 months lookback from LMP2; d) during pregnancy (from LMP2 until index date); e) 3 months lookback from LMP2; f) Oxazolidine derivatives were not marketed in Sweden.

Table 183 Description of the paternal characteristics in the Primary outcome cohort in Sweden (N=6664)

NDD - paternal characteristics		
Number of offspring=6664		
	N	**%**
Father's age[a]		
≤20 years	31	0.47
21-25	373	5.60
26-30	1301	19.52
31-35	2114	31.72
36-40	1668	25.0%
>40	1177	17.66
Mean (SD)	34.86 (6.61)	
Median (25th - 75th percentile)	34.00(30.00, 39.00)	
Min, max	16.00, 77.00	
Missing	0	0.00
Year of offspring conception[b]		
2006	289	4.34
2007	422	6.33
2008	485	7.28
2009	520	7.80
2010	516	7.74
2011	493	7.40
2012	532	7.98
2013	543	8.15
2014	519	7.79
2015	528	7.92
2016	589	8.84
2017	548	8.22
2018	539	8.09
2019	141	2.12
Comorbidities[c]		
Affective disorder excluding bipolar affective disorder and mania	1193	17.90
Bipolar affective disorder	698	10.47
Mania	44	0.66
Neurotic disorder	1568	23.53
Schizophrenia, schizotypal and delusional disorders	182	2.73
Lifestyle characteristics		
Substance abuse[e]	0	0.00
Medication use		
Exposure to AEDs[f]		
Valproic Acid[g]	1284	19.27
Lamotrigine[g]	1614	24.22
Levetiracetam[g]	515	7.73
Barbiturates and derivatives[g]	32	0.48
Hydantoin derivatives[g]	93	1.40
Oxazolidine derivatives[d,g]	0	0.00
Succinimide derivatives[g]	8	0.12
Benzodiazepine derivatives[g]	213	3.20

NDD - paternal characteristics		
Number of offspring=6664		
	N	**%**
Carboxamide derivatives[g]	1461	21.92
Fatty acid derivatives[g]	1289	19.34
Other antiepileptics[g]	4191	62.89
Valproic acid in monotherapy	968	14.53
Lamotrigine in monotherapy	1262	18.94
Levetiracetam in monotherapy	221	3.32
Lamotrigine/levetiracetam in monotherapy	1483	22.25
Paternal polypharmacy index[f]		
0	3131	46.98
1-4	3075	46.14
5-10	438	6.57
>10	20	0.30
Mean (SD)	1.35 (1.90)	
Median (25^{th} - 75^{th} percentile)	1.00(0.00, 2.00)	
Min, max	0.00, 22.00	
Concomitant medications associated with valproate-indicated psychiatric conditions[e]- fathers with at least one prescription	3721	55.84
Concomitant medications associated with neuropsychiatric adverse events[e]- fathers with at least one prescription	4526	67.92
Fathers exposed to AEDs polytherapy prior to LMP2[f]	779	11.69
Fathers exposed to valproate in combination with other AEDs prior to LMP2[f]	304	4.56
Fathers switching to/from an AED other than valproate, lamotrigine, levetiracetam prior to LMP2[f]	347	5.21

AED: antiepileptic drug; CMV: cytomegalovirus; LMP2: last menstrual period + 2 weeks; NDD: neurodevelopmental disorders; SD: standard deviation

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics are described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.

a) at index (childbirth); b) at mother's LMP2; c) all available data prior to index date; c) Oxazolidine derivatives were not marketed in Sweden; e) 12 months lookback from LMP2; f) 3 months lookback from LMP2; g) in mono- or polytherapy.

15.2.2 Cumulative incidence proportion of NDD by gender

Table 184 Cumulative incidence proportion (risk) of NDD by paternal exposure group for male offspring; Primary outcome cohort for descriptive analyses (N=1,256)

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	485	771	668	103	1256
0-1 years	n	0	1	0	1	1
	n/N*100	0.00 (0.00, 0.00)	0.13 (0.00, 0.38)	0.00 (0.00, 0.00)	0.97 (0.00, 2.86)	0.08 (0.00, 0.24)
	N	462	677	593	84	1139
1-2 years	n	2	2	2	0	4
	n/N*100	0.43 (0.00, 1.03)	0.30 (0.00, 0.70)	0.34 (0.00, 0.80)	0.00 (0.00, 0.00)	0.35 (0.01, 0.69)
	N	433	599	529	70	1032
2-3 years	n	2	5	4	1	7
	n/N*100	0.46 (0.00, 1.10)	0.83 (0.11, 1.56)	0.76 (0.02, 1.49)	1.43 (0.00, 4.21)	0.68 (0.18, 1.18)
	N	402	506	453	53	908
3-4 years	n	3	3	3	0	6
	n/N*100	0.75 (0.00, 1.59)	0.59 (0.00, 1.26)	0.66 (-0.08, 1.41)	0.00 (0.00, 0.00)	0.66 (0.13, 1.19)
	N	360	438	393	45	798
4-5 years	n	3	4	4	0	7
	n/N*100	0.83 (0.00, 1.77)	0.91 (0.02, 1.80)	1.02 (0.03, 2.01)	0.00 (0.00, 0.00)	0.88 (0.23, 1.52)
	N	319	344	314	30	663
5-6 years	n	7	4	3	1	11
	n/N*100	2.19 (0.59, 3.80)	1.16 (0.03, 2.30)	0.96 (0.00, 2.03)	3.33 (0.00, 9.76)	1.66 (0.69, 2.63)
	N	268	283	259	24	551
6-7 years	n	3	6	6	0	9
	n/N*100	1.12 (0.00, 2.38)	2.12 (0.44, 3.80)	2.32 (0.48, 4.15)	0.00 (0.00, 0.00)	1.63 (0.57, 2.69)
	N	224	218	202	16	442
7-8 years	n	6	2	2	0	8
	n/N*100	2.68 (0.56, 4.79)	0.92 (0.00, 2.18)	0.99 (0.00, 2.36)	0.00 (0.00, 0.00)	1.81 (0.57, 3.05)
	N	178	165	152	13	343

8-9 years	n	3	4	4	0	7
	n/N*100	1.69 (0.00, 3.58)	2.42 (0.08, 4.77)	2.63 (0.09, 5.18)	0.00 (0.00, 0.00)	2.04 (0.54, 3.54)
	N	146	111	102	9	257
9-10 years	n	4	3	1	2	7
	n/N*100	2.74 (0.09, 5.39)	2.70 (0.00, 5.72)	0.98 (0.00, 2.89)	22.22 (0.00, 49.38)	2.72 (0.73, 4.71)
	N	108	76	69	7	184
10-11 years	n	4	0	0	0	4
	n/N*100	3.70 (0.14, 7.27)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	2.17 (0.07, 4.28)
	N	75	42	38	4	117
11-12 years	n	0	2	2	0	2
	n/N*100	0.00 (0.00, 0.00)	4.76 (0.00, 11.20)	5.26 (0.00, 12.36)	0.00 (0.00, 0.00)	1.71 (0.00, 4.06)
	N	**485**	**771**	**668**	**103**	**1256**
Overall (0-12 years)	**n**	37	36	31	5	73
	n/N*100	7.63 (5.27, 9.99)	4.67 (3.18, 6.16)	4.64 (3.05, 6.24)	4.85 (0.70, 9.00)	5.81 (4.52, 7.11)

NDD: neurodevelopmental disorders
Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) are presented.

Table 185 Cumulative incidence proportion (risk) of NDD by paternal exposure group for female offspring; Primary outcome cohort for descriptive analyses (N=1,195)

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	483	712	594	118	1195
0-1 years	n	1	3	3	0	4
	n/N*100	0.21 (0.00, 0.61)	0.42 (0.00, 0.90)	0.51 (0.00, 1.08)	0.00 (0.00, 0.00)	0.33 (0.01, 0.66)
	N	455	618	521	97	1073
1-2 years	n	2	0	0	0	2
	n/N*100	0.44 (0.00, 1.05)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.19 (0.00, 0.44)
	N	428	540	463	77	968
2-3 years	n	0	1	0	1	1
	n/N*100	0.00 (0.00, 0.00)	0.19 (0.00, 0.55)	0.00 (0.00, 0.00)	1.30 (0.00, 3.83)	0.10 (0.00, 0.31)
	N	388	465	403	62	853
3-4 years	n	3	1	1	0	4
	n/N*100	0.77 (0.00, 1.64)	0.22 (0.00, 0.64)	0.25 (0.00, 0.73)	0.00 (0.00, 0.00)	0.47 (0.01, 0.93)
	N	353	393	348	45	746

4-5 years	n	0	2	1	1	2
	n/N*10 0	0.00 (0.00, 0.00)	0.51 (0.00, 1.21)	0.29 (0.00, 0.85)	2.22 (0.00, 6.53)	0.27 (0.00, 0.64)
	N	312	333	302	31	645
5-6 years	n	1	1	1	0	2
	n/N*10 0	0.32 (0.00, 0.95)	0.30 (0.00, 0.89)	0.33 (0.00, 0.98)	0.00 (0.00, 0.00)	0.31 (0.00, 0.74)
	N	267	268	249	19	535
6-7 years	n	1	1	1	0	2
	n/N*10 0	0.37 (0.00, 1.11)	0.37 (0.00, 1.10)	0.40 (0.00, 1.19)	0.00 (0.00, 0.00)	0.37 (0.00, 0.89)
	N	232	227	211	16	459
7-8 years	n	1	1	1	0	2
	n/N*10 0	0.43 (0.00, 1.27)	0.44 (0.00, 1.30)	0.47 (0.00, 1.40)	0.00 (0.00, 0.00)	0.44 (0.00, 1.04)
	N	196	173	162	11	369
8-9 years	n	2	3	2	1	5
	n/N*10 0	1.02 (0.00, 2.43)	1.73 (0.00, 3.68)	1.23 (0.00, 2.93)	9.09 (0.00, 26.08)	1.36 (0.18, 2.53)
	N	160	124	120	4	284
9-10 years	n	1	2	2	0	3
	n/N*10 0	0.63 (0.00, 1.85)	1.61 (0.00, 3.83)	1.67 (0.00, 3.96)	0.00 (0.00, 0.00)	1.06 (0.00, 2.25)
	N	123	79	76	3	202
10-11 years	n	0	1	1	0	1
	n/N*10 0	0.00 (0.00, 0.00)	1.27 (0.00, 3.73)	1.32 (0.00, 3.88)	0.00 (0.00, 0.00)	0.50 (0.00, 1.46)
	N	77	47	45	2	124
11-12 years	n	3	0	0	0	3
	n/N*10 0	3.90 (0.00, 8.22)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	2.42 (0.00, 5.12)
	N	**483**	**712**	**594**	**118**	**1195**
Overall (0-12 years)	**n**	15	16	13	3	31
	n/N*10 0	3.11 (1.56, 4.65)	2.25 (1.16, 3.34)	2.19 (1.01, 3.37)	2.54 (-0.30, 5.38)	2.59 (1.69, 3.50)

NDD: neurodevelopmental disorders
Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) are presented.

15.2.3 Cumulative incidence rate and time to NDD diagnosis by gender

Table 186 Cumulative incidence rate of NDD by paternal exposure group for males; Primary outcome cohort for descriptive analysis (N=1,256)

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	476. 81	725.11	628.64	96.47	1201.92
0-1 years	n	0	1	0	1	1
	n/PY*1000	0 (-, 7.74)	1.38 (0.03, 7.68)	0 (-, 5.87)	10.37 (0.26, 57.76)	0.83 (0.02, 4.64)
	PY	920.25	1367.1	1193.55	173.55	2287.35
0-2 years	n	2	3	2	1	5
	n/PY*1000	2.17 (0.26, 7.85)	2.19 (0.45, 6.41)	1.68 (0.20, 6.05)	5.76 (0.15, 32.10)	2.19 (0.71, 5.10)
	PY	1336.93	1922.14	1687.12	235.02	3259.07
0-3 years	n	4	8	6	2	12
	n/PY*1000	2.99 (0.82, 7.66)	4.16 (1.80, 8.20)	3.56 (1.31, 7.74)	8.51 (1.03, 30.74)	3.68 (1.90, 6.43)
	PY	1715.22	2395.25	2111.32	283.93	4110.47
0-4 years	n	7	11	9	2	18
	n/PY*1000	4.08 (1.64, 8.41)	4.59 (2.29, 8.22)	4.26 (1.95, 8.09)	7.04 (0.85, 25.45)	4.38 (2.60, 6.92)
	PY	2055.76	2784.98	2463.57	321.41	4840.74
0-5 years	n	10	15	13	2	25
	n/PY*1000	4.86 (2.33, 8.95)	5.39 (3.01, 8.88)	5.28 (2.81, 9.02)	6.22 (0.75, 22.48)	5.16 (3.34, 7.62)
	PY	2348.9	3095.9	2747.48	348.42	5444.81
0-6 years	n	17	19	16	3	36
	n/PY*1000	7.24 (4.22, 11.59)	6.14 (3.69, 9.58)	5.82 (3.33, 9.46)	8.61 (1.78, 25.16)	6.61 (4.63, 9.15)
	PY	2593.63	3343.62	2977.27	366.36	5937.25
0-7 years	n	20	25	22	3	45

	n/PY*1000	7.71 (4.71, 11.91)	7.48 (4.84, 11.04)	7.39 (4.63, 11.19)	8.19 (1.69, 23.93)	7.58 (5.53, 10.14)
	PY	2793.57	3539.02	3157.88	381.14	6332.59
0-8 years	n	26	27	24	3	53
	n/PY*1000	9.31 (6.08, 13.64)	7.63 (5.03, 11.10)	7.6 (4.87, 11.31)	7.87 (1.62, 23.00)	8.37 (6.27, 10.95)
	PY	2956.54	3677.55	3284.94	392.61	6634.08
0-9 years	n	29	31	28	3	60
	n/PY*1000	9.81 (6.57, 14.09)	8.43 (5.73, 11.97)	8.52 (5.66, 12.32)	7.64 (1.58, 22.33)	9.04 (6.90, 11.64)
	PY	3083.66	3772.04	3371.36	400.68	6855.7
0-10 years	n	33	34	29	5	67
	n/PY*1000	10.7 (7.37, 15.03)	9.01 (6.24, 12.60)	8.6 (5.76, 12.35)	12.48 (4.05, 29.12)	9.77 (7.57, 12.41)
	PY	3174.62	3831.27	3425.11	406.16	7005.88
0-11 years	n	37	34	29	5	71
	n/PY*1000	11.65 (8.21, 16.06)	8.87 (6.15, 12.40)	8.47 (5.67, 12.16)	12.31 (4.00, 28.73)	10.13 (7.92, 12.78)
	PY	3233.49	3859.52	3450.46	409.06	7093.01
0-12 years	**n**	37	36	31	5	73
	n/PY*1000	11.44 (8.06, 15.77)	9.33 (6.53, 12.91)	8.98 (6.10, 12.75)	12.22 (3.97, 28.52)	10.29 (8.07, 12.94)

NDD: neurodevelopmental disorders; PY: person-year
Legend: Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) are presented.

Table 187 Cumulative incidence rate of NDD by paternal exposure group for females; Primary outcome cohort for descriptive analyses (N=1,195)

		Paternal exposure group				
NDD		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Follow-up period						
0-1 years	PY	467.44	663.77	558.03	105.74	1131.21
	n	1	3	3	0	4
	n/PY*1000	2.14 (0.05, 11.92)	4.52 (0.93, 13.21)	5.38 (1.11, 15.71)	0 (-, 34.89)	3.54 (0.96, 9.05)
0-2 years	PY	908.22	1240.59	1047.4	193.19	2148.8
	n	3	3	3	0	6
	n/PY*1000	3.3 (0.68, 9.65)	2.42 (0.50, 7.07)	2.86 (0.59, 8.37)	0 (-, 19.09)	2.79 (1.02, 6.08)
0-3 years	PY	1317.37	1744.70	1481.72	262.98	3062.07
	n	3	4	3	1	7
	n/PY*1000	2.28 (0.47, 6.66)	2.29 (0.62, 5.87)	2.02 (0.42, 5.92)	3.8 (0.10, 21.19)	2.29 (0.92, 4.71)
0-4 years	PY	1685.55	2174.97	1857.23	317.75	3860.52
	n	6	5	4	1	11
	n/PY*1000	3.56 (1.31, 7.75)	2.3 (0.75, 5.36)	2.15 (0.59, 5.51)	3.15 (0.08, 17.53)	2.85 (1.42, 5.10)
0-5 years	PY	2019.83	2536.13	2182.44	353.69	4555.96
	n	6	7	5	2	13
	n/PY*1000	2.97 (1.09, 6.47)	2.76 (1.11, 5.69)	2.29 (0.74, 5.35)	5.65 (0.68, 20.43)	2.85 (1.52, 4.88)
0-6 years	PY	2310.22	2839.92	2459.91	380.02	5150.14
	n	7	8	6	2	15
	n/PY*1000	3.03 (1.22, 6.24)	2.82 (1.22, 5.55)	2.44 (0.90, 5.31)	5.26 (0.64, 19.01)	2.91 (1.63, 4.80)
	PY	2558.42	3089.14	2691.45	397.69	5647.56

0-7 years	n	8	9	7	2	17
	n/PY*1000	3.13 (1.35, 6.16)	2.91 (1.33, 5.53)	2.6 (1.05, 5.36)	5.03 (0.61, 18.17)	3.01 (1.75, 4.82)
	PY	2770.07	3287.4	2876.16	411.24	6057.47
0-8 years	n	9	10	8	2	19
	n/PY*1000	3.25 (1.49, 6.17)	3.04 (1.46, 5.59)	2.78 (1.20, 5.48)	4.86 (0.59, 17.57)	3.14 (1.89, 4.90)
	PY	2948.58	3435.67	3015.39	420.28	6384.24
0-9 years	n	11	13	10	3	24
	n/PY*1000	3.73 (1.86, 6.68)	3.78 (2.01, 6.47)	3.32 (1.59, 6.10)	7.14 (1.47, 20.86)	3.76 (2.41, 5.59)
	PY	3090.04	3537.31	3113.74	423.57	6627.35
0-10 years	n	12	15	12	3	27
	n/PY*1000	3.88 (2.01, 6.78)	4.24 (2.37, 6.99)	3.85 (1.99, 6.73)	7.08 (1.46, 20.70)	4.07 (2.68, 5.93)
	PY	3191.82	3598.72	3172.37	426.35	6790.54
0-11 years	n	12	16	13	3	28
	n/PY*1000	3.76 (1.94, 6.57)	4.45 (2.54, 7.22)	4.1 (2.18, 7.01)	7.04 (1.45, 20.56)	4.12 (2.74, 5.96)
	PY	3249.79	3633.12	3205.16	427.96	6882.91
0-12 years	**n**	15	16	13	3	31
	n/PY*1000	4.62 (2.58, 7.61)	4.4 (2.52, 7.15)	4.06 (2.16, 6.94)	7.01 (1.45, 20.49)	4.5 (3.06, 6.39)

NDD: neurodevelopmental disorders; PY: person-year

Legend: Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) are presented.

Table 188 Time to NDD by paternal exposure group stratified by offspring gender

	Paternal exposure group				
NDD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Male offspring					
Number of events	37	36	31	5	73
Number of censor	448	735	637	98	1183
Survival time					
5th percentile	73.67 (52.63, 122.53)	79.23 (46.30, 134.43)	79.23 (46.30, 137.60)	61.37 (10.70, -)	74.53 (53.40, 111.87)
10th percentile	107.43 (78.20, -)	108.40 (82.47, -)	108.40 (82.57, -)	111.87 (33.97, -)	108.40 (87.77, 129.03)
25th percentile	-(-,-)	-(137.6,-)	-(137.6,-)	120.2(111.87,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
Female offspring					
Number of events	15	16	13	3	31
Number of censor	468	696	581	115	1164
Survival time					
5th percentile	136.00 (74.30, -)	112.50 (95.27, -)	113.07 (95.27, -)	107.37 (25.70, -)	117.63 (95.27, -)
10th percentile	144.83 (117.63, -)	107.37 (25.70, -)	-(-,-)	-(-,-)	-(-,-)
25th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)

NDD: neurodevelopmental disorders;
Legend: Due to low number of events the median time-to-event could not be calculated. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event

15.2.4 Variables estimates from propensity score

Table 189 Variable importance metric from random forest propensity score model; Primary outcome cohort in Sweden

NDD Variable (or interaction)[a]	Variable importance
Offspring risk factors/confounders	
Gender [b]	-0.01
Congenital CMV [c]	0.00
Tuberous sclerosis [c]	0.00
Maternal risk factors/confounders	
Affective disorder [d]	0.00
Diabetes [d]	0.00
Gestational diabetes [e]	0.00

NDD Variable (or interaction)[a]	Variable importance
Neurotic disorder [d]	0.00
Schizophrenia, schizotypal and delusional disorders [d]	0.00
Obesity [f]	0.00
CMV [f]	0.00
Alcohol abuse prior to LMP2 [f]	0.00
Alcohol abuse during pregnancy [e]	0.00
Substance abuse prior to LMP2 [f]	0.00
Substance abuse during pregnancy [e]	0.00
Smoking prior to LMP2 [f]	-0.01
Smoking during pregnancy [e]	0.00
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.01
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.00
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	-0.02
Paternal risk factors/confounders	
Affective disorder [d,g]	0.02
Bipolar affective disorder [d]	0.01
Mania [d]	0.00
Neurotic disorder [d]	0.00
Schizophrenia, schizotypal and delusional disorders [d]	0.00
Substance abuse [f]	0.00
Paternal polypharmacy index [h] (categorical)	0.01
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with atleast one prescription	0.01
Year of offspring conception [i]	0.03

Table 190 Variable estimates from logistic regression informed by random forest propensity score model; Primary outcome cohort in Sweden (N=2355)

NDD		Estimate	
Variable (or interaction)[a]	OR	95% CI	P-value
Offspring risk factors/confounders			
Gender [b]			
Male	Reference	-	-
Female	1.07	0.89 - 1.30	0.4698
Maternal risk factors/confounders			
Smoking prior to LMP2 [f]			
No	Reference	-	-

Yes	1.12	0.85 - 1.47	0.4219
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.64	0.46 - 0.90	0.0109
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.89	0.73 - 1.09	0.2704
Paternal risk factors/confounders			
Affective disorder [d,g]	0.23	0.16 - 0.33	<.0001
Bipolar affective disorder [d]	0.34	0.25 - 0.47	<.0001
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with at least one prescription	0.70	0.57 - 0.86	0.0005
Year of offspring conception [i,j]			
2006-2010	Reference	-	-
2011-2015	0.59	0.47 - 0.73	<.0001
2016-2019	0.26	0.20 - 0.34	<.0001

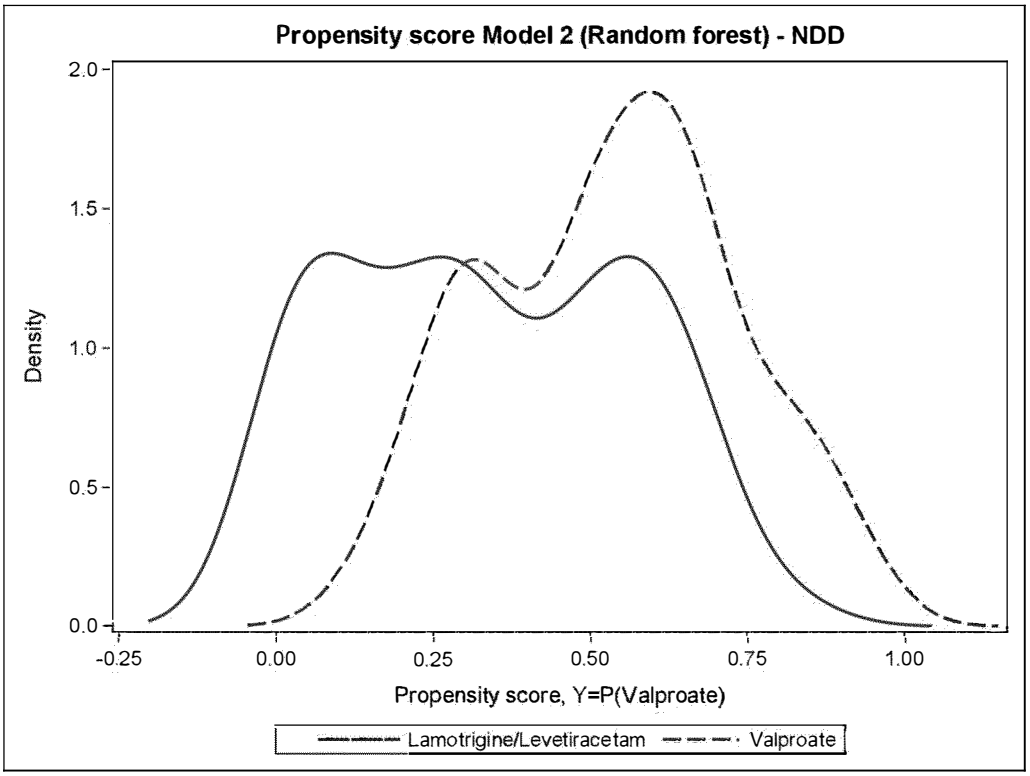
Legend: Odds ratios (OR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.
a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.
b) at index (childbirth)
c) between index and exit date
d) all available data prior to index date
e) during pregnancy (from LMP2 until index date)
f) 12 months lookback from LMP2
g) excluding bipolar affective disorder and mania
i) at mother's LMP2
j) calendar years were grouped in each country according to the length of the study period

Table 191: Balance of risk factors/confounders after PS weighting (PS scores obtained using logistic regression); primary outcome SE

NDD	Absolute standardized difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0,04	Yes	0,99	Yes
Congenital CMV [d]	0,04	Yes	-	- ***
Congenital rubella [d]	-	- **	-	- ***
Foetal alcohol syndrome [d]	-	- **	-	- ***
Fragile X syndrome [d]	-	- **	-	- ***
Lejeune/cri du chat syndrome [d]	-	- **	-	- ***
Tuberous sclerosis [d]	0,04	Yes	-	- ***
Maternal risk factors/confounders				
Mother's age [c] (categorical)	0.00*	Yes	0,98	Yes
Affective disorder [e]	0,05	Yes	0,83	Yes
Diabetes [e]	0,14	No	-	- ***
Gestational diabetes [f]	0,02	Yes	0,85	Yes

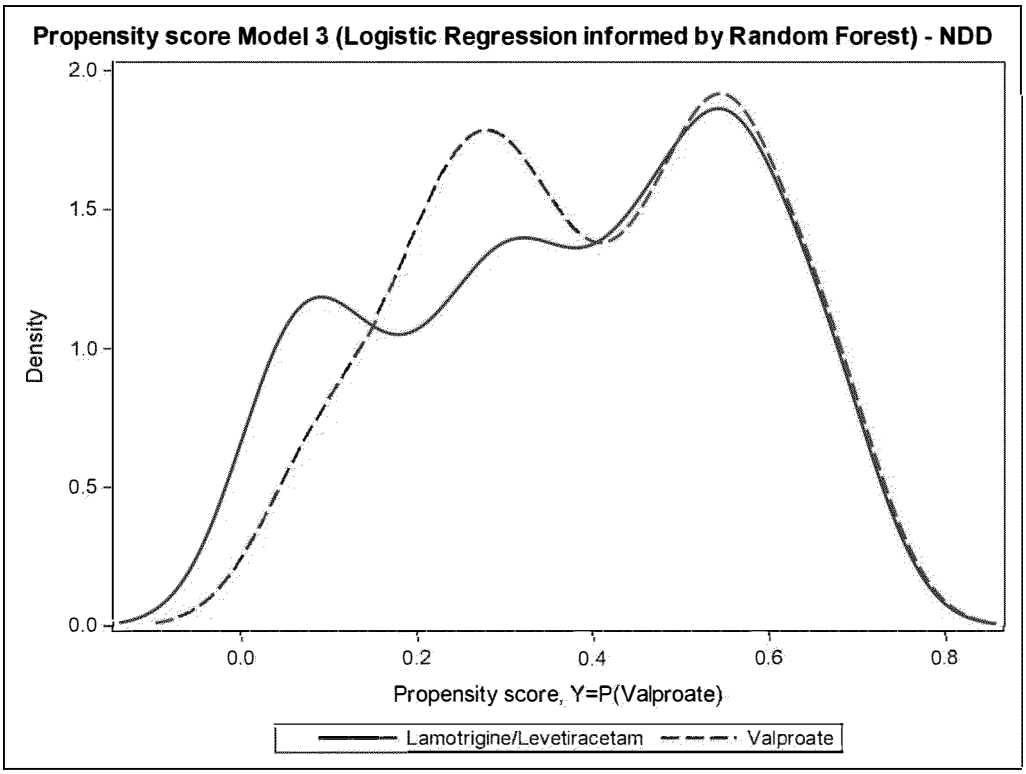
Neurotic disorder [e]	0,02	Yes	0,93	Yes
Schizophrenia, schizotypal and delusional disorders [e]	-	- [**]	-	- [***]
Obesity [g]	0,04	Yes	0,63	Yes
CMV [g]	0,04	Yes	-	- [***]
Rubella [g]	-	- [**]	-	- [***]
Alcohol abuse prior to LMP2 [g]	0,10	Yes	-	- [***]
Alcohol abuse during pregnancy [f]	-	- [**]	-	- [***]
Substance abuse prior to LMP2 [g]	0,03	Yes	-	- [***]
Substance abuse during pregnancy [f]	-	- [**]	-	- [***]
Smoking prior to LMP2 [g]	0,01	Yes	0,96	Yes
Smoking during pregnancy [f]	0,01	Yes	0,94	Yes
Maternal polypharmacy index prior to LMP2 [i] (categorical)	0.00*	Yes	1,01	Yes
Maternal polypharmacy index during pregnancy [f] (categorical)	0.00*	Yes	0,92	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g] - mothers with at least one prescription	0,07	Yes	0,82	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f] - mothers with at least one prescription	0,05	Yes	0,81	Yes
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [g] - mothers with at least one prescription	0,01	Yes	0,98	Yes
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [f] - mothers with at least one prescription	0,00	Yes	0,98	Yes
Paternal risk factors/confounders				
Affective disorder [e,h]	0,03	Yes	0,94	Yes
Bipolar affective disorder [e]	0,01	Yes	0,97	Yes
Mania [e]	0,04	Yes	0,62	Yes
Neurotic disorder [e]	0,01	Yes	0,97	Yes
Schizophrenia, schizotypal and delusional disorders [e]	0,00	Yes	0,98	Yes
Substance abuse [g]	0,02	Yes	1,46	Yes
Paternal polypharmacy index [i] (categorical)	0.00*	Yes	0,95	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] - fathers with at least one prescription	0,09	Yes	0,93	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] - fathers with atleast one prescription	0,01	Yes	0,99	Yes
Father's age [c] (categorical)	0.00*	Yes	1,03	Yes
Year of offspring conception [j]	0.00*	Yes	0,99	Yes

a) absolute standardized difference below 0.1
b) variance ratio between 0 and 2
c) at index (childbirth)
d) between index and exit date
e) all available data prior to index date
f) during pregnancy (from LMP2 until index date)
g) 12 months lookback from LMP2
h) excluding bipolar affective disorder and mania
i) 3 months lookback from LMP2
j) at mother's LMP2
* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardized difference is not calculated if a binary variable has only 1 category level in the weighted patient data.
*** The variance ratio is not calculated if a variable has only 1 category level in one of valproate and comparator groups (the denominator of the variance ratio is 0).



NDD: neurodevelopmental disorders

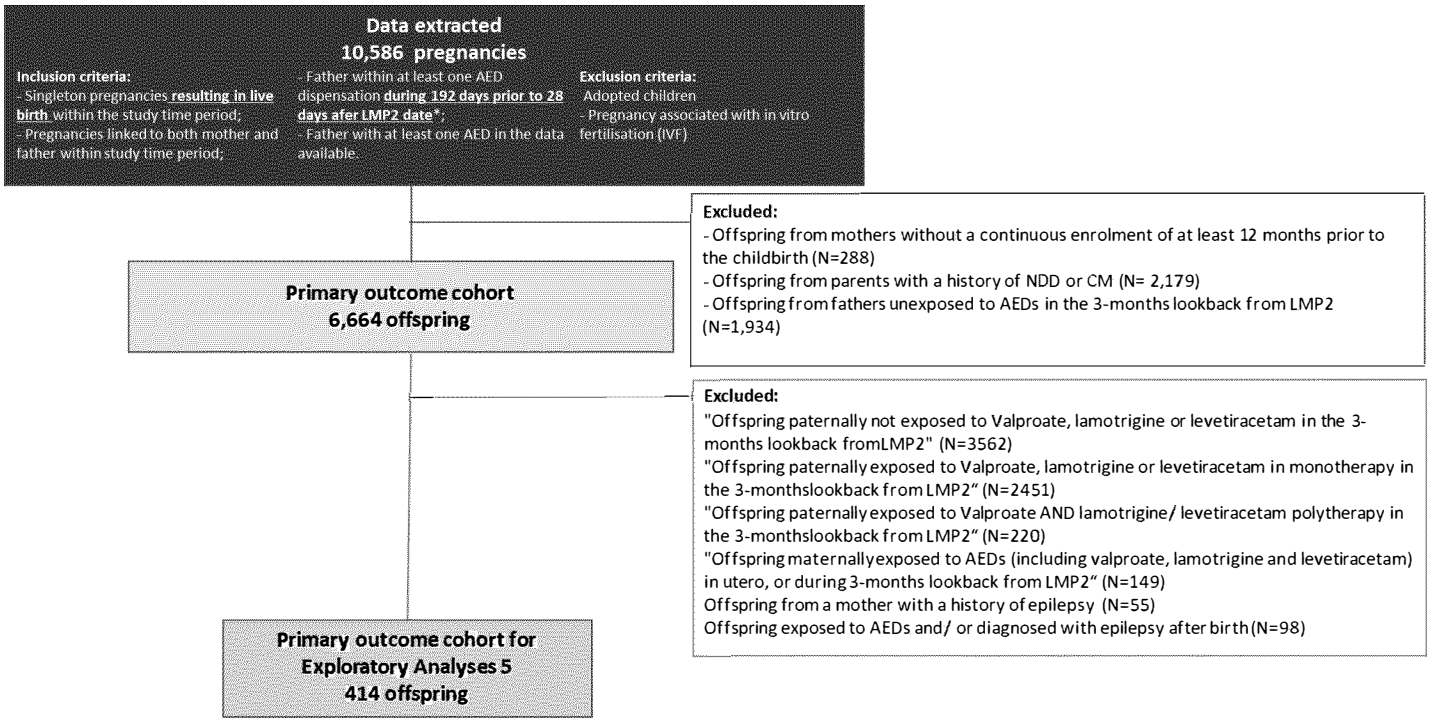
Figure 34 Balance of Propensity Score Model 2- Random Forest; Primary outcome cohort in Sweden.



NDD: neurodevelopmental disorders

Figure 35 Balance of PS Model 3- Logistic Regression Informed by Random Forest; Primary outcome cohort in Sweden.

15.2.5 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Exploratory analysis 5)



CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 36 Study population of Primary outcome cohort for Exploratory Analyses 5 in Sweden

Table 192 Offspring demographic characteristics by paternal exposure group; primary outcome (N=414)

NDD Number of offspring	Paternal exposure group: Valproate (polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322	
	N	%	N	%
Gestational age (weeks)				
<28 (extremely preterm)	2	2.17	1	0.31
28-31 (very preterm)	0	0.00	3	0.93
32-36 (moderate to late preterm)	7	7.61	14	4.35
37-41 (at term)	78	84.78	287	89.13
≥42 (post-term)	5	5.43	17	5.28
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	2	2.17	3	0.93
1000-1499 (very low)	0	0.00	1	0.31
1500-2499 (low)	2	2.17	10	3.11
≥2500	87	94.57	308	95.65
Missing	1	1.09	0	0.00
Gender [a]				
Male	45	48.91	163	50.62
Female	47	51.09	159	49.38
Missing	0	0.00	0	0.00
Year of birth				
2007	13	14.13	13	4.04
2008	10	10.87	21	6.52
2009	10	10.87	28	8.70
2010	7	7.61	38	11.80
2011	12	13.04	25	7.76
2012	6	6.52	29	9.01
2013	8	8.70	24	7.45
2014	7	7.61	20	6.21
2015	5	5.43	26	8.07
2016	4	4.35	29	9.01
2017	1	1.09	24	7.45
2018	3	3.26	25	7.76
2019	6	6.52	20	6.21
Total number of years of follow-up	716.99		1990.36	
Mean follow-up year	7.79		6.18	

NDD: Neurodevelopmental Disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index (childbirth)

Table 193 Offspring clinical characteristics by paternal exposure group; primary outcome (N=414)

NDD Number of offspring	Paternal exposure group: Valproate (polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322	
	N	%	N	%
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Epilepsy	0	0.00	0	0.00
Foetal alcohol syndrome	0	0.00	0	0.00
Fragile X syndrome	0	0.00	0	0.00
Lejeune/cri du chat syndrome	0	0.00	0	0.00
Tuberous sclerosis	0	0.00	0	0.00
Medication use				
Exposure to AEDs [a]	0	0.00	0	0.00

NDD Number of offspring	Paternal exposure group: Valproate (polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322	
	N	%	N	%
Outcomes				
ASD (ever, not only as 1st diagnosis)	1	1.09	8	2.48
ASD (as 1st diagnosis)	1	1.09	6	1.86
NDD including ASD	8	8.70	24	7.45
Age at the first diagnosis (years)				
ASD (ever, not only as 1st diagnosis) [b,c]				
0-1	0	0.00	0	0.00
2-3	0	0.00	2	25.00
4-5	0	0.00	4	50.00
6-7	0	0.00	0	0.00
8-9	1	100.00	2	25.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	1	100	8	100
NDD including ASD [b,c]				
0-1	0	0.00	2	8.33
2-3	0	0.00	5	20.83
4-5	0	0.00	8	33.33
6-7	0	0.00	2	8.33
8-9	2	25.00	5	20.83
10-11	6	75.00	2	8.33
Total (offspring with the outcome)	8	100	24	100

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; ASD: Autism Spectrum Disorders; AED: Antiepileptic Drug; SD: Standard Deviation
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) between index (childbirth) and exit date
b) Categories may be adapted according to the data.
c) Denominator for the percentage is the number of offspring with the outcome.

Table 194 Maternal demographic characteristics by paternal exposure group; primary outcome (N=414)

NDD Number of offspring	Paternal exposure group: Valproate (polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322	
	N	%	N	%
Mother's age [a]				
≤20 years	3	3.26	7	2.17
21-25	16	17.39	39	12.11
26-30	32	34.78	99	30.75
31-35	25	27.17	102	31.68
36-40	13	14.13	57	17.70
>40	3	3.26	18	5.59
Mean (SD)	30.01 (5.69)		31.38 (5.47)	
Median (25th - 75th percentile)	29.5(26.50, 34.00)		31(28.00, 35.00)	
Min, max	18.00, 43.00		18.00, 46.00	
Missing	0	0.00	0	0.00

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages are calculated over the total number of offspring.
a) at index (childbirth)

Table 195 Maternal clinical characteristics by paternal exposure group; primary outcome (N=414)

NDD Number of offspring	Paternal exposure group Valproate(polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322	
	N	%	N	%
Comorbidities				
Affective disorder [a]	5	5.43	34	10.56
Diabetes [a]	0	0.00	7	2.17
Epilepsy [a]	0	0.00	0	0.00
Neurotic disorder [a]	5	5.43	32	9.94
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Obesity [b]	1	1.09	8	2.48
CMV [c]	0	0.00	0	0.00
Gestational diabetes [c]	1	1.09	11	3.42
Rubella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	2	0.62
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	2	0.62
Substance abuse during pregnancy [c]	0	0.00	1	0.31
Smoking prior to LMP2 [b]				
Yes	18	19.57	57	17.70
No	67	72.83	253	78.57
Missing	7	7.61	12	3.73
Smoking during pregnancy [c]				
Yes	6	6.52	29	9.01
No	81	88.04	286	88.82
Missing	5	5.43	7	2.17
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AED during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K-means cluster prior to LMP2 [d]				
unexposed	92	100.00	322	100.00
K-means cluster during pregnancy [c]				
unexposed	92	100.00	322	100.00
Maternal polypharmacy index prior to LMP2 [d]				

	Paternal exposure group			
NDD Number of offspring	**Valproate(polytherapy) N=92**		**Lamotrigine/levetiracetam (polytherapy) N=322**	
0	59	64.13	222	68.94
1-4	32	34.78	96	29.81
5-10	1	1.09	4	1.24
>10	0	0.00	0	0.00
Mean (SD)	0.72 (1.24)		0.60 (1.16)	
Median (25^{th} - 75^{th} percentile)	0(0.00, 1.00)		0(0.00, 1.00)	
Min, max	0.00,5.00		0.00,7.00	
Maternal polypharmacy index during pregnancy [c]				
0	46	50.00	172	53.42
1-4	41	44.57	138	42.86
5-10	5	5.43	12	3.73
>10	0	0.00	0	0.00
Mean (SD)	1.09 (1.71)		0.98 (1.42)	
Median (25^{th} - 75^{th} percentile)	0.5(0.00, 1.00)		0(0.00, 1.00)	
Min, max	0.00,9.00		0.00,8.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	14	15.22	39	12.11
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	7	7.61	21	6.52
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] -mothers with at least one prescription	71	77.17	190	59.01
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	40	43.48	139	43.17

NDD: Neurodevelopmental Disorders; LMP2: Last Menstrual Period Date Plus 2 weeks; SD: Standard Deviation; Min: Minimum; Max: Maximum

*** Masked values indicated that data was calculated but not disclosed

Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.

a) all available data prior to index date (childbirth)

b) 12 months lookback from LMP2

c) during pregnancy (from LMP2 until index date)

d) 3 months lookback from LMP2

e) Oxazolidine derivatives were not sold in Sweden during the study period

Table 196 Paternal demographic characteristics by paternal exposure group; primary outcome (N=414)

NDD Number of offspring	Paternal exposure group: Valproate (polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322	
	N	%	N	%
Father's age [a]				
≤20 years	1	1.09	1	0.31
21-25	9	9.78	17	5.28
26-30	24	26.09	66	20.50
31-35	20	21.74	119	36.96
36-40	23	25.00	67	20.81
>40	15	16.30	52	16.15
Mean (SD)	33.77 (6.71)		34.27 (6.25)	
Median (25^{th} - 75^{th} percentile)	33 (29.00, 39.00)		33 (30.00, 38.00)	
Min, max	20.00, 52.00		20.00, 57.00	
Missing	0	0.00	0	0.00
Year of offspring conception [b]				
2006	11	11.96	10	3.11
2007	10	10.87	16	4.97
2008	9	9.78	21	6.52
2009	9	9.78	47	14.60
2010	11	11.96	27	8.39
2011	6	6.52	26	8.07
2012	5	5.43	24	7.45
2013	10	10.87	21	6.52
2014	6	6.52	28	8.70
2015	2	2.17	23	7.14
2016	4	4.35	27	8.39
2017	3	3.26	27	8.39
2018	5	5.43	17	5.28
2019	1	1.09	8	2.48

NDD: Neurodevelopmental Disorders; LMP2: Last Menstrual Period Date Plus 2 weeks; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index (childbirth)
b) at mother's LMP2

Table 197 Paternal clinical characteristics by paternal exposure group; primary outcome (N=414)

NDD Number of offspring	Paternal exposure group: Valproate (polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322	
	N	%	N	%
Comorbidities				
Affective disorder excluding bipolar affective disorder and mania [a]	13	14.13	42	13.04
Bipolar affective disorder [a]	8	8.70	17	5.28
Mania [a]	1	1.09	0	0.00
Neurotic disorder [a]	20	21.74	56	17.39
Schizophrenia, schizotypal and delusional disorders [a]	4	4.35	3	0.93
Lifestyle characteristics				
Substance abuse [c]	0	0.00	6	1.86
Medication use				
Exposure to AEDs[d, e]				
Fatty acid derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Barbiturates derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Fatty acid derivatives and other antiepileptics	32	34.78	0	0.00
Carboxamide derivatives and other antiepileptics	0	0.00	161	50.00
Fatty acid derivatives and Carboxamide derivatives	31	33.70	0	0.00
Benzodiazepine derivatives and other antiepileptics	0	0.00	10	3.11
Benzodiazepine derivatives and Fatty acid derivatives	13	14.13	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives	0	0.00	0	0.00
Succinimide derivatives and other antiepileptics	0	0.00	1	0.31
Succinimide derivatives and Fatty acid derivatives	5	5.43	0	0.00
Carboxamide derivatives and Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives and Fatty acid derivatives	3	3.26	0	0.00
Hydantoin derivatives and Carboxamide derivatives	0	0.00	0	0.00
Hydantoin derivatives and other antiepileptics	0	0.00	11	3.42
Hydantoin derivatives and Succinimide derivatives	0	0.00	0	0.00
Barbiturates derivatives and other antiepileptics	0	0.00	2	0.62
Barbiturates derivatives and Fatty acid derivatives	2	2.17	0	0.00
Barbiturates derivatives and	0	0.00	0	0.00

NDD Number of offspring	Paternal exposure group Valproate (polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322	
Carboxamide derivatives				
Barbiturates derivatives and Benzodiazepine derivatives	0	0.00	0	0.00
Barbiturates derivatives and Hydantoin derivatives	0	0.00	0	0.00
Carboxamide derivatives and Fatty acid derivatives and Benzodiazepine derivatives	1	1.09	0	0.00
Benzodiazepine derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Carboxamide derivatives and Fatty acid derivatives and other antiepileptics	5	5.43	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	1	0.31
Hydantoin derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	2	0.62
Hydantoin derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Hydantoin derivatives and Barbiturates derivatives and other antiepileptics	0	0.00	1	0.31
Fatty acid derivatives and Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	1	0.31
Hydantoin derivatives and Barbiturates derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
AED indication				
Epilepsy	68	73.91	279	86.65
Bipolar affective disorder and mania	7	7.61	15	4.66
Other/unknown	17	18.48	28	8.70
K-means cluster [d]				
Cluster A	62	67.39	149	46.27
Cluster B	30	32.61	173	53.73
Paternal polypharmacy index [d]				
0	55	59.78	205	63.66
1-4	30	32.61	100	31.06
5-10	7	7.61	17	5.28
>10	0	0.00	0	0.00
Mean (SD)	0.99 (1.84)		0.95 (1.77)	
Median (25^{th} - 75^{th} percentile)	0(0.00, 1.00)		0(0.00, 1.00)	
Min, max	0.00, 9.00		0.00, 10.00	

NDD Number of offspring	Paternal exposure group: Valproate (polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	52	56.52	211	65.53
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	58	63.04	193	59.94

NDD: Neurodevelopmental Disorders; AED: Antiepileptic Drug; SD: Standard Deviation; Min: Minimum; Max: Maximum
Cluster A: constant low exposure, cluster B: constant high exposure
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) Valproate or lamotrigine/levetiracetam in combination with other AED(s). Each combination found in the data were listed here.

Table 198 Association between potential offspring risk factors/confounders for NDD by paternal exposure group; primary outcome (N=414)

NDD Number of offspring	Paternal exposure group: Valproate (polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322		Comparison: Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -
	N	%	N	%	
Offspring risk factors/confounders					
Gender [a]					
Male	45	48.91	163	50.62	-
Female	47	51.09	159	49.38	-
Missing	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.08 (0.7726)
Congenital CMV [b]	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	-
Foetal alcohol syndrome [b]	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	0	0.00	-

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) between index and exit date

Table 199 Association between potential maternal risk factors/confounders for NDD by paternal exposure group; primary outcome (N=414)

	Paternal exposure group				Comparison
NDD Number of offspring	**Valproate(polytherapy) N=92**		**Lamotrigine/levetiracetam (polytherapy) N=322**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
Maternal risk factors/confounders					
Mother's age [a] (categorical)					
≤20 years	3	3.26	7	2.17	-
21-25	16	17.39	39	12.11	-
26-30	32	34.78	99	30.75	-
31-35	25	27.17	102	31.68	-
36-40	13	14.13	57	17.70	-
>40	3	3.26	18	5.59	-
Test statistics	-	-	-	-	4.00 (0.5497)
Mother's age [a] (continuous)					
Mean (SD)	30.01 (5.69)		31.38 (5.47)		17027.50 (0.0413)*
Median (25^{th} - 75^{th} percentile)	29.5(26.50, 34.00)		31(28.00, 35.00)		-
Min, max	18.00, 43.00		18.00, 46.00		-
Missing	0	0.00	0	0.00	-
Affective disorder [b]	5	5.43	34	10.56	2.20 (0.1378)
Diabetes [b]	0	0.00	7	2.17	0.35 (0.3564)*
Gestational diabetes [c]	1	1.09	11	3.42	0.47 (0.4783)*
Neurotic disorder [b]	5	5.43	32	9.94	1.78 (0.1818)
Schizophrenia, schizotypal and delusional disorders [b]	0	0.00	0	0.00	-
Obesity [d]	1	1.09	8	2.48	0.69 (0.6905)*
CMV [c]	0	0.00	0	0.00	-
Rubella [c]	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [d]	0	0.00	2	0.62	1.00 (1.0000)*
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [d]	0	0.00	2	0.62	1.00 (1.0000)*
Substance abuse during pregnancy [c]	0	0.00	1	0.31	1.00 (1.0000)*
Smoking prior to LMP2 [d]					
Yes	18	19.57	57	17.70	-
No	67	72.83	253	78.57	-
Missing	7	7.61	12	3.73	-
Test statistics without 'Missing' category	-	-	-	-	2.79 (0.2475)
Smoking during pregnancy [c]					
Yes	6	6.52	29	9.01	-

NDD Number of offspring	Paternal exposure group: Valproate(polytherapy) N=92		Paternal exposure group: Lamotrigine/levetiracetam (polytherapy) N=322		Comparison: Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -
	N	%	N	%	
No	81	88.04	286	88.82	-
Missing	5	5.43	7	2.17	-
Test statistics without 'Missing' category	-	-	-	-	3.15 (0.2068)
Maternal polypharmacy index prior to LMP2 [e](categorical)					
0	59	64.13	222	68.94	-
1-4	32	34.78	96	29.81	-
5-10	1	1.09	4	1.24	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.83 (0.6603)
Maternal polypharmacy index prior to LMP2 [e] (continuous)					
Mean (SD)	0.72 (1.24)		0.60 (1.16)		-
Median (25^{th} - 75^{th} percentile)	0(0.00, 1.00)		0(0.00, 1.00)		-
Min, max	0.00,5.00		0.00,7.00		-
Maternal polypharmacy index during pregnancy [c](categorical)					
0	46	50.00	172	53.42	-
1-4	41	44.57	138	42.86	-
5-10	5	5.43	12	3.73	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.72 (0.6993)
Maternal polypharmacy index during pregnancy[c] (continuous)					
Mean (SD)	1.09 (1.71)		0.98 (1.42)		-
Median (25^{th} - 75^{th} percentile)	0.5(0.00, 1.00)		0(0.00, 1.00)		-
Min, max	0.00,9.00		0.00,8.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	14	15.22	39	12.11	0.62 (0.4317)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	7	7.61	21	6.52	0.13 (0.7143)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] -mothers with at least one prescription	71	77.17	190	59.01	10.14 (0.0015)

NDD Number of offspring	Paternal exposure group: Valproate(polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322		Comparison: Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -
	N	%	N	%	
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	40	43.48	139	43.17	0.00 (0.9577)

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. *Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2

Table 200 Association between potential paternal risk factors/confounders for NDD by paternal exposure group; primary outcome (N=414)

NDD Number of offspring	Paternal exposure group: Valproate(polytherapy) N=92		Lamotrigine/levetiracetam (polytherapy) N=322		Comparison: Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -
Paternal risk factors/confounders					
Affective disorder excluding bipolar affective disorder and mania [a]	13	14.13	42	13.04	
Bipolar affective disorder [a]	8	8.70	17	5.28	1.47 (0.2251)
Mania [a]	1	1.09	0	0.00	0.22 (0.2222)*
Neurotic disorder [a]	20	21.74	56	17.39	0.90 (0.3421)
Schizophrenia, schizotypal and delusional disorders [a]	4	4.35	3	0.93	0.04 (0.0463)*
Substance abuse [c]	0	0.00	6	1.86	0.34 (0.3456)*
Paternal polypharmacy index [d] (categorical)					
0	55	59.78	205	63.66	-
1-4	30	32.61	100	31.06	-
5-10	7	7.61	17	5.28	-

	Paternal exposure group				Comparison
NDD Number of offspring	**Valproate(polytherapy) N=92**		**Lamotrigine/levetiracetam (polytherapy) N=322**		**Vaproate (polytherapy) vs Lamotrigine/levetiracetam (polytherapy)**
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.90 (0.6388)
Paternal polypharmacy index [d] (continuous)					
Mean (SD)	0.99 (1.84)		0.95 (1.77)		-
Median (25th - 75th percentile)	0(0.00, 1.00)		0(0.00, 1.00)		-
Min, max	0.00, 9.00		0.00, 10.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	52	56.52	211	65.53	2.50 (0.1135)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	58	63.04	193	59.94	0.29 (0.5908)
Father's age [e] (categorical)					
≤20 years	1	1.09	1	0.31	-
21-25	9	9.78	17	5.28	-
26-30	24	26.09	66	20.50	-
31-35	20	21.74	119	36.96	-
36-40	23	25.00	67	20.81	-
>40	15	16.30	52	16.15	-
Test statistics	-	-	-	-	9.75 (0.0827)
Father's age [e] (continuous)					
Mean (SD)	33.77 (6.71)		34.27 (6.25)		-
Median (25th - 75th percentile)	33(29.00, 39.00)		33(30.00, 38.00)		-
Min, max	20.00, 52.00		20.00, 57.00		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [f,g]					
2006-2010	50	54.35	121	37.58	-
2011-2015	29	31.52	122	37.89	-
2016-2019	13	14.13	79	24.53	-
Test statistics	-	-	-	-	9.15 (0.0103)

NDD Number of offspring	Paternal exposure group Valproate(polytherapy) N=92	Lamotrigine/levetiracetam (polytherapy) N=322	Comparison Vaproate (polytherapy) vs Lamotrigine/levetiracetam (polytherapy) -

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum, LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. *Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period

Table 201 Association between potential offspring risk factors/confounders and NDD; primary outcome (N=414)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Offspring risk factors/confounders								
Gender [a]								
Male	208	50.24	25	12.02	183	87.98	Reference	-
Female	206	49.76	7	3.40	199	96.60	0.26(0.11, 0.61)	-
Missing	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	9.52 (0.0020)
Congenital CMV [b]							-	-
No	414	100.00	32	7.73	382	92.27	-	-
Yes	0	0.00	0	0.00	0	0.00		
Congenital rubella [b]							-	-
No	414	100.00	32	7.73	382	92.27	-	-
Yes	0	0.00	0	0.00	0	0.00		
Foetal alcohol syndrome [b]							-	-
No	414	100.00	32	7.73	382	92.27	-	-
Yes	0	0.00	0	0.00	0	0.00		
Fragile X syndrome [b]							-	-
No	414	100.00	32	7.73	382	92.27	-	-
Yes	0	0.00	0	0.00	0	0.00		
Lejeune/cri du chat syndrome [b]							-	-
No	414	100.00	32	7.73	382	92.27	-	-
Yes	0	0.00	0	0.00	0	0.00		
Tuberous sclerosis [b]							-	-
No	414	100.00	32	7.73	382	92.27	-	-
Yes	0	0.00	0	0.00	0	0.00		

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; OR: Odds Ratio; CI; Confidence Interval
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage is calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at index (childbirth)

b) between index and exit date

Table 202 Association between potential maternal risk factors/confounders and NDD; primary outcome (N=414)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Maternal risk factors/confounders								
Mother's age [a] (categorical)								
≤20 years	10	2.42	2	20.00	8	80.00	3.84 (0.70, 21.18)	-
21-25	55	13.29	5	9.09	50	90.91	1.54 (0.48, 4.93)	-
26-30	131	31.64	8	6.11	123	93.89	Reference	-
31-35	127	30.68	8	6.30	119	93.70	1.03 (0.38, 2.84)	-
36-40	70	16.91	6	8.57	64	91.43	1.44 (0.48, 4.33)	-
>40	21	5.07	3	14.29	18	85.71	2.56 (0.62, 10.56)	-
Wald test	-	-	-	-	-	-	-	4.12 (0.5324)
Affective disorder [b]								
No	375	90.58	30	8.00	345	92.00	Reference	-
Yes	39	9.42	2	5.13	37	94.87	0.62 (0.14,I)	0.40 (0.5264)
Diabetes [b]								
No	407	98.31	32	7.86	375	92.14	Reference	-
Yes	7	1.69	0	0.00	7	100.00	0.00 (0.00,I)	0.00 (0.9827)
Gestational diabetes [c]								
No	402	97.10	32	7.96	370	92.04	Reference	-
Yes	12	2.90	0	0.00	12	100.00	0.00(0.00,I)	0.00 (0.9774)
Neurotic disorder [b]								
No	377	91.06	29	7.69	348	92.31	Reference	-
Yes	37	8.94	3	8.11	34	91.89	1.06 (0.31, 3.66)	0.01 (0.9280)
Schizophrenia, schizotypal and delusional disorders [b]								
No	414	100.00	32	7.73	382	92.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Obesity [d]								
No	405	97.83	31	7.65	374	92.35	Reference	-
Yes	9	2.17	1	11.11	8	88.89	1.51 (0.18, 12.45)	0.15 (0.7029)
CMV [c]								
No	414	100.00	32	7.73	382	92.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Rubella [c]								
No	414	100.00	32	7.73	382	92.27	-	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse prior to LMP2 [d]								
No	412	99.52	32	7.77	380	92.23	Reference	-
Yes	2	0.48	0	0.00	2	100.00	0.00 (0.00,I)	0.00 (0.9908)
Alcohol abuse during pregnancy [c]								
No	414	100.00	32	7.73	382	92.27	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Substance abuse prior to LMP2 [d]								
No	412	99.52	32	7.77	380	92.23	Reference	-
Yes	2	0.48	0	0.00	2	100.00	0.00 (0.00,I)	0.00 (0.9908)
Substance abuse during pregnancy [c]								
No	413	99.76	32	7.75	381	92.25	Reference	-
Yes	1	0.24	0	0.00	1	100.00	0.00(0.00,I)	0.00 (0.9935)
Smoking prior to LMP2 [d]								
Yes	75	18.12	11	14.67	64	85.33	2.58 (1.18, 5.65)	-
No	320	77.29	20	6.25	300	93.75	Reference	-
Missing	19	4.59	1	5.26	18	94.74	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	5.61 (0.0178)
Smoking during pregnancy [c]								
Yes	35	8.45	4	11.43	31	88.57	1.62 (0.53, 4.94)	-
No	367	88.65	27	7.36	340	92.64	Reference	-
Missing	12	2.90	1	8.33	11	91.67	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	0.73 (0.3925)
Maternal polypharmacy index prior to LMP2 [e](categorical)								
0	281	67.87	21	7.47	260	92.53	Reference	-
1-4	128	30.92	11	8.59	117	91.41	1.16 (0.54, 2.49)	-
5-10	5	1.21	0	0.00	5	100.00	0.00(0.00,I)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	0.15 (0.9263)
Maternal polypharmacy index during pregnancy [c](categorical)								
0	218	52.66	14	6.42	204	93.58	Reference	-
1-4	179	43.24	17	9.50	162	90.50	1.53 (0.73, 3.19)	-
5-10	17	4.11	1	5.88	16	94.12	0.91 (0.11, 7.37)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	1.37 (0.5037)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription								
No	361	87.20	26	7.20	335	92.80	Reference	-
Yes	53	12.80	6	11.32	47	88.68	1.64(0.64, 4.21)	1.08(0.2988)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription								
No	386	93.24	30	7.77	356	92.23	Reference	-
Yes	28	6.76	2	7.14	26	92.86	0.91 (0.21, 4.03)	0.01 (0.9042)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription								
No	153	36.96	10	6.54	143	93.46	Reference	-
Yes	261	63.04	22	8.43	239	91.57	1.32 (0.61, 2.86)	0.48 (0.4875)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription								
No	235	56.76	14	5.96	221	94.04	Reference	-
Yes	179	43.24	18	10.06	161	89.94	1.76 (0.85, 3.65)	2.34 (0.1258)

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; OR: Odds Ratio; CI; Confidence Interval

Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage is calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.

a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2

Table 203 Association between potential paternal risk factors/confounders and NDD; primary outcome (N=414)

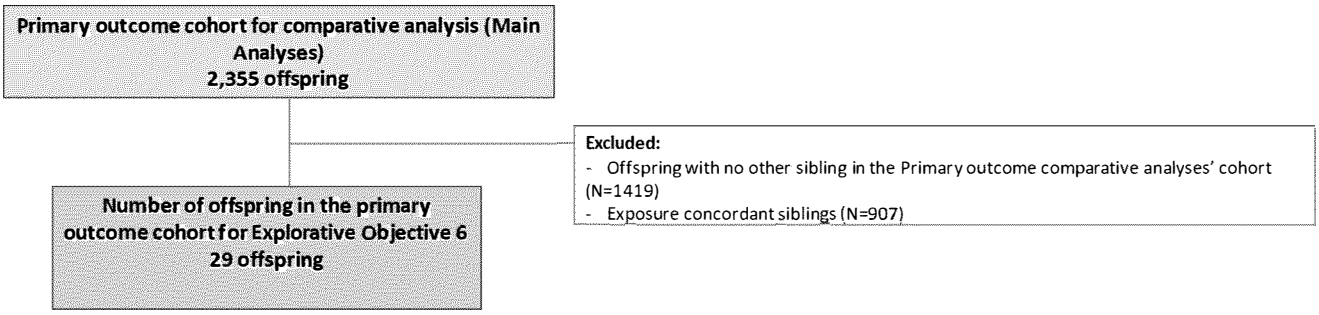
NDD	Overall	Event	Non-event	Association

	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Paternal risk factors/confounders								
Affective disorder excluding bipolar affective disorder and mania [a]								
No	359	86.71	28	7.80	331	92.20	Reference	-
Yes	55	13.29	4	7.27	51	92.73	0.93 (0.31, 2.75)	0.02 (0.8917)
Bipolar affective disorder [a]								
No	389	93.96	30	7.71	359	92.29	Reference	-
Yes	25	6.04	2	8.00	23	92.00	1.04 (0.23, 4.63)	0.00 (0.9577)
Mania [a]								
No	413	99.76	32	7.75	381	92.25	Reference	-
Yes	1	0.24	0	0.00	1	100.00	0.00 (0.00,I)	0.00 (0.9935)
Neurotic disorder [a]								
No	338	81.64	26	7.69	312	92.31	Reference	-
Yes	76	18.36	6	7.89	70	92.11	1.03 (0.41, 2.59)	0.00 (0.9520)
Schizophrenia, schizotypal and delusional disorders [a]								
No	407	98.31	30	7.37	377	92.63	Reference	-
Yes	7	1.69	2	28.57	5	71.43	5.03 (0.94, 27.01)	3.54 (0.0597)
Substance abuse [c]								
No	408	98.55	29	7.11	379	92.89	Reference	-
Yes	6	1.45	3	50.00	3	50.00	13.07 (2.52, 67.66)	9.39 (0.0022)
Paternal polypharmacy index [d] (categorical)								
0	260	62.80	18	6.92	242	93.08	Reference	-
1-4	130	31.40	13	10.00	117	90.00	1.49 (0.71, 3.15)	-
5-10	24	5.80	1	4.17	23	95.83	0.58 (0.07, 4.58)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	1.57 (0.4569)
Concomitant medications associated with valproate-indicated psychiatric conditions [c] -fathers with at least one prescription								
No	151	36.47	13	8.61	138	91.39	Reference	-
Yes	263	63.53	19	7.22	244	92.78	0.83 (0.40, 1.73)	0.26 (0.6119)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription								
No	163	39.37	9	5.52	154	94.48	Reference	-
Yes	251	60.63	23	9.16	228	90.84	1.73 (0.78, 3.83)	1.80 (0.1796)
Father's age [a] (categorical)								
≤20 years	2	0.48	0	0.00	2	100.00	0.00(0.00,I)	-
21-25	26	6.28	2	7.69	24	92.31	2.23 (0.41, 12.18)	-
26-30	90	21.74	5	5.56	85	94.44	1.58 (0.44, 5.61)	-
31-35	139	33.57	5	3.60	134	96.40	Reference	-
36-40	90	21.74	8	8.89	82	91.11	2.61 (0.83, 8.26)	-
>40	67	16.18	12	17.91	55	82.09	5.85 (1.97, 17.38)	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Wald test	-	-	-	-	-	-	-	12.08 (0.0338)
Year of offspring conception [f,g]								
2006-2010	171	41.30	24	14.04	147	85.96	Reference	-
2011-2015	151	36.47	8	5.30	143	94.70	0.34(0.15, 0.79)	-
2016-2019	92	22.22	0	0.00	92	100.00	-	-
Wald test	-	-	-	-	-	-	-	6.36 (0.0416)

NDD: Neurodevelopmental Disorders; OR: Odds Ratio; CI; Confidence Interval, LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage is calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index (date of childbirth)
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period

15.2.6 Exposure to valproate or lamotrigine/levetiracetam in paternally and maternally matched siblings (Exploratory analysis 6)



CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 37 Study population of Primary outcome cohort for Exploratory Analyses 6 in Sweden

Table 204 Offspring demographic characteristics by paternal exposure group; primary outcome (N=29)

NDD Number of offspring	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam (composite) N=14	
	N	%	N	%
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	0	0.00
28-31 (very preterm)	0	0.00	1	7.14
32-36 (moderate to late preterm)	1	6.67	2	14.29
37-41 (at term)	13	86.67	11	78.57
≥42 (post-term)	1	6.67	0	0.00
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	0	0.00
1000-1499 (very low)	0	0.00	0	0.00
1500-2499 (low)	0	0.00	3	21.43
≥2500	15	100.00	11	78.57
Missing	0	0.00	0	0.00
Gender [a]				
Male	8	53.33	3	21.43
Female	7	46.67	11	78.57
Missing	0	0.00	0	0.00
Year of birth				
2007	1	6.67	0	0.00
2008	4	26.67	0	0.00
2009	3	20.00	1	7.14
2010	1	6.67	2	14.29
2011	1	6.67	3	21.43
2012	0	0.00	0	0.00
2013	1	6.67	2	14.29
2014	2	13.33	2	14.29
2015	1	6.67	1	7.14
2016	1	6.67	2	14.29
2017	0	0.00	1	7.14
2018	0	0.00	0	0.00
2019	0	0.00	0	0.00
Total number of years of follow-up	128.48		87.32	
Mean follow-up year	8.57		6.24	

NDD: Neurodevelopmental Disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 205 Offspring clinical characteristics by paternal exposure group; primary outcome (N=29)

NDD Number of offspring	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam (composite) N=14	
	N	%	N	%
Comorbidities				
Congenital CMV [a]	0	0.00	0	0.00
Congenital rubella [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00

NDD Number of offspring	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam (composite) N=14	
	N	%	N	%
Foetal alcohol syndrome [a]	0	0.00	0	0.00
Fragile X syndrome [a]	0	0.00	0	0.00
Lejeune/cri du chat syndrome [a]	0	0.00	0	0.00
Tuberous sclerosis [a]	0	0.00	0	0.00
Medication use				
Exposure to AEDs [a]	0	0.00	0	0.00
Outcomes				
ASD (ever, not only as 1st diagnosis)	0	0.00	0	0.00
ASD (as 1st diagnosis)	0	0.00	0	0.00
NDD including ASD	2	13.33	1	7.14
Age at the first diagnosis (years)				
ASD (ever, not only as 1st diagnosis) [b,c]				
0-1	0	0.00	0	0.00
2-3	0	0.00	0	0.00
4-5	0	0.00	0	0.00
6-7	0	0.00	0	0.00
8-9	0	0.00	0	0.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	0	0.00	0	0.00
NDD including ASD [b,c]				
0-1	0	0.00	0	0.00
2-3	0	0.00	0	0.00
4-5	0	0.00	1	100.00
6-7	0	0.00	0	0.00
8-9	1	50.00	0	0.00
10-11	1	50.00	0	0.00
Total (offspring with the outcome)	2	100	1	100

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; AED: Antiepileptic Drug; ASD: Autism Spectrum Disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between index (childbirth) and exit date
b) ICD-10 codes refer to all records of NDD including ASD during the entire follow-up. Since offspring might have more than one distinct ICD-10 code, the sum of the distinct ICD-10 codes might not coincide with the total number of offspring with the composite outcome
c) Categories may be adapted according to the data.
d) Denominator for the percentage is the number of offspring with the outcome.

Table 206 Maternal demographic characteristics by paternal exposure group; primary outcome (N=29)

NDD Number of offspring	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam(composite) N=14	
	N	%	N	%
Mother's age [a]				
≤20 years	0	0.00	0	0.00
21-25	2	13.33	1	7.14
26-30	4	26.67	3	21.43
31-35	8	53.33	4	28.57
36-40	1	6.67	5	35.71
>40	0	0.00	1	7.14
Mean (SD)	31.00 (4.46)		33.71 (4.45)	
Median (25th - 75th percentile)	32(29.00, 34.00)		35(30.00, 36.00)	
Min, max	22.00, 39.00		24.00, 41.00	
Missing	0	0.00	0	0.00

NDD Number of offspring	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam(composite) N=14	
	N	%	N	%

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 207 Maternal clinical characteristics by paternal exposure group; primary outcome (N=29)

NDD Number of pregnancies	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam (composite) N=14	
	N	%	N	%
Comorbidities				
Affective disorder [a]	2	13.33	2	14.29
Diabetes [a]	1	6.67	1	7.14
Epilepsy [a]	0	0.00	0	0.00
Neurotic disorder [a]	4	26.67	4	28.57
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Obesity [b]	0	0.00	0	0.00
CMV [c]	0	0.00	0	0.00
Gestational diabetes [c]	1	6.67	1	7.14
Rubella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	1	6.67	1	7.14
Substance abuse during pregnancy [c]	1	6.67	1	7.14
Smoking prior to LMP2 [b]				
Yes	7	46.67	2	14.29
No	8	53.33	11	78.57
Missing	0	0.00	1	7.14
Smoking during pregnancy [c]				
Yes	3	20.00	1	7.14
No	12	80.00	12	85.71
Missing	0	0.00	1	7.14
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00

NDD Number of pregnancies	Paternal exposure group Valproate N=15		Lamotrigine/levetiracetam (composite) N=14	
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AED during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K-means cluster prior to LMP2 [d]				
unexposed	15	100.00	14	100.00
K-means cluster during pregnancy [c]				
unexposed	15	100.00	14	100.00
Maternal polypharmacy index prior to LMP2 [d]				
0	5	33.33	7	50.00
1-4	8	53.33	6	42.86
5-10	2	13.33	1	7.14
>10	0	0.00	0	0.00
Mean (SD)	1.53 (2.13)		1.07 (1.49)	
Median (25^{th} - 75^{th} percentile)	1(0.00, 2.00)		0.5(0.00, 2.00)	
Min, max	0.00,7.00		0.00,5.00	
Maternal polypharmacy index during pregnancy [c]				
0	3	20.00	4	28.57
1-4	12	80.00	10	71.43
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	1.47 (1.06)		1.14 (1.03)	
Median (25^{th} - 75^{th} percentile)	1(1.00, 2.00)		1(0.00, 2.00)	
Min, max	0.00,3.00		0.00,3.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	3	20.00	3	21.43
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	3	20.00	3	21.43

NDD Number of pregnancies	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam (composite) N=14	
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] - mothers with at least one prescription	12	80.00	9	64.29
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	12	80.00	9	64.29

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; AED: Antiepileptic Drug; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until index date)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Sweden during the study period

Table 208 Paternal demographic characteristics by paternal exposure group; primary outcome (N=29)

NDD Number of offspring	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam(composite) N=14	
	N	%	N	%
Father's age [a]				
≤20 years	0	0.00	0	0.00
21-25	0	0.00	0	0.00
26-30	2	13.33	1	7.14
31-35	4	26.67	5	35.71
36-40	9	60.00	2	14.29
>40	0	0.00	6	42.86
Mean (SD)	35.20 (3.38)		37.29 (5.01)	
Median (25^{th} - 75^{th} percentile)	36 (34.00, 38.00)		37 (32.00, 42.00)	
Min, max	28.00, 39.00		30.00, 44.00	
Missing	0	0.00	0	0.00
Year of offspring conception [b]				
2006	1	6.67	0	0.00
2007	3	20.00	0	0.00
2008	4	26.67	0	0.00
2009	0	0.00	3	21.43
2010	2	13.33	3	21.43
2011	0	0.00	0	0.00
2012	1	6.67	2	14.29
2013	1	6.67	2	14.29
2014	2	13.33	0	0.00
2015	1	6.67	3	21.43
2016	0	0.00	1	7.14
2017	0	0.00	0	0.00
2018	0	0.00	0	0.00
2019	0	0.00	0	0.00

	Paternal exposure group	
NDD Number of offspring	**Valproate N=15**	**Lamotrigine/levetiracetam(composite) N=14**

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) at mother's LMP2

Table 209 Paternal clinical characteristics by paternal exposure group; primary outcome (N=29)

	Paternal exposure group			
NDD Number of offspring	**Valproate N=15**		**Lamotrigine/levetiracetam (composite) N=14**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder excluding bipolar affective disorder and mania [a]	4	26.67	5	35.71
Bipolar affective disorder [a]	4	26.67	4	28.57
Mania [a]	0	0.00	0	0.00
Neurotic disorder [a]	3	20.00	6	42.86
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Lifestyle characteristics				
Substance abuse [c]	1	6.67	1	7.14
Medication use				
AED indication				
Epilepsy	10	66.67	8	57.14
Bipolar affective disorder and mania	4	26.67	4	28.57
Other/unknown	1	6.67	2	14.29
K-means cluster [d]				
Cluster A	8	53.33	8	57.14
Cluster B	7	46.67	4	28.57
Cluster C	0	0.00	2	14.29
Paternal polypharmacy index [d]				
0	8	53.33	6	42.86
1-4	7	46.67	8	57.14
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.80 (1.01)		0.71 (0.83)	
Median (25^{th} - 75^{th} percentile)	0(0.00, 2.00)		1(0.00, 1.00)	
Min, max	0.00,3.00		0.00,3.00	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	3	20.00	6	42.86
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	10	66.67	9	64.29

NDD: Neurodevelopmental Disorders; AED: Antiepileptic Drug; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
Cluster A: constant high exposure; Cluster B: low-to-high exposure and Cluster C: high-to-low exposure

Table 210 Association between potential offspring risk factors/confounders for NDD by paternal exposure group; primary outcome (N=29)

	Paternal exposure group	Comparison

NDD Number of offspring	Valproate N=15		Lamotrigine/levetiracetam (composite) N=14		Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Offspring risk factors/confounders					
Gender [a]					
Male	8	53.33	3	21.43	-
Female	7	46.67	11	78.57	-
Missing	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.12 (0.1281)*
Congenital CMV [b]	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	-
Foetal alcohol syndrome [b]	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	0	0.00	-

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) between index and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 211 Association between potential maternal risk factors/confounders for NDD by paternal exposure group; primary outcome (N=29)

	Paternal exposure group				Comparison
NDD Number of offspring	Valproate N=15		Lamotrigine/levetiracetam (composite) N=14		Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Maternal risk factors/confounders					
Mother's age [a] **(categorical)**					
≤20 years	0	0.00	0	0.00	-
21-25	2	13.33	1	7.14	-
26-30	4	26.67	3	21.43	-
31-35	8	53.33	4	28.57	-
36-40	1	6.67	5	35.71	-
>40	0	0.00	1	7.14	-
Test statistics	-	-	-	-	5.45 (0.2443)
Mother's age [a] **(continuous)**					
Mean (SD)	31.00 (4.46)		33.71 (4.45)		-1.64 (0.1124)
Median (25th - 75th percentile)	32(29.00, 34.00)		35(30.00, 36.00)		-
Min, max	22.00, 39.00		24.00, 41.00		-
Missing	0	0.00	0	0.00	-

NDD Number of offspring	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam (composite) N=14		Comparison: Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Affective disorder [b]	2	13.33	2	14.29	1.00 (1.0000)*
Diabetes [b]	1	6.67	1	7.14	1.00 (1.0000)*
Gestational diabetes [c]	1	6.67	1	7.14	1.00 (1.0000)*
Neurotic disorder [b]	4	26.67	4	28.57	1.00 (1.0000)*
Schizophrenia, schizotypal and delusional disorders [b]	0	0.00	0	0.00	-
Obesity [d]	0	0.00	0	0.00	-
CMV [c]	0	0.00	0	0.00	-
Rubella [c]	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [d]	0	0.00	0	0.00	-
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [d]	1	6.67	1	7.14	1.00 (1.0000)*
Substance abuse during pregnancy [c]	1	6.67	1	7.14	1.00 (1.0000)*
Smoking prior to LMP2 [d]					
Yes	7	46.67	2	14.29	-
No	8	53.33	11	78.57	-
Missing	0	0.00	1	7.14	-
Test statistics without 'Missing' category	-	-	-	-	0.11 (0.1145)*
Smoking during pregnancy [c]					
Yes	3	20.00	1	7.14	-
No	12	80.00	12	85.71	-
Missing	0	0.00	1	7.14	-
Test statistics without 'Missing' category	-	-	-	-	0.60 (0.6000)*
Maternal polypharmacy index prior to LMP2 [e](categorical)					
0	5	33.33	7	50.00	-
1-4	8	53.33	6	42.86	-
5-10	2	13.33	1	7.14	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.92 (0.6316)
Maternal polypharmacy index prior to LMP2 [e] (continuous)					
Mean (SD)	1.53 (2.13)		1.07 (1.49)		196.50 (0.5493)*
Median (25th - 75th percentile)	1(0.00, 2.00)		0.5(0.00, 2.00)		-
Min, max	0.00,7.00		0.00,5.00		-

NDD Number of offspring	Paternal exposure group Valproate N=15		Lamotrigine/levetiracetam (composite) N=14		Comparison Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Maternal polypharmacy index during pregnancy [c](categorical)					
0	3	20.00	4	28.57	-
1-4	12	80.00	10	71.43	-
5-10	0	0.00	0	0.00	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.68 (0.6817)*
Maternal polypharmacy index during pregnancy[c] (continuous)					
Mean (SD)	1.47 (1.06)		1.14 (1.03)		191.00 (0.3995)*
Median (25th - 75th percentile)	1(1.00, 2.00)		1(0.00, 2.00)		-
Min, max	0.00,3.00		0.00,3.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	3	20.00	3	21.43	1.00 (1.0000)*
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	3	20.00	3	21.43	1.00 (1.0000)*
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] -mothers with at least one prescription	12	80.00	9	64.29	0.42 (0.4270)*
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	12	80.00	9	64.29	0.42 (0.4270)*

NDD Number of offspring	Paternal exposure group Valproate N=15		Lamotrigine/levetiracetam (composite) N=14		Comparison Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

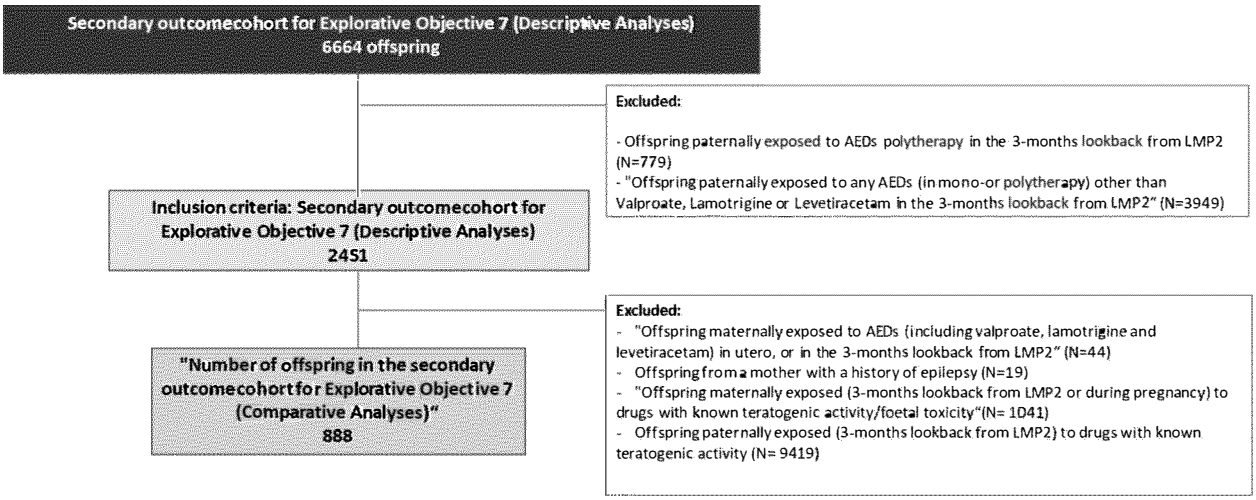
Table 212 Association between potential paternal risk factors/confounders for NDD by paternal exposure group; primary outcome (N=29)

NDD Number of offspring	Paternal exposure group Valproate N=15		Lamotrigine/levetiracetam (composite) N=14		Comparison Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Paternal risk factors/confounders					
Affective disorder [a,b]	4	26.67	5	35.71	0.28 (0.5987)
Bipolar affective disorder [a]	4	26.67	4	28.57	0.01 (0.9087)
Mania [a]	0	0.00	0	0.00	-
Neurotic disorder [a]	3	20.00	6	42.86	1.77 (0.1837)
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00	-
Substance abuse [c]	1	6.67	1	7.14	0.00 (0.9597)
Paternal polypharmacy index [d] (categorical)					
0	8	53.33	6	42.86	-
1-4	7	46.67	8	57.14	-
5-10	0	0.00	0	0.00	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.32 (0.5726)
Paternal polypharmacy index [d] (continuous)					
Mean (SD)	0.80 (1.01)		0.71 (0.83)		210.00 (1.0000)*
Median (25^{th} - 75^{th} percentile)	0(0.00, 2.00)		1(0.00, 1.00)		-
Min, max	0.00,3.00		0.00,3.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	3	20.00	6	42.86	1.77 (0.1837)

NDD Number of offspring	Paternal exposure group: Valproate N=15		Lamotrigine/levetiracetam (composite) N=14		Comparison: Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	10	66.67	9	64.29	0.02 (0.8928)
Father's age [e] (categorical)					
≤20 years	0	0.00	0	0.00	-
21-25	0	0.00	0	0.00	-
26-30	2	13.33	1	7.14	-
31-35	4	26.67	5	35.71	-
36-40	9	60.00	2	14.29	-
>40	0	0.00	6	42.86	-
Test statistics	-	-	-	-	10.88 (0.0124)
Father's age [e] (continuous)					
Mean (SD)	35.20 (3.38)		37.29 (5.01)		-1.30 (0.2055)
Median (25th - 75th percentile)	36(34.00, 38.00)		37(32.00, 42.00)		-
Min, max	28.00, 39.00		30.00, 44.00		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [f,g]					
2006-2010	10	66.67	6	42.86	-
2011-2015	5	33.33	7	50.00	-
2016-2019	0	0.00	1	7.14	-
Test statistics	-	-	-	-	2.30 (0.3164)

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) all available data prior to index date (childbirth)
b) excluding bipolar affective disorder and mania
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

15.2.7 Risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment at the time of conception (Exploratory analysis 7)



CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 38 Study population of Secondary outcome cohort for Exploratory Analyses 7 in Sweden

Table 213 Offspring demographic characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM Number of offspring	**Valproate N=968**		**Lamotrigine/levetiracetam(composite) N=1483**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	3	0.31	1	0.07
28-31 (very preterm)	6	0.62	11	0.74
32-36 (moderate to late preterm)	39	4.03	61	4.11
37-41 (at term)	858	88.64	1310	88.33
≥42 (post-term)	62	6.40	100	6.74
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	2	0.21	0	0.00
1000-1499 (very low)	6	0.62	7	0.47
1500-2499 (low)	33	3.41	41	2.76
≥2500	927	95.76	1433	96.63
Missing	0	0.00	2	0.13
Gender [a]				
Male	485	50.10	771	51.99
Female	483	49.90	712	48.01

CM Number of offspring	Paternal exposure group: Valproate N=968		Lamotrigine/levetiracetam(composite) N=1483	
	N	%	N	%
Missing	0	0.00	0	0.00
Year of birth				
2007	91	9.40	42	2.83
2008	82	8.47	58	3.91
2009	87	8.99	69	4.65
2010	75	7.75	85	5.73
2011	74	7.64	105	7.08
2012	80	8.26	107	7.22
2013	77	7.95	107	7.22
2014	93	9.61	124	8.36
2015	77	7.95	148	9.98
2016	68	7.02	140	9.44
2017	67	6.92	166	11.19
2018	49	5.06	153	10.32
2019	48	4.96	179	12.07
Total number of years of follow-up	5987.03		6886.67	
Mean follow-up year	6.18		4.64	

CM: Congenital Malformations
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 214 Offspring clinical characteristics by paternal exposure group; primary outcome

CM Number of pregnancies	Paternal exposure group: Valproate N=968		Lamotrigine/levetiracetam(composite) N=1483	
	N	%	N	%
Comorbidities [a]				
Congenital CMV	0	0.00	1	0.07
Congenital Herpes Simplex	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00
Congenital varicella	2	0.21	2	0.13
Foetal alcohol syndrome	0	0.00	0	0.00
Outcomes				
CM	101	10.43	156	10.52
Major CM (at any time)	54	5.58	81	5.46
Minor CM (at any time)	57	5.89	85	5.73
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]				
Stillbirth	0	0.00	0	0.00
Spontaneous abortion [c]	NA	NA	NA	NA
Intrauterine growth retardation	37	36.63	44	28.21
Perinatal mortality	1	0.99	2	1.28

CM: Congenital Malformations; CMV: Cytomegalovirus; NA: Not available
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between index (birthdate of live offspring in Sweden) and exit date
b) Denominator for the percentage is the number of offspring with CM.
c) Information on spontaneous abortion is not available in Sweden.

Table 215 Maternal demographic characteristics by paternal exposure group; secondary outcome

CM Number of pregnancies	Paternal exposure group: Valproate N=968		Lamotrigine/levetiracetam(composite) N=1483	
	N	%	N	%
Mother's age [a]				
≤20 years	20	2.07	24	1.62
21-25	150	15.50	177	11.94
26-30	301	31.10	442	29.80
31-35	298	30.79	489	32.97
36-40	168	17.36	305	20.57
>40	31	3.20	46	3.10
Mean (SD)	30.72 (5.29)		31.40 (5.24)	
Median (25^{th} - 75^{th} percentile)	31 (27.00, 35.00)		31 (28.00, 35.00)	
Min, max	18.00, 45.00		16.00, 53.00	
Missing	0	0.00	0	0.00

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (birthdate of live offspring in Sweden)

Table 216 Maternal clinical characteristics by paternal exposure group; secondary outcome

CM Number of offspring	Paternal exposure group: Valproate N=968		Lamotrigine/levetiracetam (composite) N=1483	
	N	%	N	%
Comorbidities				
Diabetes [a]	11	1.14	18	1.21
Epilepsy [a]	8	0.83	11	0.74
Obesity [b]	11	1.14	16	1.08
CMV [c]	0	0.00	1	0.07
Folate deficiency [c]	0	0.00	0	0.00
Gestational diabetes [c]	26	2.69	47	3.17
Herpes simplex virus [c]	2	0.21	3	0.20
Rubella [c]	0	0.00	0	0.00
Toxoplasmosis [c]	0	0.00	0	0.00
Varicella [c]	3	0.31	2	0.13
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	9	0.93	2	0.13
Alcohol abuse during pregnancy [c]	1	0.10	2	0.13
Substance abuse prior to LMP2 [b]	5	0.52	4	0.27
Substance abuse during pregnancy [c]	2	0.21	2	0.13
Smoking prior to LMP2 [b]				
Yes	158	16.32	188	12.68
No	768	79.34	1211	81.66
Missing	42	4.34	84	5.66
Smoking during pregnancy [c]				
Yes	76	7.85	81	5.46
No	864	89.26	1357	91.50
Missing	28	2.89	45	3.03
Medication use				

CM Number of offspring	Paternal exposure group: Valproate N=968		Paternal exposure group: Lamotrigine/levetiracetam (composite) N=1483	
	N	%	N	%
Exposure to AEDs prior to LMP2 [d]				
Valproate	1	0.10	3	0.20
Lamotrigine	6	0.62	21	1.42
Levetiracetam	1	0.10	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	2	0.13
Carboxamide derivatives	1	0.10	2	0.13
Fatty acid derivatives	1	0.10	3	0.20
Other antiepileptics	10	1.03	24	1.62
Exposure to AEDs during pregnancy [c]				
Valproate	2	0.21	3	0.20
Lamotrigine	5	0.52	18	1.21
Levetiracetam	1	0.10	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	1	0.07
Carboxamide derivatives	0	0.00	2	0.13
Fatty acid derivatives	2	0.21	3	0.20
Other antiepileptics	8	0.83	22	1.48
K-means cluster prior to LMP2 [d]				
unexposed	956	98.76	1455	98.11
Cluster A[1]	6	0.62	20	1.35
Cluster B[1]	6	0.62	8	0.54
K-means cluster during pregnancy [c]				
unexposed	959	99.07	1458	98.31
Cluster A[2]	7	0.72	17	1.15
Cluster B[2]	2	0.21	8	0.54
Maternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [d] - mothers with at least one prescription	252	26.03	407	27.44
Maternal exposure to teratogenic activity/foetal toxicity during pregnancy [c] - mothers with atleast one prescription	283	29.24	494	33.31

CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; AED: Antiepileptic Drug
Cluster A1: constant high exposure, Cluster B1: constant low exposure
Cluster A2: constant low exposure, Cluster B2: constant high exposure
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) all available data prior to index date (birthdate of live offspring in Sweden)
b) 12 months lookback from LMP2

CM Number of offspring	Paternal exposure group: Valproate N=968		Lamotrigine/levetiracetam (composite) N=1483	
	N	%	N	%

c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Sweden during the study period

Table 217 Paternal demographic characteristics by paternal exposure group; secondary outcome

CM Number of offspring	Paternal exposure group: Valproate N=968		Lamotrigine/levetiracetam(composite) N=1483	
	N	%	N	%
Father's age [a]				
≤20 years	6	0.62	9	0.61
21-25	72	7.44	80	5.39
26-30	217	22.42	298	20.09
31-35	324	33.47	521	35.13
36-40	233	24.07	368	24.81
>40	116	11.98	207	13.96
Mean (SD)	33.61 (6.04)		34.31 (6.19)	
Median (25^{th} - 75^{th} percentile)	33(29.00, 38.00)		34(30.00, 38.00)	
Min, max	17.00, 63.00		16.00, 77.00	
Missing	0	0.00	0	0.00
Year of offspring conception [b]				
2006	67	6.92	32	2.16
2007	83	8.57	56	3.78
2008	89	9.19	60	4.05
2009	77	7.95	88	5.93
2010	73	7.54	99	6.68
2011	72	7.44	104	7.01
2012	85	8.78	102	6.88
2013	85	8.78	132	8.90
2014	90	9.30	120	8.09
2015	61	6.30	160	10.79
2016	73	7.54	158	10.65
2017	47	4.86	162	10.92
2018	56	5.79	161	10.86
2019	10	1.03	49	3.30

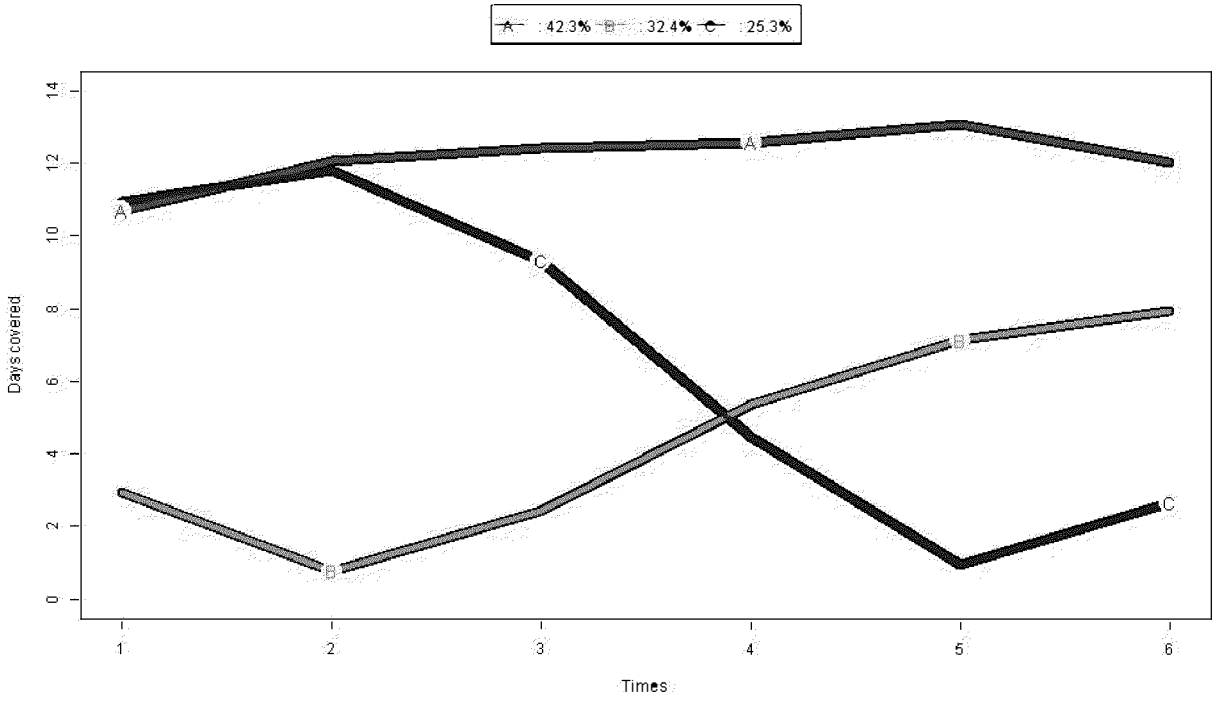
CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (birthdate of live offspring in Sweden)
b) at mother's LMP2

Table 218 Paternal clinical characteristics by paternal exposure group; secondary outcome

CM Number of offspring	Paternal exposure group: Valproate N=968	Lamotrigine/levetiracetam (composite) N=1483

	N	%	N	%
Medication use				
AED indication				
Epilepsy	684	70.66	683	46.06
Bipolar affective disorder and mania	124	12.81	429	28.93
Other/unknown	160	16.53	371	25.02
K-means cluster prior to LMP2 [a]				
Cluster A	400	41.32	637	42.95
Cluste B	299	30.89	494	33.31
Cluste C	269	27.79	352	23.74
Paternal exposure to teratogenic activity/foetal toxicity [a]	272	28.10	669	45.11

Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
Cluster A: constant high exposure; Cluster B: low-to-high exposure and Cluster C: high-to-low exposure.
AED: Antiepileptic Drug, LMP2: Last Menstrual Period Date Plus 2 weeks, CM: Congenital Malformations
a) 3 months lookback fromLMP2



Legend: Times refers to the 14-days interval during which exposure is assessed (in this case, 6 14 days interval [i.e.3 months]); Days covered refers to days covered in each 14-day interval; Defined Daily Dose (DDD) trajectories: Cluster A: constant high exposure; Cluster B: low-to-high exposure and Cluster C: high-to-low exposure. The percentage shows the proportion of fathers exposed to valproate and lamotrigine/levetiracetam in each cluster.

Figure 39 Mean Defined Daily Dose trajectories for fathers exposed to AEDs in the 3 months lookback prior to Last Menstrual Period Date Plus 2 weeks (LMP2) – Exploratory analyses 7

Table 219 Cumulative incidence proportion (risk) of CM by paternal exposure group; secondary outcome

Paternal exposure group

CM		Valproate	Lamotrigine /levetiracetam (composite)
Follow-up in years from index date			
	N	968	1483
0-1 years	n	72	125
	n/N*100	7.44 (5.79, 9.09)	8.43 (7.01, 9.84)
	N	850	1184
1-2 years	n	14	14
	n/N*100	1.65 (0.79, 2.50)	1.18 (0.57, 1.80)
	N	788	1039
2-3 years	n	5	3
	n/N*100	0.63 (0.08, 1.19)	0.29 (-0.04, 0.62)
	N	719	890
3-4 years	n	2	3
	n/N*100	0.28 (-0.11, 0.66)	0.34 (-0.04, 0.72)
	N	649	761
4-5 years	n	2	3
	n/N*100	0.31 (-0.12, 0.73)	0.39 (-0.05, 0.84)
	N	576	624
5-6 years	n	2	6
	n/N*100	0.35 (-0.13, 0.83)	0.96 (0.20, 1.73)
	N	492	501
6-7 years	n	2	1
	n/N*100	0.41 (-0.16, 0.97)	0.20 (-0.19, 0.59)
	N	420	407
7-8 years	n	1	1
	n/N*100	0.24 (-0.23, 0.70)	0.25 (-0.24, 0.73)
	N	346	314
8-9 years	n	0	0
	n/N*100	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	N	284	223
9-10 years	n	0	0
	n/N*100	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	N	220	145
10-11 years	n	1	0
	n/N*100	0.45 (-0.43, 1.34)	0.00 (0.00, 0.00)
	N	146	84
11-12+ [a] years	n	0	0

	n/N*100	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	N	968	1483
Overall (0-12+ years)	n	101	156
	n/N*100	10.43 (8.51, 12.36)	10.52 (8.96, 12.08)

Legend: Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with 95% confidence interval (CI) were presented.
[a] For countries where the index date is the 12th or 22nd week of pregnancy, follow-up time in years were longer than age in years, therefore some offspring were >12 years of follow-up by the time they are censored upon 12th birthday. For this reason, the table shows '12+ years'.
CM: Congenital Malformations

Table 220 Association between potential offspring risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				Comparison
CM Number of offspring	**Valproate N=418**		**Lamotrigine/levetiracetam (composite) N=470**		**Valproatevs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	
Offspring risk factors/confounders[a]					
Congenital CMV	0	0.00	1	0.21	1.00 (1.0000)*
Congenital Herpes Simplex	0	0.00	0	0.00	-
Congenital rubella	0	0.00	0	0.00	-
Congenital toxoplasmosis	0	0.00	0	0.00	-
Congenital varicella	0	0.00	1	0.21	1.00 (1.0000)*
Foetal alcohol syndrome	0	0.00	0	0.00	-

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) between index (birthdate of live offspring in Sweden) and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.
CM: Congenital Malformations

Table 221 Association between potential maternal risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				Comparison *
CM Number of offspring	**Valproate N=418**		**Lamotrigine/levetiracetam (composite) N=470**		**Valproatevs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	
Maternal risk factors/confounders					
Mother´s age [a](categorical)					
≤20 years	9	2.15	11	2.34	-
21-25	77	18.42	61	12.98	-
26-30	130	31.1	151	32.13	-

CM Number of offspring	Paternal exposure group Valproate N=418		Lamotrigine/levetiracetam (composite) N=470		Comparison * Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
31-35	134	32.06	170	36.17	-
36-40	60	14.35	73	15.53	-
>40	8	1.91	4	0.85	-
Test statistics	-	-	-	-	7.47 (0.1878)
Mother´s age [a](continuous)					
Mean (SD)	30.03 (5.10)		30.64 (4.87)		178355.50 (0.0506)*
Median (25th - 75th percentile)	30(27.00, 34.00)		31(27.00, 34.00)		-
Min, max	19.00, 45.00		17.00, 43.00		-
Missing	0	0.00	0	0.00	-
Diabetes [b]	2	0.48	2	0.43	1.00 (1.0000)*
Obesity [c]	1	0.24	7	1.49	0.07 (0.0728)*
Alcohol abuse prior to LMP2 [c]	4	0.96	0	0.00	0.04 (0.0487)*
Alcohol abuse during pregnancy [d]	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [c]	0	0.00	2	0.43	0.50 (0.5012)*
Substance abuse during pregnancy [d]	0	0.00	1	0.21	1.00 (1.0000)*
Smoking prior to LMP2 [c]					
Yes	62	14.83	54	11.49	-
No	342	81.82	396	84.26	-
Missing	14	3.35	20	4.26	-
Test statistics without 'Missing' category	-	-	-	-	2.03 (0.1541)
Smoking during pregnancy [d]					
Yes	23	5.50	28	5.96	-
No	384	91.87	432	91.91	-
Missing	11	2.63	10	2.13	-
Test statistics without 'Missing' category	-	-	-	-	0.07 (0.7855)
CMV [d]	0	0.00	1	0.21	1.00 (1.0000)*
Folate deficiency [d]	0	0.00	0	0.00	-
Gestational diabetes [d]	5	1.20	6	1.28	0.01 (0.9139)
Herpes simplex virus [d]	0	0.00	0	0.00	-
Rubella [d]	0	0.00	0	0.00	-
Toxoplasmosis [d]	0	0.00	0	0.00	-
Varicella [d]	0	0.00	1	0.21	1.00 (1.0000)*

CM Number of offspring	Paternal exposure group Valproate N=418		Lamotrigine/levetiracetam (composite) N=470		Comparison * Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (birthdate of live offspring in Sweden)
b) all available data prior to index date
c) 12 months lookback from LMP2
d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 222 Association between potential paternal risk factors/confounders for CM by paternal exposure group; secondary outcome

CM Number of offspring	Paternal exposure group Valproate N=418		Lamotrigine/levetiracetam (composite) N=470		Comparison * Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	
Paternal risk factors/confounders					
Father´s age [a](categorical)					
≤20 years	4	0.96	5	1.06	-
21-25	40	9.57	24	5.11	-
26-30	102	24.40	122	25.96	-
31-35	145	34.69	178	37.87	-
36-40	89	21.29	99	21.06	-
>40	38	9.09	42	8.94	-
Test statistics	-	-	-	-	6.98 (0.2222)
Father´s age [a] (continuous)					
Mean (SD)	32.85 (5.99)		33.10 (5.37)		182193.00 (0.3436)*
Median (25^{th} - 75^{th} percentile)	32 (29.00, 36.00)		33 (30.00, 37.00)		-
Min, max	19.00, 55.00		18.00, 52.00		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [b,c]					
2006-2010	167	39.95	118	25.11	-
2011-2015	170	40.67	184	39.15	-
2016-2019	81	19.38	168	35.74	-
Test statistics	-	-	-	-	36.46 (<.0001)

	Paternal exposure group				Comparison *
CM Number of offspring	Valproate N=418		Lamotrigine/levetiracetam (composite) N=470		Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (birthdate of live offspring in Sweden)
b) at mother's LMP2
c) calendar years were grouped in each country according to the length of the study period
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 223 Association between potential offspring risk factors/confounders and CM; secondary outcome

CM	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Offspring risk factors/confounders [a]								
Congenital CMV (Yes)								
No	887	99.89	97	10.94	790	89.06	Reference	-
Yes	1	0.11	0	0.00	1	100.00	0.00(0.00,I)	0.00(0.9884)
Congenital Herpes Simplex (Yes)								
No	888	100.00	97	10.92	791	89.08	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital rubella (Yes)								
No	888	100.00	97	10.92	791	89.08	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital toxoplasmosis (Yes)								
No	888	100.00	97	10.92	791	89.08	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital varicella (Yes)								
No	887	99.89	97	10.94	790	89.06	Reference	-
Yes	1	0.11	0	0.00	1	100.00	0.00(0.00,I)	0.00(0.9884)
Foetal alcohol syndrome (Yes)								
No	888	100.00	97	10.92	791	89.08	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-

CM: Congenital Malformations; OR: Odds Ratio; CI: Confidence Interval; CMV: Cytomegalovirus

Legend: Percentages are calculated over the total number of offspring. The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.

a) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date

Table 224 Association between potential maternal risk factors/confounders and CM; secondary outcome

CM	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Maternal risk factors/confounders								
Mother's age [a] (categorical)								

CM	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
≤20 years	20	2.25	3	15.00	17	85.00	1.59 (0.44, 5.78)	-
21-25	138	15.54	18	13.04	120	86.96	1.36 (0.72, 2.55)	-
26-30	281	31.64	28	9.96	253	90.04	Reference	-
31-35	304	34.23	39	12.83	265	87.17	1.33 (0.79, 2.23)	-
36-40	133	14.98	8	6.02	125	93.98	0.58 (0.26, 1.31)	-
>40	12	1.35	1	8.33	11	91.67	0.82 (0.10, 6.60)	-
Wald test	-	-	-	-	-	-	-	5.56 (0.3518)
Diabetes [b]								
No	884	99.55	96	10.86	788	89.14	Reference	-
Yes	4	0.45	1	25.00	3	75.00	2.74 (0.28, 26.57)	0.75 (0.3853)
Obesity [c]								
No	880	99.10	96	10.91	784	89.09	Reference	-
Yes	8	0.90	1	12.50	7	87.50	1.17 (0.14, 9.58)	0.02 (0.8859)
Alcohol abuse prior to LMP2 [c]								
No	884	99.55	97	10.97	787	89.03	Reference	-
Yes	4	0.45	0	0.00	4	100.00	0.00 (0.00,I)	0.00 (0.9846)
Alcohol abuse during pregnancy [d]								
No	888	100.00	97	10.92	791	89.08	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Substance abuse prior to LMP2 [c]								
No	886	99.77	97	10.95	789	89.05	Reference	-
Yes	2	0.23	0	0.00	2	100.00	0.00 (0.00,I)	0.00 (0.9891)
Substance abuse during pregnancy [d]								
No	887	99.89	97	10.94	790	89.06	Reference	-
Yes	1	0.11	0	0.00	1	100.00	0.00 (0.00,I)	0.00 (0.9884)
Smoking prior to LMP2 [c]								
Yes	116	13.06	16	13.79	100	86.21	1.35 (0.76, 2.41)	-
No	738	83.11	78	10.57	660	89.43	Reference	-
Missing	34	3.83	3	8.82	31	91.18	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	1.06 (0.3035)
Smoking during pregnancy [d]								
Yes	51	5.74	5	9.80	46	90.20	0.87(0.34, 2.24)	-
No	816	91.89	91	11.15	725	88.85	Reference	-
Missing	21	2.36	1	4.76	20	95.24	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	0.09 (0.7662)
CMV [d]								
No	887	99.89	97	10.94	790	89.06	Reference	-
Yes	1	0.11	0	0.00	1	100.00	0.00(0.00,I)	0.00 (0.9884)

CM	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Folate deficiency [d]								
No	888	100.00	97	10.92	791	89.08	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Gestational diabetes [d]								
No	877	98.76	92	10.49	785	89.51	Reference	-
Yes	11	1.24	5	45.45	6	54.55	7.11 (2.13, 23.76)	10.16 (0.0014)
Herpes simplex virus [d]								
No	888	100.00	97	10.92	791	89.08	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Rubella [d]								
No	888	100.00	97	10.92	791	89.08	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Toxoplasmosis [d]								
No	888	100.00	97	10.92	791	89.08	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Varicella [d]								
No	887	99.89	97	10.94	790	89.06	Reference	-
Yes	1	0.11	0	0.00	1	100.00	0.00(0.00,I)	0.00(0.9884)

CM: Congenital Malformations; OR: Odds Ratio; CI: Confidence Interval; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage is calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome is tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test are reported.
a) at index (birthdate of live offspring in Sweden)
b) all available data prior to index date
c) 12 months lookback from LMP2
d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)

Table 225 Association between potential paternal risk factors/confounders and CM; secondary outcome

CM	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value

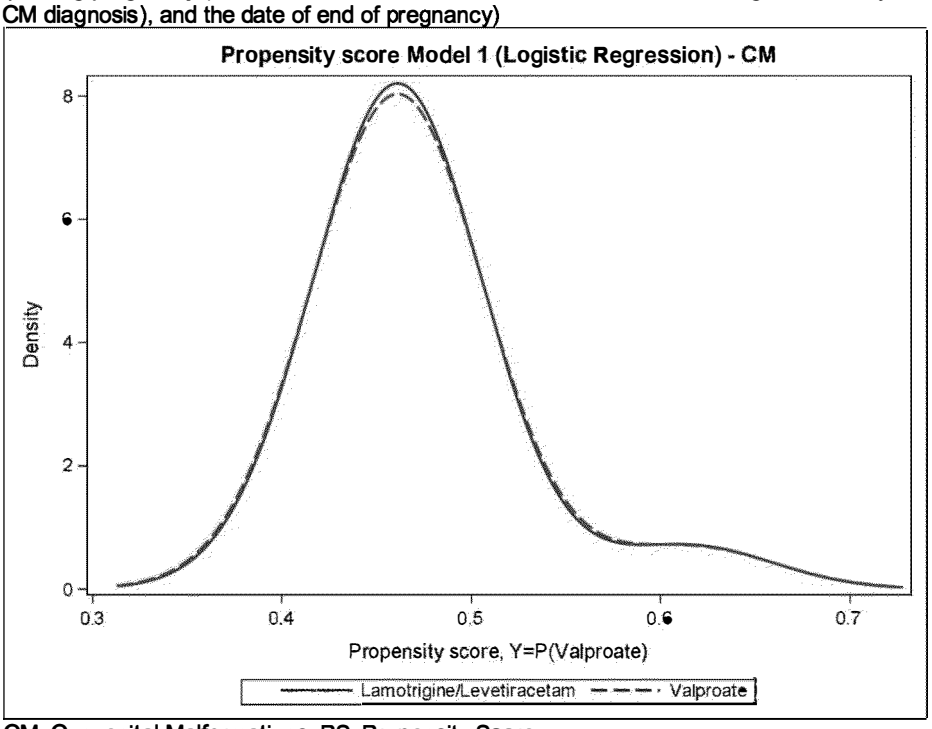
CM	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Paternal risk factors/confounders for CM								
Father's age [a] (categorical)								
≤20 years	9	1.01	2	22.22	7	77.78	2.35 (0.47, 11.76)	-
21-25	64	7.21	13	20.31	51	79.69	2.10 (1.04, 4.24)	-
26-30	224	25.23	25	11.16	199	88.84	1.03 (0.60, 1.78)	-
31-35	323	36.37	35	10.84	288	89.16	Reference	-
36-40	188	21.17	18	9.57	170	90.43	0.87 (0.48, 1.59)	-
>40	80	9.01	4	5.00	76	95.00	0.43 (0.15, 1.26)	-
Wald test	-	-	-	-	-	-	-	9.60(0.0875)
Year of offspring conception [b,c]								
2006-2010	285	32.09	38	13.33	247	86.67	Reference	-
2011-2015	354	39.86	34	9.60	320	90.40	0.69 (0.42, 1.13)	-
2016-2019	249	28.04	25	10.04	224	89.96	0.73 (0.42, 1.24)	-
Wald test	-	-	-	-	-	-	-	2.52(0.2841)

CM: Congenital Malformations; OR; Odds Ratio; CI: Confidence Interval
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at index (birthdate of live offspring in Sweden)
b) at mother's LMP2
c) calendar years were grouped in each country according to the length of the study period

Table 226 Variable estimates from logistic regression propensity score model; secondary outcome

CM Variable (or interaction) [a]	OR	Estimate 95% CI	P-value
Maternal risk factors/confounders			
Smoking prior to LMP2 [e]			
No	Reference	-	-
Yes	1.86	1.10 - 3.13	0.0198
Smoking during pregnancy [f]			
No	Reference	-	-
Yes	0.46	0.22 - 0.99	0.0483

CM: Congenital Malformations; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Odds ratios (OR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.
a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.
e) 12 months lookback from LMP2
f) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)



CM: Congenital Malformations; PS: Propensity Score

Figure 40 Plot of PS scores (stratified by exposure group)

Variable estimates from propensity score (figures show the balance)

15.3 Norway

15.3.1.1 Description of the offspring, maternal and paternal characteristics in the Primary outcome cohort

Characteristics of the offspring, mothers and fathers from the Primary outcome cohort are reported to from Table 227 to Table 229. Among the 4,648 offspring from the Primary outcome cohort, 52.4% were male, 1.4% were diagnosed with epilepsy, and 0.9% were exposed to AEDs during the period they were followed-up (Table 227). Please note that all these offspring were excluded from the comparative analyses, therefore distribution of these characteristics might differ in those analyses (see Figure 9).

Regarding maternal characteristics of this group, the median (IQR) age of mothers at childbirth was 30 (27-34) years. The most frequent maternal comorbidities diagnosed prior to childbirth were neurotic disorder (10.3%), affective disorder (6.5%), gestational diabetes (5.8%), diabetes (1.8%), and epilepsy (1.3%). Majority of the mothers were non-smokers prior to LMP2 (61.5%) and during pregnancy (78.1%); however, missing values were observed for 24.2% and 12.7% of mothers, respectively (Table 228).

Maternal exposure to AEDs prior to LMP2 and during pregnancy was low, and the proportion of use of each AED (including valproate, lamotrigine and levecetiracteam) was lower than 1%, except for the category of 'Other antiepileptics' (1.4%); these mothers were excluded from the comparative analysis. In total, 44.0% of mothers had at least one prescription of concomitant medications during pregnancy associated with neuropsychiatric adverse events, while prior to LMP2 this percentage was 67.5% (Table 228).

Regarding paternal characteristics of this group, the median (IQR) age of fathers at childbirth was 34 (30-38) years. The most frequent paternal comorbidities diagnosed prior to childbirth were neurotic disorder (9.9%), affective disorder excluding bipolar affective disorder and mania (9.9%), and bipolar affective disorder (8.8%). With regard to paternal exposure to AEDs, 13.8% of fathers were exposed to valproate in monotherapy, and 29.7% were exposed to lamotrigine/levetiracetam in monotherapy in the 3 months lookback period from LMP2, the remaining ones were exposed to other AEDs. Only 1.4% of conceptions occurred in 2019; this small proportion is due to study period ending in December 2019, which resulted in the inclusion only of those conceptions that occurred in the first months of the year and which resulted in a childbirth in the same year (Table 229).

Table 227 Description of the offspring characteristics in the Primary outcome cohort in Norway (N=4648)

NDD - offspring characteristics		
Number of offspring	**4648**	
	N	**%**
Gestational age (weeks)		
<28 (extremely preterm)	13	0.28
28-31 (very preterm)	21	0.45
32-36 (moderate to late preterm)	206	4.43
37-41 (at term)	4184	90.02
≥42 (post-term)	224	4.82
Missing	0	0.00
Birth weight (g)		
<1000 (extremely low)	19	0.41

NDD - offspring characteristics		
Number of offspring	**4648**	
	N	**%**
1000-1499 (very low)	17	0.37
1500-2499 (low)	140	3.01
≥2500	4471	96.19
Missing	1	0.02
Gender [a]		
Male	2436	52.41
Female	2212	47.59
Missing	0	0.00
Comorbidities [b]		
Congenital CMV	0	0.00
Congenital rubella	0	0.00
Epilepsy	66	1.42
Foetal alcohol syndrome	0	0.00
Fragile X syndrome	0	0.00
Lejeune/cri du chat syndrome	0	0.00
Tuberous sclerosis	2	0.04
Medication use [b]		
Exposure to AEDs	44	0.95

AED: antiepileptic drugs; CMV: Cytomegalovirus; NDD: neurodevelopmental disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) between index and exit date

Table 228 Description of the maternal characteristics in the Primary outcome cohort in Norway (N=4648)

NDD - offspring characteristics		
Number of offspring	**4648**	
	N	**%**
Mother's age [a]		
≤20 years	98	2.11
21-25	730	15.71
26-30	1504	32.36
31-35	1506	32.40
36-40	667	14.35
>40	143	3.08
Mean (SD)	30.54 (5.22)	
Median (25th - 75th percentile)	30.00 (27.00, 34.00)	
Min, max	16.00, 47.00	
Missing	0	0.00
Comorbidities		
Affective disorder [b]	302	6.50
Diabetes [b]	82	1.76
Epilepsy [b]	62	1.33
Neurotic disorder [b]	477	10.26
Schizophrenia, schizotypal and delusional disorders [b]	6	0.13
Obesity [c]	35	0.75
CMV [d]	0	0.00
Gestational diabetes [d]	272	5.85
Rubella [d]	0	0.00
Lifestyle characteristics		
Alcohol abuse prior to LMP2 [c]	12	0.26
Alcohol abuse during pregnancy [d]	5	0.11
Substance abuse prior to LMP2 [c]	21	0.45
Substance abuse during pregnancy [d]	28	0.60
Smoking prior to LMP2 [c]		
Yes	663	14.26
No	2859	61.51
Missing	1126	24.23
Smoking during pregnancy [d]		
Yes	428	9.21
No	3632	78.14
Missing	588	12.65
Medication use		
Exposure to AEDs prior to LMP2 [e]		
Valproate	2	0.04
Lamotrigine	36	0.77
Levetiracetam	2	0.04
Barbiturates and derivatives	0	0.00
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [f]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	18	0.39

NDD - offspring characteristics		
Number of offspring	**4648**	
	N	**%**
Carboxamide derivatives	11	0.24
Fatty acid derivatives	2	0.04
Other antiepileptics	64	1.38
Exposure to AEDs during pregnancy [d]		
Valproate	0	0.00
Lamotrigine	35	0.75
Levetiracetam	3	0.06
Barbiturates and derivatives	1	0.02
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [f]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	13	0.28
Carboxamide derivatives	12	0.26
Fatty acid derivatives	0	0.00
Other antiepileptics	62	1.33
Maternal polypharmacy index prior to LMP2 [e]		
0	2973	63.96
1-4	1614	34.72
5-10	59	1.27
>10	2	0.04
Mean (SD)	0.65 (1.12)	
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 1.00)	
Min, max	0.00, 12.00	
Maternal polypharmacy index during pregnancy [d]		
0	2351	50.58
1-4	2181	46.92
5-10	115	2.47
>10	1	0.02
Mean (SD)	0.94 (1.32)	
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 1.00)	
Min, max	0.00, 11.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [c] - mothers with at least one prescription	501	10.78
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least 1 prescription	264	5.68
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [c] -mothers with at least one prescription	3137	67.49
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [d] - mothers with at least one prescription	2044	43.98

NDD - offspring characteristics		
Number of offspring	**4648**	
	N	**%**

AED: antiepileptic drugs; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; NDD: neurodevelopmental disorders; SD: Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) all available data prior to index date
c) 12 months lookback from LMP2
d) during pregnancy (from LMP2 until index date)
e) 3 months lookback from LMP2
f) Oxazolidine derivatives were not sold in Norway during the study period

Table 229 Description of the paternal characteristics in the Primary outcome cohort in Norway

NDD - paternal characteristics		
Number of offspring	**4648**	
	N	**%**
Father's age [a]		
≤20 years	21	0.45
21-25	323	6.95
26-30	996	21.43
31-35	1502	32.31
36-40	1054	22.68
>40	752	16.18
Mean (SD)	34.30 (6.55)	
Median (25^{th} - 75^{th} percentile)	34.00 (30.00, 38.00)	
Min, max	18.00, 67.00	
Missing	0	0.00
Year of offspring conception [b]		
2005	214	4.60
2006	295	6.35
2007	349	7.51
2008	377	8.11
2009	364	7.83
2010	376	8.09
2011	318	6.84
2012	355	7.64
2013	323	6.95
2014	350	7.53
2015	357	7.68
2016	322	6.93
2017	296	6.37
2018	286	6.15
2019	66	1.42
Comorbidities [c]		
Affective disorder excluding bipolar affective disorder and mania	462	9.94
Bipolar affective disorder	410	8.82
Mania	16	0.34
Neurotic disorder	462	9.94

NDD - paternal characteristics		
Number of offspring	**4648**	
	N	**%**
Schizophrenia, schizotypal and delusional disorders	55	1.18
Lifestyle characteristics		
Substance abuse [e]	78	1.68
Medication use		
Exposure to AEDs [f]		
Valproate [g]	922	19.84
Lamotrigine [g]	1462	31.45
Levetiracetam [g]	428	9.21
Barbiturates and derivatives [g]	39	0.84
Hydantoin derivatives [g]	47	1.01
Oxazolidine derivatives [d,g]	0	0.00
Succinimide derivatives [g]	6	0.13
Benzodiazepine derivatives [g]	282	6.07
Carboxamide derivatives [g]	870	18.72
Fatty acid derivatives [g]	923	19.86
Other antiepileptics [g]	3010	64.76
Valproate in monotherapy	640	13.77
Lamotrigine in monotherapy	1185	25.49
Levetiracetam in monotherapy	194	4.17
Lamotrigine/levetiracetam in monotherapy	1379	29.67
Paternal polypharmacy index [f]		
0	2213	47.61
1-4	2210	47.55
5-10	217	4.67
>10	8	0.17
Mean (SD)	1.17 (1.62)	
Median (25^{th} - 75^{th} percentile)	1.00 (0.00, 2.00)	
Min, max	0.00, 15.00	
Concomitant medications associated with valproate-indicated psychiatric conditions [e] - fathers with at least one prescription	2281	49.07
Concomitant medications associated with neuropsychiatric adverse events [e] - fathers with atleast one prescription	3270	70.35
Fathers exposed to AEDs polytherapy prior to LMP2 [f]	632	13.60
Fathers exposed to valproate in combination with other AEDs prior to LMP2 [f]	277	5.96
Fathers switching to/from an AED other than valproate, lamotrigine, levetiracetam prior to LMP2 [f]	326	7.01

AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks; NDD: neurodevelopmental disorders; SD: Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) at mother's LMP2
c) all available data prior to index date
d) Oxazolidine derivatives were not sold in Norway during the study period
e) 12 months lookback from LMP2

NDD - paternal characteristics		
Number of offspring	**4648**	
	N	**%**

f) 3 months lookback from LMP2
g) in mono- or polytherapy

15.3.1.2 Description of the offspring, maternal and paternal characteristics in the secondary outcome cohort

Characteristics of the offspring, mothers and fathers from the Secondary outcome cohort are reported from Table 230 to Table 232.

Among the 4676 offspring in the Secondary outcome cohort, 52.4% were male, 89.6%, were born at term, 95.8% were weighing ≥2500 g. The comorbidities of congenital herpes simplex and congenital varicella were present in <5 offspring, while the rest were absent (Table 230).

Regarding maternal characteristics of mothers from the Secondary outcome cohort, the median (IQR) age of mothers at childbirth was 30 (26, 34) years. The most frequent maternal comorbidities prior to childbirth were diabetes (1.7%) and gestational diabetes (1.5%). Smoking status prior to LMP2 was 14.3% and during pregnancy 9.2%. However, missing data for smoking status prior to LMP2 and during pregnancy were 24.4% and 12.8%, respectively. Exposure to other antiepileptics 3 months prior to LMP2 and during pregnancy was observed among 1.4% and 1.3% of mothers, respectively (Table 231).

Regarding characteristics of fathers from the Secondary outcome cohort, the median (IQR) age of fathers at childbirth was 33 (29, 38) years. With regards to exposure to any AEDs, 13.8% of fathers were exposed to valproate in monotherapy and 29.6% were exposed to lamotrigine/levetiracetam in monotherapy in the 3 months lookback period from LMP2, while the remaining fathers were exposed to other antiepileptics Considering the Secondary outcome cohort for descriptive analyses, 62.9% of fathers were Paternal exposure due to teratogenic activity/foetal toxicity prior to LMP2 (Table 232).

Table 230 Description of the offspring characteristics for the Secondary outcome cohort in Norway (N=4676)

CM - offspring characteristics		
Number of offspring	**4676**	
	N	**%**
Gestational age (weeks)		
<28 (extremely preterm)	26	0.56
28-31 (very preterm)	25	0.53
32-36 (moderate to late preterm)	213	4.56
37-41 (at term)	4188	89.56
≥42 (post-term)	224	4.79
Missing	0	0.00
Birth weight (g)		
<1000 (extremely low)	32	0.68
1000-1499 (very low)	21	0.45
1500-2499 (low)	142	3.04
≥2500	4479	95.79
Missing	2	0.04
Gender		

CM - offspring characteristics		
Number of offspring	**4676**	
Male	2450	52.40
Female	2223	47.54
Missing	3	0.06
Comorbidities [a]		
Congenital CMV	0	0.00
Congenital Herpes Simplex	1	0.02
Congenital rubella	0	0.00
Congenital toxoplasmosis	0	0.00
Congenital varicella	1	0.02
Foetal alcohol syndrome	0	0.00

CM: Congenital Malformations; CMV: Cytomegalovirus
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between 12th week of gestation in Norway and exit date

Table 231 Description of the maternal characteristics for the Secondary outcome cohort in Norway (N=4676)

CM - maternal characteristics		
Number of offspring	**4676**	
	N	**%**
Mother's age at index date [a]		
≤20 years	124	2.65
21-25	821	17.56
26-30	1575	33.68
31-35	1432	30.62
36-40	615	13.15
>40	109	2.33
Mean (SD)	30.03 (5.22)	
Median (25th - 75th percentile)	30.00(26.00, 34.00)	
Min, max	16.00, 46.00	
Missing	0	0.00
Comorbidities		
Diabetes [b]	80	1.71
Epilepsy [b]	62	1.33
Obesity [c]	35	0.75
CMV [d]	0	0.00
Folate deficiency [d]	0	0.00
Gestational diabetes [d]	71	1.52
Herpes simplex virus [d]	5	0.11
Rubella [d]	0	0.00
Toxoplasmosis [d]	0	0.00
Varicella [d]	4	0.09
Lifestyle characteristics		
Alcohol abuse prior to LMP2 [c]	12	0.26
Alcohol abuse during pregnancy [d]	5	0.11

CM - maternal characteristics		
Number of offspring	**4676**	
	N	**%**
Substance abuse prior to LMP2 [c]	21	0.45
Substance abuse during pregnancy [d]	21	0.45
Smoking prior to LMP2 [c]		
Yes	668	14.29
No	2869	61.36
Missing	1139	24.36
Smoking during pregnancy [d]		
Yes	430	9.20
No	3650	78.06
Missing	596	12.75
Medication use		
Exposure to AEDs prior to LMP2 [e]		
Valproate	2	0.04
Lamotrigine	36	0.77
Levetiracetam	2	0.04
Barbiturates and derivatives	0	0.00
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [e]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	19	0.41
Carboxamide derivatives	11	0.24
Fatty acid derivatives	2	0.04
Other antiepileptics	65	1.39
Exposure to AEDs during pregnancy [d]		
Valproate	0	0.00
Lamotrigine	35	0.75
Levetiracetam	2	0.04
Barbiturates and derivatives	1	0.02
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [e]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	10	0.21
Carboxamide derivatives	10	0.21
Fatty acid derivatives	0	0.00
Other antiepileptics	61	1.30
Maternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [f] - mothers with at least one prescription	1364	29.17
Maternal exposure to teratogenic activity/foetal toxicity during pregnancy [d] - mothers with at least one prescription	1350	28.87

CM - maternal characteristics		
Number of offspring	**4676**	
	N	**%**

AED: antiepileptic drugs; CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks,
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at 12th week of gestation in Norway
b) all available data prior to index date
c) 12 months lookback from LMP2
d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
e) Oxazolidine derivatives were not sold in Norway during the study period
3 months lookback from LMP2

Table 232 Description of the paternal characteristics for the Secondary outcome cohort in Norway(N=4676)

CM - paternal characteristics		
Number of offspring	**4676**	
	N	**%**
Father's age [a]		
≤20 years	34	0.73
21-25	369	7.89
26-30	1097	23.46
31-35	1514	32.38
36-40	984	21.04
>40	678	14.50
Mean (SD)	33.81 (6.56)	
Median (25th - 75th percentile)	33.00 (29.00, 38.00)	
Min, max	17.00, 66.00	
Missing	0	0.00
Year of child conception [b]		
2005	214	4.58
2006	298	6.37
2007	354	7.57
2008	382	8.17
2009	365	7.81
2010	378	8.08
2011	321	6.86
2012	358	7.66
2013	324	6.93
2014	350	7.49
2015	355	7.59
2016	323	6.91
2017	299	6.39
2018	288	6.16
2019	67	1.43
Medication use		
Exposure to AEDs		

CM - paternal characteristics		
Number of offspring	**4676**	
	N	**%**
Valproate [d]	927	19.82
Lamotrigine [d]	1465	31.33
Levetiracetam [d]	430	9.20
Barbiturates and derivatives [d]	39	0.83
Hydantoin derivatives [d]	47	1.01
Oxazolidine derivatives [d,e]	0	0.00
Succinimide derivatives [d]	6	0.13
Benzodiazepine derivatives [d]	285	6.09
Carboxamide derivatives [d]	877	18.76
Fatty acid derivatives [d]	928	19.85
Other antiepileptics [d]	3026	64.71
Valproate in monotherapy	644	13.77
Lamotrigine in monotherapy	1188	25.41
Levetiracetam in monotherapy	195	4.17
Lamotrigine/levetiracetam in monotherapy	1383	29.58
Fathers exposed to AEDs polytherapy prior to LMP2 [c]	636	13.60
Fathers exposed to valproate in combination with other AEDs prior to LMP2 [c]	278	5.95
Fathers switching to/from an AED other than valproate, lamotrigine, levetiracetam prior to LMP2 [c]	328	7.01
Paternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [c,f]	2939	62.85

AED: antiepileptic drugs; CM: Congenital Malformations; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at 12th week of gestation in Norway

b) at mother's LMP2

c) 3 months lookback from LMP2

d) in mono- or polytherapy

e) Oxazolidine derivatives were not sold in Norway during the study period 3 months lookback from LMP2

f) Please note, that the list of teratogens include 'All other AEDs'

15.3.2 Cumulative incidence proportion of NDD by gender

Table 233 Cumulative incidence proportion (risk) of NDD by paternal exposure group for male offspring; primary outcome

		Paternal exposure group				
NDD		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Follow-up period						
	N	322	732	618	114	1054
0-1 years	n	2	0	0	0	2
	n/N*100	0.62 (-0.24, -1.48)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00 0.00)	0.19 (-0.07, 0.45)
	N	305	671	572	99	976
1-2 years	n	0	0	0	0	0
	n/N*100	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	N	281	616	527	89	897
2-3 years	n	0	4	4	0	4
	n/N*100	0.00 (0.00, 0.00)	0.65 (0.02, 1.28)	0.76 (0.02, 1.50)	0.00 (0.00, 0.00)	0.45 (0.01, 0.88)
	N	258	556	478	78	814
3-4 years	n	1	7	6	1	8
	n/N*100	0.39 (-0.37, 1.15)	1.26 (0.33, 2.19)	1.26 (0.26, 2.25)	1.28 (-1.21, 3.78)	0.98 (0.31, 1.66)
	N	236	488	424	64	724
4-5 years	n	5	5	4	1	10
	n/N*100	2.12 (0.28, 3.96)	1.02 (0.13, 1.92)	0.94 (0.02, 1.86)	1.56 (-1.48, 4.60)	1.38 (0.53, 2.23)
	N	216	429	376	53	645
5-6 years	n	1	3	2	1	4
	n/N*100	0.46 (-0.44, 1.37)	0.70 (-0.09, 1.49)	0.53 (-0.20, 1.27)	1.89 (-1.78, 5.55)	0.62 (0.01, 1.23)
	N	194	354	313	41	548
6-7 years	n	3	6	6	0	9
	n/N*100	1.55 (-0.19, 3.28)	1.69 (0.35, 3.04)	1.92 (0.40 3.44)	0.00 (0.00, 0.00)	1.64 (0.58, 2.71)
	N	167	289	261	28	456
7-8 years	n	7	3	3	0	10
	n/N*100	4.19 (1.15, 7.23)	1.04 (-0.13, 2.21)	1.15 (-0.14, 2.44)	0.00 (0.00, 0.00)	2.19 (0.85, 3.54)
	N	139	249	223	26	388
8-9 years	n	2	6	6	0	8
	n/N*100	1.44 (-0.54, 3.42)	2.41 (0.50, 4.31)	2.69 (0.57, 4.81)	0.00 (0.00, 0.00)	2.06 (0.65, 3.48)
	N	113	196	174	22	309
9-10 years	n	3	3	2	1	6
	n/N*100	2.65 (-0.31, 5.62)	1.53 (-0.19, 3.25)	1.15 (-0.43, 2.73)	4.55 (-4.16, 13.25)	1.94 (0.40, 3.48)

		Paternal exposure group				
NDD		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Follow-up period						
	N	97	149	134	15	246
10-11 years	n	0	2	1	1	2
	n/N*100	0.00 (0.00, 0.00)	1.34 (-0.51, 3.19)	0.75 (-0.71, 2.20)	6.67 (-5.96, 19.29)	0.81 (-0.31, 1.94)
	N	70	96	88	8	166
11-12 years	n	2	2	2	0	4
	n/N*100	2.86 (-1.05, 6.76)	2.08 (-0.77, 4.94)	2.27 (-0.84, 5.39)	0.00 (0.00, 0.00)	2.41 (0.08, 4.74)
	N	322	732	618	114	1054
Overall (0-12 years)	n	26	41	36	5	67
	n/N*100	8.07 (5.10, 11.05)	5.60 (3.94, 7.27)	5.83 (3.98, 7.67)	4.39 (0.63, 8.15)	6.36 (4.88, 7.83)

NDD: neurodevelopmental disorders
Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which were determined based on the results of the univariate analyses. As an example, this table presents incidence proportions stratified by gender. Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) were presented.

Table 234 Cumulative incidence proportion (risk) of NDD by paternal exposure group for female offspring; primary outcome

		Paternal exposure group				
NDD		Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Follow-up period						
	N	318	647	567	80	965
0-1 years	n	0	0	0	0	0
	n/N*100	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	N	302	597	524	73	899
1-2 years	n	1	2	2	0	3
	n/N*100	0.33 (-0.32, 0.98)	0.34 (-0.13, 0.80)	0.38 (-0.15, 0.91)	0.00 (0.00, 0.00)	0.33 (-0.04, 0.71)
	N	284	551	484	67	835
2-3 years	n	2	2	2	0	4
	n/N*100	0.70 (-0.27, 1.68)	0.36 (-0.14, 0.87)	0.41 (-0.16, 0.98)	0.00 (0.00, 0.00)	0.48 (0.01, 0.95)
	N	258	492	431	61	750
3-4 years	n	1	0	0	0	1
	n/N*100	0.39 (-0.37, 1.15)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.13 (-0.13, 0.39)
	N	235	430	382	48	665
4-5 years	n	2	3	2	1	5

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	n/N*100	0.85 (-0.32, 2.03)	0.70 (-0.09, 1.48)	0.52 (-0.20, 1.25)	2.08 (-1.96, 6.12)	0.75 (0.10, 1.41)
	N	204	381	340	41	585
5-6 years	n	4	1	1	0	5
	n/N*100	1.96 (0.06, 3.86)	0.26 (-0.25, 0.78)	0.29 (-0.28, 0.87)	0.00 (0.00, 0.00)	0.85 (0.11, 1.60)
	N	180	334	302	32	514
6-7 years	n	1	0	0	0	1
	n/N*100	0.56 (-0.53, 1.64)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.19 (-0.19, 0.58)
	N	157	293	265	28	450
7-8 years	n	3	1	1	0	4
	n/N*100	1.91 (-0.23, 4.05)	0.34 (-0.3, 1.01)	0.38 (-0.36, 1.12)	0.00 (0.00, 0.00)	0.89 (0.02, 1.76)
	N	134	248	227	21	382
8-9 years	n	1	2	2	0	3
	n/N*100	0.75 (-0.71, 2.20)	0.81 (-0.31, 1.92)	0.88 (-0.33, 2.10)	0.00 (0.00, 0.00)	0.79 (-0.10, 1.67)
	N	115	183	167	16	298
9-10 years	n	1	2	1	1	3
	n/N*100	0.87 (-0.83, 2.57)	1.09 (-0.41, 2.60)	0.60 (-0.57, 1.77)	6.25 (-5.61, 18.11)	1.01 (-0.13, 2.14)
	N	97	142	128	14	239
10-11 years	n	1	1	1	0	2
	n/N*100	1.03 (-0.98, 3.04)	0.70 (-0.67, 2.08)	0.78 (-0.74, 2.31)	0.00 (0.00, 0.00)	0.84 (-0.32, 1.99)
	N	79	92	84	8	171
11-12 years	n	0	0	0	0	0
	n/N*100	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)
	N	318	647	567	80	965
Overall (0-12 years)	n	17	14	12	2	31
	n/N*100	5.35 (2.87, 7.82)	2.16 (1.04, 3.28)	2.12 (0.93, 3.30)	2.50 (-0.92, 5.92)	3.21 (2.10, 4.32)

NDD: neurodevelopmental disorders

Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which were determined based on the results of the univariate analyses. As an example, this table presents incidence proportions stratified by gender. Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) were presented.

15.3.3 Cumulative incidence rate and time to NDD diagnosis by gender

Table 235 Cumulative incidence rate of NDD by paternal exposure group for males; primary outcome

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow, up period						
	PY	312.03	703.01	596.27	106.74	1015.04
0, 1 years	n	2	0	0	0	2
	n/PY*1000	6.41 (0.78, 23.15)	0 (, -5.25)	0 (, -6.19)	0 (, -34.56)	1.97 (0.24, 7.12)
	PY	602.89	1344.93	1143.96	200.97	1947.81
0, 2 years	n	2	0	0	0	2
	n/PY*1000	3.32 (0.40, 11.98)	0 (, -2.74)	0 (, -3.22)	0 (, -18.36)	1.03 (0.12, 3.71)
	PY	872.25	1930.44	1646.47	283.96	2802.69
0, 3 years	n	2	4	4	0	6
	n/PY*1000	2.29 (0.28, 8.28)	2.07 (0.56, 5.31)	2.43 (0.66, 6.22)	0 (, ,12.99)	2.14 (0.79, 4.66)
	PY	1119.86	2450.94	2095.31	355.63	3570.8
0, 4 years	n	3	11	10	1	14
	n/PY*1000	2.68 (0.55, 7.83)	4.49 (2.24, 8.03)	4.77 (2.29, 8.78)	2.81 (0.07, 15.67)	3.92 (2.14, 6.58)
	PY	1347.22	2908.06	2494.51	413.56	4255.28
0, 5 years	n	8	16	14	2	24
	n/PY*1000	5.94 (2.56, 11.70)	5.5 (3.14, 8.93)	5.61 (3.07, 9.42)	4.84 (0.59, 17.47)	5.64 (3.61, 8.39)
	PY	1553.28	3295.43	2834.19	461.24	4848.71
0, 6 years	n	9	19	16	3	28
	n/PY*1000	5.79 (2.65, 11.00)	5.77 (3.47, 9.00)	5.65 (3.23, 9.17)	6.5 (1.34, 19.01)	5.77 (3.84, 8.35)
	PY	1733.47	3618.17	3121.18	496.99	5351.64
0, 7 years	n	12	25	22	3	37
	n/PY*1000	6.92 (3.58, 12.09)	6.91 (4.47, 10.20)	7.05 (4.42, 10.67)	6.04 (1.24, 17.64)	6.91 (4.87, 9.53)
	PY	1884.75	3885.32	3361.05	524.27	5770.07
0, 8 years	n	19	28	25	3	47
	n/PY*1000	10.08 (6.07, 15.74)	7.21 (4.79, 10.42)	7.44 (4.81, 10.98)	5.72 (1.18, 16.72)	8.15 (5.98, 10.83)
	PY	2012.63	4111.47	3562.48	548.99	6124.1
0, 9 years	n	21	34	31	3	55
	n/PY*1000	10.43 (6.46, 15.95)	8.27 (5.73, 11.56)	8.7 (5.91, 12.35)	5.46 (1.13, 15.97)	8.98 (6.77, 11.69)
	PY	2119.53	4283.69	3715.91	567.78	6403.22

0, 10 years	n	24	37	33	4	61
	n/PY*1000	11.32 (7.26, 16.85)	8.64 (6.08, 11.91)	8.88 (6.11, 12.47)	7.04 (1.92, 18.04)	9.53 (7.29, 12.24)
	PY	2201.23	4406.41	3828.9	577.51	6607.64
0, 11 years	n	24	39	34	5	63
	n/PY*1000	10.9 (6.99, 16.22)	8.85 (6.29, 12.10)	8.88 (6.15, 12.41)	8.66 (2.81, 20.20)	9.53 (7.33, 12.20)
	PY	2258.39	4475.97	3894	581.97	6734.36
0, 12 years	n	26	41	36	5	67
	n/PY*1000	11.51 (7.52, 16.87)	9.16 (6.57, 12.43)	9.24 (6.48, 12.80)	8.59 (2.79, 20.05)	9.95 (7.71, 12.63)

NDD: Neurodevelopmental Disorders; PY: Person-Years

Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which were determined based on the results of the univariate analyses. As an example, this table presents incidence rates stratified by gender. Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) were presented.

Table 236 Cumulative incidence rate of NDD by paternal exposure group for females; primary outcome

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow, up period						
	PY	310.51	619.16	542.68	76.49	929.67
0, 1 years	n	0	0	0	0	0
	n/PY*1000	0 (, -11.88)	0 (, -5.96)	0 (, -6.80)	0 (, -48.23)	0 (, -3.97)
	PY	601.8	1193.96	1047.62	146.35	1795.76
0, 2 years	n	1	2	2	0	3
	n/PY*1000	1.66 (0.04, 9.26)	1.68 (0.20, 6.05)	1.91 (0.23, 6.90)	0 (, -25.21)	1.67 (0.34, 4.88)
	PY	875.42	1720.31	1511.19	209.12	2595.73
0, 3 years	n	3	4	4	0	7
	n/PY*1000	3.43 (0.71,10.01)	2.33 (0.63,5.95)	2.65 (0.72,6.78)	0 (, -17.64)	2.7 (1.08, 5.56)
	PY	1125.94	2185.2	1920.08	265.12	3311.15
0, 4 years	n	4	4	4	0	8
	n/PY*1000	3.55 (0.97, 9.10)	1.83 (0.50, 4.69)	2.08 (0.57,5.33)	0 (, 13.91)	2.42 (1.04, 4.76)
	PY	1347.01	2592.24	2282.2	310.04	3939.25
0, 5 years	n	6	7	6	1	13
	n/PY*1000	4.45 (1.63, 9.70)	2.7 (1.09, 5.56)	2.63 (0.96, 5.72)	3.23 (0.08, 17.97)	3.3 (1.76, 5.64)
	PY	1538.81	2948.8	2601.95	346.85	4487.61
0, 6 years	n	10	8	7	1	18

	n/PY*1000	6.5 (3.12, 11.95)	2.71 (1.17, 5.35)	2.69 (1.08, 5.54)	2.88 (0.07, 16.06)	4.01 (2.38, 6.34)
	PY	1708.73	3265.09	2888.59	376.51	4973.83
0, 7 years	n	11	8	7	1	19
	n/PY*1000	6.44 (3.21, 11.52)	2.45 (1.06, 4.83)	2.42 (0.97, 4.99)	2.66 (0.07, 14.80)	3.82 (2.30, 5.97)
	PY	1853.28	3538.07	3136.99	401.08	5391.35
0, 8 years	n	14	9	8	1	23
	n/PY*1000	7.55 (4.13, 12.67)	2.54 (1.16, 4.83)	2.55 (1.10, 5.02)	2.49 (0.06, 13.89)	4.27 (2.70, 6.40)
	PY	1978.05	3752.25	3333.04	419.21	5730.31
0, 9 years	n	15	11	10	1	26
	n/PY*1000	7.58 (4.24, 12.51)	2.93 (1.46, 5.25)	3 (1.44, 5.52)	2.39 (0.06, 13.29)	4.54 (2.96, 6.65)
	PY	2083.34	3915.26	3480.98	434.28	5998.6
0, 10 years	n	16	13	11	2	29
	n/PY*1000	7.68 (4.39, 12.47)	3.32 (1.77, 5.68)	3.16 (1.58, 5.65)	4.61 (0.56, 16.64)	4.83 (3.24, 6.94)
	PY	2169.99	4033.46	3587.18	446.28	6203.44
0, 11 years	n	17	14	12	2	31
	n/PY*1000	7.83 (4.56, 12.54)	3.47 (1.90, 5.82)	3.35 (1.73, 5.84)	4.48 (0.54, 16.19)	5 (3.40, 7.09)
	PY	2232.56	4105.45	3652.97	452.48	6338.01
0, 12 years	n	17	14	12	2	31
	n/PY*1000	7.61 (4.44, 12.19)	3.41 (1.86, 5.72)	3.28 (1.70, 5.74)	4.42 (0.54, 15.97)	4.89 (3.32, 6.94)

NDD: Neurodevelopmental Disorders; PY: Person-Years

Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which were determined based on the results of the univariate analyses. As an example, this table presents incidence rates stratified by gender. Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) were presented.

Table 237 Time to NDD by paternal exposure group stratified by offspring gender Primary outcome cohort in Norway

	Paternal exposure group (Male offspring)				
NDD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	26	41	36	5	67
Number of censor	296	691	582	109	987
Survival time					
5th percentile	83.10 (56.10, -)	83.60 (48.23, 137.73)	83.73 (48.23, 141.97)	120.13 (52.83, -)	83.60 (56.10, 113.63)
10th percentile	102.93 (83.10, -)	112.33 (91.57, -)	111.33 (88.90, -)	120.13 (52.83, -)	111.33 (92.27, 142.43)
25th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
	Paternal exposure group (Female offspring)				

	Paternal exposure group (Male offspring)				
NDD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
NDD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	17	14	12	2	31
Number of censor	301	633	555	78	934
Survival time					
5th percentile	89.53 (57.60, -)	132.30 (98.00, -)	117.50 (57.47, -)	115.27 (91.53, -)	-(-,-)
10th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
25th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)

NDD: neurodevelopmental disorders
Legend: Due to low number of events the median time-to-event could not be calculated. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event.

15.3.4 Variables estimate from propensity score

Table 238 Variable importance metric from random forest propensity score model; Primary outcome cohort in Norway

NDD Variable (or interaction)[a]	Variable importance
Offspring risk factors/confounders	
Maternal risk factors/confounders	
Mother's age [b] (categorical)	0.02
Affective disorder [d]	0.01
Diabetes [d]	0.02
Gestational diabetes [e]	0.02
Neurotic disorder [d]	0.01
Schizophrenia, schizotypal and delusional disorders [d]	0.01
Obesity [f]	0.03
Alcohol abuse prior to LMP2 [f]	0.01
Alcohol abuse during pregnancy [e]	0.03
Substance abuse prior to LMP2 [f]	0.01
Substance abuse during pregnancy [e]	0.02
Smoking during pregnancy [e]	0.05
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.02
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	-0.01
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] -mothers with at least one prescription	0.00
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	-0.01
Paternal risk factors/confounders	
Affective disorder [d,g]	-0.01
Bipolar affective disorder [d]	-0.01
Mania [d]	0.04
Neurotic disorder [d]	-0.02
Schizophrenia, schizotypal and delusional disorders [d]	0.05
Substance abuse [f]	0.03
Concomitant medications associated with valproate-indicated psychiatric conditions [f] - fathers with at least one prescription	0.03
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with atleast one prescription	0.01
Year of offspring conception [i]	0.03

LMP2: Last Menstrual Period Date Plus 2 weeks; NDD: neurodevelopmental disorders
Legend: Importance metric is represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.
a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. All two-way interactions were considered.
b) at index (childbirth)
c) between index and exit date
d) all available data prior to index date

NDD Variable (or interaction)[a]		Variable importance	
e) during pregnancy (from LMP2 until index date)			
f) 12 months lookback from LMP2			
g) excluding bipolar affective disorder and mania			
i) at mother's LMP2			

Table 239. Variable estimates from logistic regression informed by random forest propensity score model; Primary outcome cohort in Norway

NDD Variable (or interaction)[a]	OR	Estimate 95% CI	P-value
Offspring risk factors/confounders			
Maternal risk factors/confounders			
Mother's age [b] (categorical)			
≤20 years	1.28	(0.65, 2.54)	0.4707
21-25	0.95	(0.68, 1.32)	0.7467
26-30	Reference	-	-
31-35	0.96	(0.73, 1.25)	0.7502
36-40	0.79	(0.54, 1.14)	0.2050
>40	0.51	(0.23, 1.09)	0.0832
Affective disorder [d]	0.58	(0.32, 1.03)	0.0617
Diabetes [d]	1.15	(0.44, 2.98)	0.7797
Gestational diabetes [e]	0.80	(0.43, 1.48)	0.4747
Neurotic disorder [d]	1.33	(0.89, 1.97)	0.1631
Obesity [f]	0.80	(0.15, 4.13)	0.7902
Smoking during pregnancy [e]			
No	Reference	-	-
Yes	1.44	(0.96, 2.15)	0.0753
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.76	(0.47, 1.21)	0.2394
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.57	(0.28, 1.17)	0.1273
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.95	(0.75, 1.19)	0.6498
Paternal risk factors/confounders			
Affective disorder [d,g]	0.41	(0.25, 0.67)	0.0004
Bipolar affective disorder [d]	0.73	(0.50, 1.07)	0.1089
Mania [d]	0.50	(0.06, 4.38)	0.5287
Neurotic disorder [d]	0.46	(0.26, 0.80)	0.0063
Schizophrenia, schizotypal and delusional disorders [d]	2.43	(0.94, 6.25)	0.0662
Substance abuse [f]	0.28	(0.04, 2.14)	0.2174
Concomitant medications associated with valproate-indicated psychiatric conditions [f] – fathers with at least one prescription	0.56	(0.42, 0.75)	<.0001
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with at least one prescription	1.00	(0.79, 1.27)	0.9882
Year of offspring conception [I,J]			
2005-2009	Reference	-	-
2010-2014	0.71	(0.54, 0.94)	0.0163
2015-2019	0.62	(0.46, 0.83)	0.0016

NDD: neurodevelopmental disorders; CI: Confidence Interval; LMP2: Last Menstrual Period Date Plus 2 weeks; OR: odds ratio

Legend: Odds ratios (OR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.

a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.

NDD Variable (or interaction)[a]	OR	Estimate 95% CI	P-value

b) at index (childbirth)
d) all available data prior to index date
e) during pregnancy (from LMP2 until index date)
f) 12 months lookback from LMP2
g) excluding bipolar affective disorder and mania
i) at mother's LMP2
j) calendar years were grouped in each country according to the length of the study period

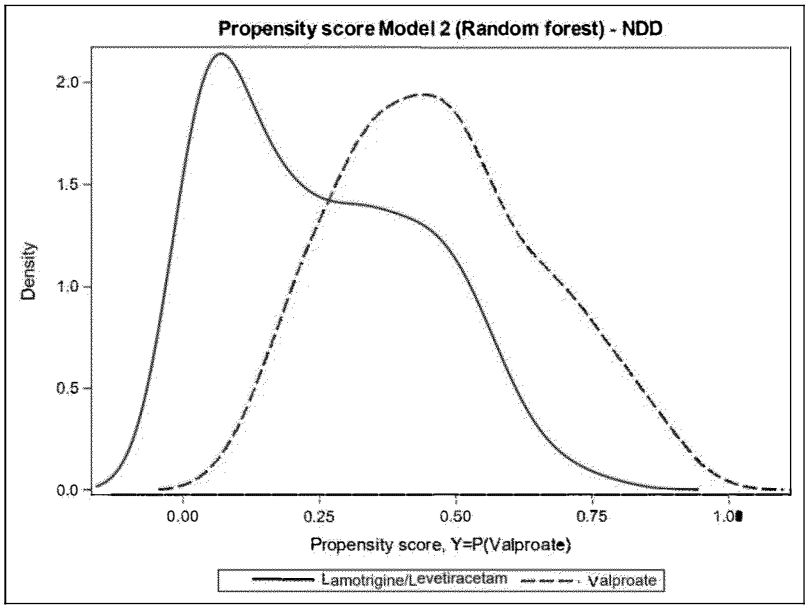
Table 240: Balance of risk factors/confounders after PS weighting (PS scores obtained using logistic regression); primary outcome

NDD	Absolute standardized difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0,02	Yes	0,99	Yes
Congenital CMV [d]	-	-**	-	-***
Congenital rubella [d]	-	-**	-	-***
Foetal alcohol syndrome [d]	-	-**	-	-***
Fragile X syndrome [d]	-	-**	-	-***
Lejeune/cri du chat syndrome [d]	-	-**	-	-***
Tuberous sclerosis [d]	-	-**	-	-***
Maternal risk factors/confounders				
Mother's age [c] (categorical)	0.00*	Yes	1,02	Yes
Affective disorder [e]	0,06	Yes	0,79	Yes
Diabetes [e]	0,03	Yes	0,76	Yes
Gestational diabetes [f]	0,05	Yes	0,78	Yes
Neurotic disorder [e]	0,03	Yes	0,91	Yes
Schizophrenia, schizotypal and delusional disorders [e]	-	-**	-	-***
Obesity [g]	0,03	Yes	0,63	Yes
CMV [g]	-	-**	-	-***
Rubella [g]	-	-**	-	-***
Alcohol abuse prior to LMP2 [g]	0,04	Yes	-	-***
Alcohol abuse during pregnancy [f]	-	-**	-	-***
Substance abuse prior to LMP2 [g]	-	-**	-	-***
Substance abuse during pregnancy [f]	-	-**	-	-***
Smoking prior to LMP2 [g]	0,05	Yes	1,15	Yes
Smoking during pregnancy [f]	0,03	Yes	1,09	Yes
Maternal polypharmacy index prior to LMP2 [i] (categorical)	0.00*	Yes	1,01	Yes
Maternal polypharmacy index during pregnancy [f] (categorical)	0.00*	Yes	0,98	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g] - mothers with at least one prescription	0,08	Yes	0,79	Yes

Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f] - mothers with at least one prescriptio	0,07	Yes	0,71	Yes
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [g] -mothers with at least one prescription	0,06	Yes	1,04	Yes
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [f] -mothers with at least one prescription	0,04	Yes	0,97	Yes
Paternal risk factors/confounders				
Affective disorder [e,h]	0,02	Yes	0,96	Yes
Bipolar affective disorder [e]	0,02	Yes	1,03	Yes
Mania [e]	0,05	Yes	0,41	Yes
Neurotic disorder [e]	0,00	Yes	1,00	Yes
Schizophrenia, schizotypal and delusional disorders [e]	0,01	Yes	0,91	Yes
Substance abuse [g]	0,09	Yes	0,36	Yes
Paternal polypharmacy index [i] (categorical)	0.01*	Yes	0,96	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] - fathers with at least one prescription	0,02	Yes	0,97	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] - fathers with atleast one prescription	0,02	Yes	0,98	Yes
Father's age [c] (categorical)	0.00*	Yes	0,95	Yes
Year of offspring conception [j]	0.00*	Yes	1,02	Yes

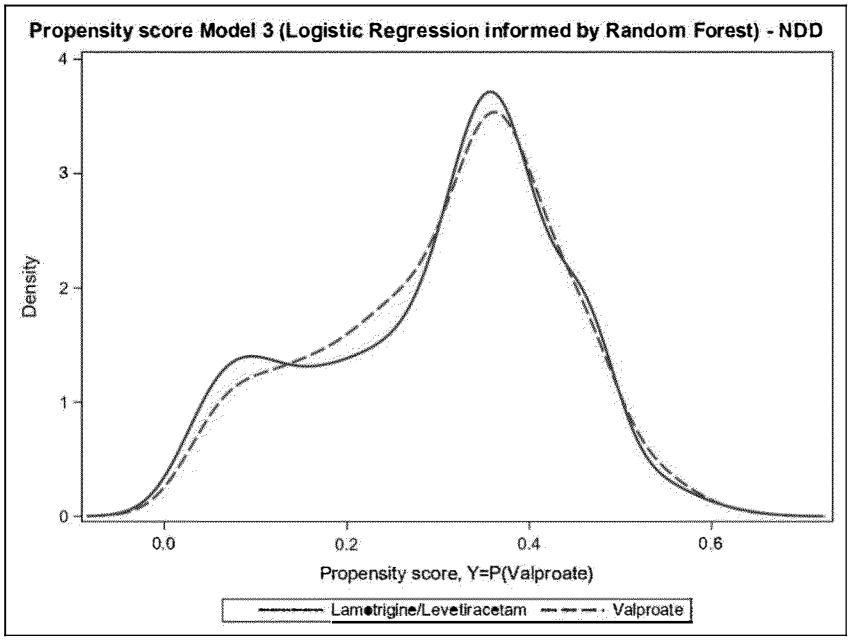
a) absolute standardized difference below 0.1
b) variance ratio between 0 and 2
c) at index (childbirth)
d) between index and exit date
e) all available data prior to index date
f) during pregnancy (from LMP2 until index date)
g) 12 months lookback from LMP2
h) excluding bipolar affective disorder and mania
i) 3 months lookback from LMP2
j) at mother's LMP2

* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardized difference is not calculated if a binary variable has only 1 category level in the weighted patient data.
*** The variance ratio is not calculated if a variable has only 1 category level in one of valproate and comparator groups (the denominator of the variance ratio is 0).



NDD: neurodevelopmental disorders

Figure 41 Balance of PS Model 2- Random Forest; Primary outcome cohort in Norway.



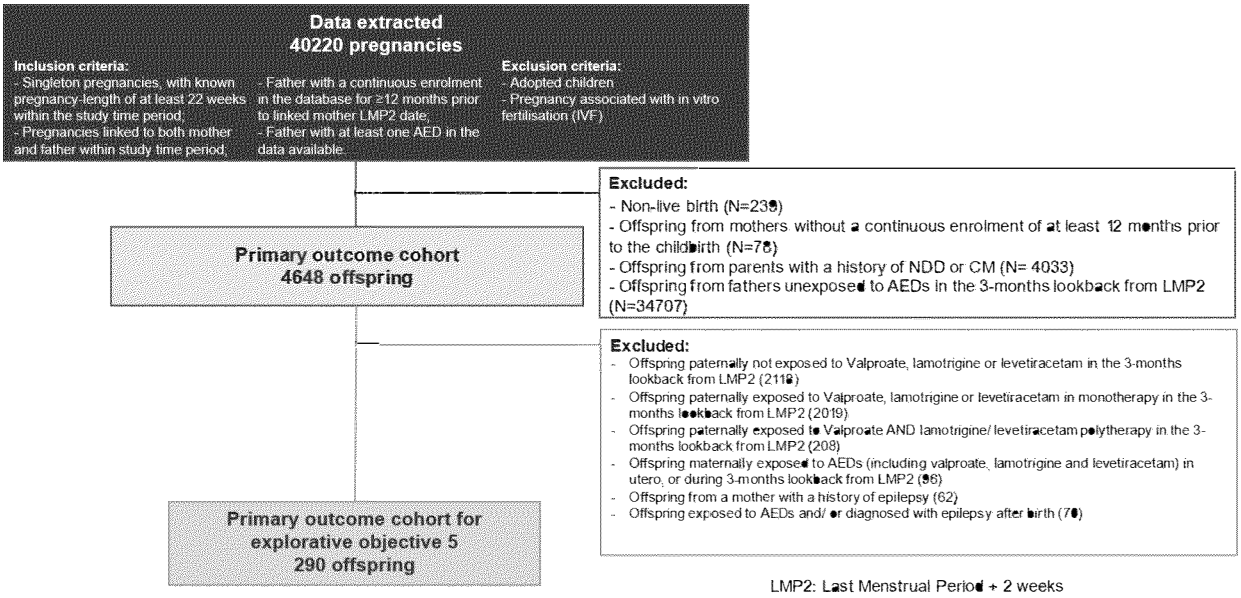
NDD: neurodevelopmental disorders.

Figure 42 Balance of PS Model 3 – Logistic Regression informed by Random Forest; Primary outcome cohort in Norway

Table 241: Balance of risk factors/confounders between offspring weighted using PS scores obtained with logistic regression; secondary outcome

CM	Absolute standardized difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Congenital CMV [c]	-	-**	-	-***
Congenital Herpes Simplex [c]	-	-**	-	-***
Congenital rubella [c]	-	-**	-	-***
Congenital toxoplasmosis [c]	-	-**	-	-***
Congenital varicella [c]	-	-**	-	-***
Foetal alcohol syndrome [c]	-	-**	-	-***
Maternal risk factors/confounders				
Mother's age [d] (categorical)	0.00*	Yes	0,80	Yes
Diabetes [e]	-	-**	-	-***
Obesity [f]	-	-**	-	-***
Alcohol abuse prior to LMP2 [f]	-	-**	-	-***
Alcohol abuse during pregnancy [g]	-	-**	-	-***
Substance abuse prior to LMP2 [f]	0,06	Yes	-	-***
Substance abuse during pregnancy [g]	-	-**	-	-***
Smoking prior to LMP2 [f]	0,04	Yes	0,92	Yes
Smoking during pregnancy [g]	0,01	Yes	0,98	Yes
CMV [g]	-	-**	-	-***
Folate deficiency [g]	-	-**	-	-***
Gestational diabetes [g]	-	-**	-	-***
Herpes simplex virus [g]	-	-**	-	-***
Rubella [g]	-	-**	-	-***
Toxoplasmosis [g]	-	-**	-	-***
Varicella [g]	0,06	Yes	-	-***
Paternal risk factors/confounders				
Father's age [d] (categorical)	0.00*	Yes	0,83	Yes
Year of offspring conception [h]	0.05*	Yes	1,07	Yes

15.3.5 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Explorative analysis 5)



An offspring may be present in more than one exclusion criterion

CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 43. Study population of Primary outcome cohort for Exploratory Analyses 5 in Norway

Table 242. Offspring demographic characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD Number of offspring	**Valproate(polytherapy) N=69**		**Lamotrigine/levetiracetam(polytherapy) N=221**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	1	0.45
28-31 (very preterm)	0	0.00	3	1.36
32-36 (moderate to late preterm)	3	4.35	8	3.62
37-41 (at term)	65	94.20	203	91.86
≥42 (post-term)	1	1.45	6	2.71
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	2	0.90
1000-1499 (very low)	0	0.00	2	0.90
1500-2499 (low)	2	2.90	7	3.17

≥2500	67	97.10	209	94.57
Missing	0	0.00	1	0.45
Gender [a]				
Male	33	47.83	113	51.13
Female	36	52.17	108	48.87
Missing	0	0.00	0	0.00
Year of birth				
2006	6	8.70	12	5.43
2007	5	7.25	20	9.05
2008	8	11.59	11	4.98
2009	5	7.25	19	8.60
2010	7	10.14	20	9.05
2011	5	7.25	20	9.05
2012	7	10.14	24	10.86
2013	2	2.90	15	6.79
2014	4	5.80	15	6.79
2015	6	8.70	15	6.79
2016	4	5.80	12	5.43
2017	1	1.45	16	7.24
2018	7	10.14	12	5.43
2019	2	2.90	10	4.52
Total number of years of follow-up	482.67		1547.39	
Mean follow-up year	7		7	

NDD: Neurodevelopmental Disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 243. Offspring clinical characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD **Number of offspring**	**Valproate(polytherapy)** **N=69**		**Lamotrigine/levetiracetam(polytherapy)** **N=221**	
	N	**%**	**N**	**%**
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Epilepsy	0	0.00	0	0.00
Foetal alcohol syndrome	0	0.00	0	0.00
Fragile X syndrome	0	0.00	0	0.00
Lejeune/cri du chat syndrome	0	0.00	0	0.00
Tuberous sclerosis	0	0.00	1	0.45
Medication use				
Exposure to AEDs [a]	0	0.00	0	0.00
Outcomes				
ASD (ever, not only as 1st diagnosis)	1	1.45	2	0.90
ASD (as 1st diagnosis)	1	1.45	1	0.45
NDD including ASD	7	10.14	12	5.43
Age at the first diagnosis (years)				
ASD (ever, not only as 1st				

diagnosis) [b,c]				
0-1	0	0.00	0	0.00
2-3	1	100.00	0	0.00
4-5	0	0.00	1	50.00
6-7	0	0.00	0	0.00
8-9	0	0.00	1	50.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	1	100	2	100
NDD including ASD [b,c]				
0-1	1	14.29	0	0.00
2-3	1	14.29	1	8.33
4-5	1	14.29	4	33.33
6-7	3	42.86	1	8.33
8-9	0	0.00	4	33.33
10-11	1	14.29	2	16.67
Total (offspring with the outcome)	7	100	12	100

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; AED: Antiepileptic Drug; ASD: Autism Spectrum Disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) between index (childbirth) and exit date
b) Categories may be adapted according to the data.
c) Denominator for the percentage is the number of offspring with the outcome.

Table 244. Maternal demographic characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD Number of offspring	**Valproate(polytherapy) N=69**		**Lamotrigine/levetiracetam(polytherapy) N=221**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	7	10.14	3	1.36
21-25	11	15.94	36	16.29
26-30	17	24.64	81	36.65
31-35	21	30.43	70	31.67
36-40	9	13.04	26	11.76
>40	4	5.80	5	2.26
Mean (SD)	29.97 (6.24)		30.17 (4.99)	
Median (25^{th} - 75^{th} percentile)	30 (25.00, 34.00)		30 (27.00, 34.00)	
Min, max	18.00, 44.00		18.00, 44.00	
Missing	0	0.00	0	0.00

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend:
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 245. Maternal clinical characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD Number of offspring	**Valproate(polytherapy) N=69**		**Lamotrigine/levetiracetam(polytherapy) N=221**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder [a]	3	4.35	10	4.52
Diabetes [a]	1	1.45	2	0.90
Epilepsy [a]	0	0.00	0	0.00
Neurotic disorder [a]	7	10.14	11	4.98
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Obesity [b]	1	1.45	1	0.45
CMV [c]	0	0.00	0	0.00
Gestational diabetes [c]	4	5.80	12	5.43
Rubella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	1	0.45
Smoking prior to LMP2 [b]				
Yes	6	8.70	23	10.41
No	42	60.87	138	62.44
Missing	21	30.43	60	27.15
Smoking during pregnancy [c]				
Yes	3	4.35	17	7.69
No	53	76.81	166	75.11
Missing	13	18.84	38	17.19
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AED during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00

	Paternal exposure group			
NDD Number of offspring	**Valproate(polytherapy) N=69**		**Lamotrigine/levetiracetam(polytherapy) N=221**	
	N	**%**	**N**	**%**
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K-means cluster prior to LMP2 [d]				
Unexposed	69	100.00	221	100.00
K-means cluster during pregnancy [c]				
Unexposed	69	100.00	221	100.00
Maternal polypharmacy index prior to LMP2 [d]				
0	46	66.67	155	70.14
1-4	23	33.33	66	29.86
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.55 (0.95)		0.48 (0.88)	
Median (25^{th} - 75^{th} percentile)	0(0.00, 1.00)		0(0.00, 1.00)	
Min, max	0.00, 4.00		0.00, 4.00	
Maternal polypharmacy index during pregnancy [c]				
0	33	47.83	121	54.75
1-4	34	49.28	94	42.53
5-10	2	2.90	6	2.71
>10	0	0.00	0	0.00
Mean (SD)	0.99 (1.42)		0.83 (1.19)	
Median (25^{th} - 75^{th} percentile)	1 (0.00, 2.00)		0 (0.00, 1.00)	
Min, max	0.00, 8.00		0.00, 6.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	7	10.14	11	4.98
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	4	5.80	5	2.26
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] -mothers with at least one	39	56.52	139	62.90

	Paternal exposure group			
NDD Number of offspring	**Valproate(polytherapy) N=69**		**Lamotrigine/levetiracetam(polytherapy) N=221**	
	N	**%**	**N**	**%**
prescription				
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	35	50.72	93	42.08

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks; AED: Antiepileptic Drug; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend:
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until index date)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Norway during the study period

Table 246. Paternal demographic characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD Number of offspring	**Valproate (polytherapy) N=69**		**Lamotrigine/levetiracetam (polytherapy) N=221**	
	N	**%**	**N**	**%**
Father's age [a]				
≤20 years	2	2.90	1	0.45
21-25	5	7.25	16	7.24
26-30	16	23.19	61	27.60
31-35	19	27.54	80	36.20
36-40	14	20.29	36	16.29
>40	13	18.84	27	12.22
Mean (SD)	33.36 (6.56)		33.26 (6.00)	
Median (25^{th} - 75^{th} percentile)	33(29.00, 37.00)		32(29.00, 36.00)	
Min, max	19.00, 48.00		20.00, 57.00	
Missing	-		-	
Year of offspring conception [b]				
2005	3	4.35	9	4.07
2006	8	11.59	16	7.24
2007	8	11.59	17	7.69
2008	3	4.35	16	7.24
2009	8	11.59	19	8.60
2010	5	7.25	20	9.05
2011	7	10.14	22	9.95
2012	3	4.35	18	8.14
2013	3	4.35	16	7.24
2014	5	7.25	13	5.88
2015	5	7.25	15	6.79
2016	2	2.90	10	4.52
2017	6	8.70	17	7.69
2018	3	4.35	11	4.98
2019	0	0.00	2	0.90

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Maximum
Legend:
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

b) at mother's Last Menstrual Period Date Plus 2 weeks (LMP2)

Table 247. Paternal clinical characteristics by paternal exposure group; primary outcome

	Paternal exposure group

NDD Number of offspring	Valproate (polytherapy) N=69		Lamotrigine/levetiracetam (polytherapy) N=221	
	N	%	N	%
Comorbidities	0	0.00	0	0.00
Affective disorder excluding bipolar affective disorder and mania [a]	5	7.25	9	4.07
Bipolar affective disorder [a]	1	1.45	7	3.17
Mania [a]	0	0.00	0	0.00
Neurotic disorder [a]	2	2.90	14	6.33
Schizophrenia, schizotypal and delusional disorders [a]	1	1.45	1	0.45
Lifestyle characteristics	0	0.00	0	0.00
Substance abuse [c]	1	1.45	1	0.45
Medication use				
Exposure to AEDs[d]				
Fatty acid derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Barbiturates derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Fatty acid derivatives and other antiepileptics	20	28.99	0	0.00
Carboxamide derivatives and other antiepileptics	0	0.00	101	45.70
Fatty acid derivatives and Carboxamide derivatives	31	44.93	0	0.00
Benzodiazepine derivatives and other antiepileptics	0	0.00	13	5.88
Benzodiazepine derivatives and Fatty acid derivatives	4	5.80	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives	0	0.00	0	0.00
Succinimide derivatives and other antiepileptics	0	0.00	1	0.45
Succinimide derivatives and Fatty acid derivatives	2	2.90	0	0.00
Carboxamide derivatives and Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives and Fatty acid derivatives	0	0.00	0	0.00
Hydantoin derivatives and Carboxamide derivatives	0	0.00	0	0.00
Hydantoin derivatives and other antiepileptics	0	0.00	9	4.07
Hydantoin derivatives and Succinimide derivatives	0	0.00	0	0.00
Barbiturates derivatives and other	0	0.00	0	0.00

	Paternal exposure group			
NDD Number of offspring	**Valproate (polytherapy) N=69**		**Lamotrigine/levetiracetam (polytherapy) N=221**	
	N	**%**	**N**	**%**
antiepileptics				
Barbiturates derivatives and Fatty acid derivatives	1	1.45	0	0.00
Barbiturates derivatives and Carboxamide derivatives	0	0.00	0	0.00
Barbiturates derivatives and Benzodiazepine derivatives	0	0.00	0	0.00
Barbiturates derivatives and Hydantoin derivatives	0	0.00	0	0.00
Carboxamide derivatives and Barbiturates derivatives and Hydantoin derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Carboxamide derivatives and Fatty acid derivatives and other antiepileptics	6	8.70	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	2	0.90
Benzodiazepine derivatives and Succinimide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Hydantoin derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	0	0.00
Hydantoin derivatives and Carboxamide derivatives and Fatty acid derivatives	1	1.45	0	0.00
Barbiturates derivatives and Carboxamide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Fatty acid derivatives and Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	1	0.45
Hydantoin derivatives and Succinimide derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
AED indication				
Epilepsy	39	56.52	141	63.80
Bipolar affective disorder and mania	1	1.45	7	3.17
Other/unknown	29	42.03	73	33.03
K-means cluster [d]				

	Paternal exposure group			
NDD Number of offspring	**Valproate (polytherapy) N=69**		**Lamotrigine/levetiracetam (polytherapy) N=221**	
	N	**%**	**N**	**%**
Cluster A	43	62.32	156	70.59
Cluster B	26	37.68	65	29.41
Paternal polypharmacy index [d]				
0	38	55.07	147	66.52
1-4	28	40.58	70	31.67
5-10	3	4.35	4	1.81
>10	0	0.00	0	0.00
Mean (SD)	1.00 (1.53)		0.68 (1.30)	
Median (25^{th} - 75^{th} percentile)	0(0.00, 1.00)		0(0.00, 1.00)	
Min, max	0.00, 7.00		0.00, 9.00	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	48	69.57	116	52.49
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	43	62.32	125	56.56

NDD: Neurodevelopmental Disorders; AED: Antiepileptic Drug; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend:
Cluster A: constant high exposure; Cluster B: constant low exposure
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)

c) 12 months lookback from LMP2

d) 3 months lookback from LMP2

Table 248. Association between potential offspring risk factors/confounders for NDD by paternal exposure group; primary outcome

	Paternal exposure group				Comparison *
NDD Number of offspring	**Valproate (polytherapy) N=69**		**Lamotrigine/levetiracetam (polytherapy) N=221**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
Offspring risk factors/confounders Gender [a]					
Male	33	47.83	113	51.13	-
Female	36	52.17	108	48.87	-

Missing	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.23 (0.6317)
Congenital CMV [b]	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	-
Foetal alcohol syndrome [b]	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	1	0.45	1.00 (1.0000)*

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) between index and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 249. Association between potential maternal risk factors/confounders for NDD by paternal exposure group; primary outcome

Paternal exposure group					**Comparison**
NDD **Number of offspring**	**Valproate(polytherapy)** **N=69**		**Lamotrigine/levetiracetam(polytherapy)** **N=221**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)** -
	N	**%**	**N**	**%**	
Maternal risk factors/confounders **Mother's age [a] (categorical)**					
≤20 years	7	10.14	3	1.36	-
21-25	11	15.94	36	16.29	-
26-30	17	24.64	81	36.65	-
31-35	21	30.43	70	31.67	-
36-40	9	13.04	26	11.76	-
>40	4	5.80	5	2.26	-
Test statistics	-	-	-	-	16.24 (0.0062)
Mother's age [a] (continuous)					
Mean (SD)	29.97 (6.24)		30.17 (4.99)		-0.24 (0.8117)
Median (25^{th} - 75^{th} percentile)	30 (25.00, 34.00)		30 (27.00, 34.00)		-
Min, max	18.00, 44.00		18.00, 44.00		-
Missing	0	0.00	0	0.00	-
Affective disorder [b]	3	4.35	10	4.52	1.00 (1.0000)*
Diabetes [b]	1	1.45	2	0.90	0.55 (0.5589)*
Gestational diabetes [c]	4	5.80	12	5.43	1.00 (1.0000)*
Neurotic disorder [b]	7	10.14	11	4.98	2.41 (0.1204)
Schizophrenia, schizotypal and delusional disorders [b]	0	0.00	0	0.00	-
Obesity [d]	1	1.45	1	0.45	0.41 (0.4199)*
CMV [c]	0	0.00	0	0.00	-
Rubella [c]	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [d]	0	0.00	0	0.00	-
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [d]	0	0.00	0	0.00	-
Substance abuse during pregnancy [c]	0	0.00	1	0.45	1.00 (1.0000)*
Smoking prior to LMP2 [d]					
Yes	6	8.70	23	10.41	-
No	42	60.87	138	62.44	-
Missing	21	30.43	60	27.15	-
Test statistics without 'Missing' category	-	-	-	-	0.10 (0.7534)
Smoking during pregnancy [c]					
Yes	3	4.35	17	7.69	-
No	53	76.81	166	75.11	-
Missing	13	18.84	38	17.19	-

Paternal exposure group					Comparison
NDD Number of offspring	**Valproate(polytherapy) N=69**		**Lamotrigine/levetiracetam(polytherapy) N=221**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
Test statistics without 'Missing' category	-	-	-	-	0.42 (0.4232)*
Maternal polypharmacy index prior to LMP2 [e](categorical)					
0	46	66.67	155	70.14	-
1-4	23	33.33	66	29.86	-
5-10	0	0.00	0	0.00	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.30 (0.5855)
Maternal polypharmacy index prior to LMP2 [e] (continuous)					
Mean (SD)	0.55 (0.95)		0.48 (0.88)		10325.50 (0.5635)*
Median (25^{th} - 75^{th} percentile)	0 (0.00, 1.00)		0 (0.00, 1.00)		-
Min, max	0.00, 4.00		0.00, 4.00		-
Maternal polypharmacy index during pregnancy [c](categorical)					
0	33	47.83	121	54.75	-
1-4	34	49.28	94	42.53	-
5-10	2	2.90	6	2.71	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	1.02 (0.5997)
Maternal polypharmacy index during pregnancy[c] (continuous)					
Mean (SD)	0.99 (1.42)		0.83 (1.19)		10556.00 (0.3526)*
Median (25^{th} - 75^{th} percentile)	1 (0.00, 2.00)		0 (0.00, 1.00)		-
Min, max	0.00, 8.00		0.00, 6.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	7	10.14	11	4.98	2.41 (0.1204)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	4	5.80	5	2.26	0.22 (0.2239)*
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] -mothers with at least one prescription	39	56.52	139	62.90	0.90 (0.3424)

Paternal exposure group					Comparison
NDD Number of offspring	**Valproate(polytherapy) N=69**		**Lamotrigine/levetiracetam(polytherapy) N=221**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	35	50.72	93	42.08	1.59 (0.2069)

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum; CMV: Cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's eact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2

Table 250. Association between potential paternal risk factors/confounders for NDD by paternal exposure group; primary outcome

	Paternal exposure group				Comparison
NDD Number of offspring	**Valproate(polytherapy) N=69**		**Lamotrigine/levetiracetam(polytherapy) N=221**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
Paternal risk factors/confounders					
Affective disorder excluding bipolar affective disorder and mania [a]	5	7.25	9	4.07	1.15 (0.2829)
Bipolar affective disorder [a]	1	1.45	7	3.17	0.68 (0.6850)*
Mania [a]	0	0.00	0	0.00	-
Neurotic disorder [a]	2	2.90	14	6.33	0.37 (0.3741)*
Schizophrenia, schizotypal and delusional disorders [a]	1	1.45	1	0.45	0.41 (0.4199)*
Substance abuse [c]	1	1.45	1	0.45	0.41 (0.4199)*
Paternal polypharmacy index [d] (categorical)					
0	38	55.07	147	66.52	-
1-4	28	40.58	70	31.67	-
5-10	3	4.35	4	1.81	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	3.72 (0.1559)
Paternal polypharmacy index [d] (continuous)					
Mean (SD)	1.00 (1.53)		0.68 (1.30)		11009.00 (0.0628)*
Median (25^{th} - 75^{th} percentile)	0 (0.00, 1.00)		0 (0.00, 1.00)		-
Min, max	0.00, 7.00		0.00, 9.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] – fathers with at least one prescription	48	69.57	116	52.49	6.24 (0.0125)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	43	62.32	125	56.56	0.72 (0.3977)
Father's age [e] (categorical)					
≤20 years	2	2.90	1	0.45	-
21-25	5	7.25	16	7.24	-
26-30	16	23.19	61	27.60	-
31-35	19	27.54	80	36.20	-
36-40	14	20.29	36	16.29	-
>40	13	18.84	27	12.22	-
Test statistics	-	-	-	-	6.74 (0.2404)
Father's age [e] (continuous)					

	Paternal exposure group				Comparison
NDD Number of offspring	**Valproate(polytherapy) N=69**		**Lamotrigine/levetiracetam(polytherapy) N=221**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
Mean (SD)	33.36 (6.56)		33.26 (6.00)		10393.00 (0.5610)*
Median (25th - 75th percentile)	33(29.00, 37.00)		32(29.00, 36.00)		-
Min, max	19.00, 48.00		20.00, 57.00		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [f,g]					
2005-2009	30	43.48	77	34.84	-
2010-2014	23	33.33	89	40.27	-
2015-2019	16	23.19	55	24.89	-
Test statistics	-	-	-	-	1.78 (0.4106)

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period

Table 251. Association between potential offspring risk factors/confounders and NDD; primary outcome

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Offspring risk factors/confounders								
Gender [a]								
Male	146	50.34	16	10.96	130	89.04	Reference	-
Female	144	49.66	3	2.08	141	97.92	0.17 (0.05, 0.61)	-
Missing	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	7.50,0.0062
Congenital CMV [b]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital rubella [b]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Foetal alcohol syndrome [b]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Fragile X syndrome [b]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Lejeune/cri du chat syndrome [b]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Tuberous sclerosis [b]								
No	289	99.66	19	6.57	270	93.43	Reference	-
Yes	1	0.34	0	0.00	1	100.00	0.00(0.00,I)	0.00,0.9940

NDD: Neurodevelopmental Disorders; CMV: Cytomegalovirus; OR: Odds Ratio; CI: Confidence Interval
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome is tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at index (childbirth)
b) between index and exit date
Event: Neurodevelopmental Disorders (NDD) with Autism Spectrum Disorders (ASD);
Non-Event: No NDD with ASD

Table 252. Association between potential maternal risk factors/confounders and NDD; primary outcome

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Maternal risk factors/confounders								
Mother's age [a] (categorical)								
≤20 years	10	3.45	1	10.00	9	90.00	1.70 (0.18, 15.76)	-
21-25	47	16.21	5	10.64	42	89.36	1.83 (0.53, 6.32)	-
26-30	98	33.79	6	6.12	92	93.88	Reference	-
31-35	91	31.38	5	5.49	86	94.51	0.89 (0.26, 3.03)	-
36-40	35	12.07	1	2.86	34	97.14	0.45 (0.05, 3.88)	-
>40	9	3.10	1	11.11	8	88.89	1.92 (0.20, 17.95)	-
Wald test	-	-	-	-	-	-	-	2.59,0.7626
Affective disorder [b]								
No	277	95.52	18	6.50	259	93.50	Reference	-
Yes	13	4.48	1	7.69	12	92.31	1.20 (0.15, 9.74)	0.03,0.8651
Diabetes [b]								
No	287	98.97	18	6.27	269	93.73	Reference	-
Yes	3	1.03	1	33.33	2	66.67	7.47(0.65, 86.37)	2.59,0.1072
Gestational diabetes [c]								
No	274	94.48	18	6.57	256	93.43	Reference	-
Yes	16	5.52	1	6.25	15	93.75	0.95 (0.12, 7.59)	0.00,0.9600
Neurotic disorder [b]								
No	272	93.79	18	6.62	254	93.38	Reference	-
Yes	18	6.21	1	5.56	17	94.44	0.83 (0.10, 6.60)	0.03,0.8602
Schizophrenia, schizotypal and delusional disorders [b]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Obesity [d]								

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
No	288	99.31	19	6.60	269	93.40	Reference	-
Yes	2	0.69	0	0.00	2	100.00	0.00(0.00,I)	0.00,0.9915
CMV [c]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Rubella [c]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse prior to LMP2 [d]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse during pregnancy [c]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Substance abuse prior to LMP2 [d]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Substance abuse during pregnancy [c]								
No	289	99.66	19	6.57	270	93.43	Reference	-
Yes	1	0.34	0	0.00	1	100.00	0.00(0.00,I)	0.00,0.9940
Smoking prior to LMP2 [d]								
Yes	29	10.00	6	20.69	23	79.31	6.45 (1.99, 20.86)	-
No	180	62.07	7	3.89	173	96.11	Reference	-
Missing	81	27.93	6	7.41	75	92.59	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	9.68,0.0019
Smoking during pregnancy [c]								
Yes	20	6.90	4	20.00	16	80.00	3.96 (1.16, 13.56)	-
No	219	75.52	13	5.94	206	94.06	Reference	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Missing	51	17.59	2	3.92	49	96.08	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	4.81,0.0284
Maternal polypharmacy index prior to LMP2 [e](categorical)								
0	201	69.31	11	5.47	190	94.53	Reference	-
1-4	89	30.69	8	8.99	81	91.01	1.71 (0.66, 4.40)	-
5-10	0	0.00	0	0.00	0	0.00	-	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	1.22,0.2690
Maternal polypharmacy index during pregnancy [c](categorical)								
0	154	53.10	8	5.19	146	94.81	Reference	-
1-4	128	44.14	10	7.81	118	92.19	1.55 (0.59, 4.04)	-
5-10	8	2.76	1	12.50	7	87.50	2.61 (0.29, 23.84)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	1.22,0.5429
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription								
No	272	93.79	16	5.88	256	94.12	Reference	-
Yes	18	6.21	3	16.67	15	83.33	3.20 (0.84, 12.20)	2.90,0.0885
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription								
No	281	96.90	18	6.41	263	93.59	Reference	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Yes	9	3.10	1	11.11	8	88.89	1.83 (0.22, 15.42)	0.31,0.5799
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription								
No	112	38.62	5	4.46	107	95.54	Reference	-
Yes	178	61.38	14	7.87	164	92.13	1.83 (0.64, 5.22)	1.27,0.2606
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least oneprescription								
No	162	55.86	9	5.56	153	94.44	Reference	-
Yes	128	44.14	10	7.81	118	92.19	1.44 (0.57, 3.66)	0.59,0.4425

NDD: Neurodevelopmental Disorders; OR: Odds Ratio; CI: Confidence Interval
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome was tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test were reported.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2
Event: NDD with ASD, Non-Event. No NDD with ASD

Table 253. Association between potential paternal risk factors/confounders and NDD; primary outcome

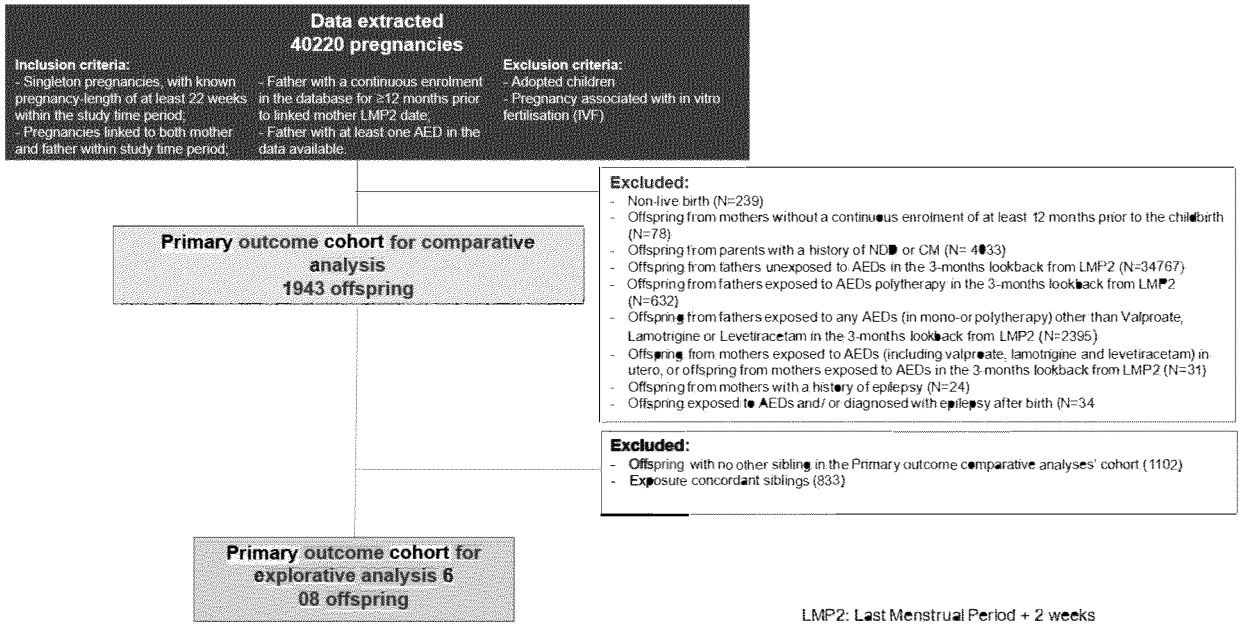
NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Paternal risk factors/confounders								
Affective disorder excluding bipolar affective disorder and mania [a]								
No	276	95.17	18	6.52	258	93.48	Reference	-
Yes	14	4.83	1	7.14	13	92.86	1.10 (0.14, 8.91)	0.01,0.9270
Bipolar affective disorder [a]								
No	282	97.24	18	6.38	264	93.62	Reference	-
Yes	8	2.76	1	12.50	7	87.50	2.10 (0.24, 17.97)	0.46,0.4998
Mania [a]								
No	290	100.00	19	6.55	271	93.45	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Neurotic disorder [a]								
No	274	94.48	19	6.93	255	93.07	Reference	-
Yes	16	5.52	0	0.00	16	100.00	0.00(0.00,I)	0.00,0.9759
Schizophrenia, schizotypal and delusional disorders [a]								
No	288	99.31	19	6.60	269	93.40	Reference	-
Yes	2	0.69	0	0.00	2	100.00	0.00 (0.00,I)	0.00,0.9915
Substance abuse [c]								
No	288	99.31	18	6.25	270	93.75	Reference	-
Yes	2	0.69	1	50.00	1	50.00	15.00 (0.90, 249.79)	3.56,0.0591
Paternal polypharmacy index [d] (categorical)								
0	185	63.79	10	5.41	175	94.59	Reference	-
1-4	98	33.79	6	6.12	92	93.88	1.14 (0.40, 3.24)	-
5-10	7	2.41	3	42.86	4	57.14	13.12 (2.58, 66.78)	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	9.88,0.0072
Concomitant medications associated with valproate-indicated psychiatric conditions [c] -fathers with at least one prescription								
No	126	43.45	7	5.56	119	94.44	Reference	-
Yes	164	56.55	12	7.32	152	92.68	1.34 (0.51, 3.51)	0.36,0.5491
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers withat least one prescription								
No	122	42.07	8	6.56	114	93.44	Reference	-
Yes	168	57.93	11	6.55	157	93.45	1.00 (0.39, 2.56)	0.00,0.9974
Father's age [e] (categorical)								
≤20 years	3	1.03	0	0.00	3	100.00	0.00 (0.00,I)	-
21-25	21	7.24	4	19.05	17	80.95	2.09 (0.59, 7.46)	-
26-30	77	26.55	3	3.90	74	96.10	0.36 (0.10, 1.36)	-
31-35	99	34.14	10	10.10	89	89.90	Reference	-
36-40	50	17.24	2	4.00	48	96.00	0.37 (0.08, 1.76)	-
>40	40	13.79	0	0.00	40	100.00	0.37 (0.08, 1.76)	-
Wald test	-	-	-	-	-	-	-	6.30,0.2777
Year of offspring conception [f,g]								
2005-2009	107	36.90	11	10.28	96	89.72	Reference	-
2010-2014	112	38.62	8	7.14	104	92.86	0.67 (0.26, 1.74)	-
2015-2019	71	24.48	0	0.00	71	100.00	-	-
Wald test	-	-	-	-	-	-	-	0.68,0.7127

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)

NDD: Neurodevelopmental Disorders; OR: Odds Ratio; CI: Confidence Interval
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage is calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, i.e. row percentage). The association between each characteristics and the outcome is tested by fitting a logistic regression model, and the Odds ratios (OR) with 95% confidence intervals (CI) and likelihood ratio (Wald) test are reported.
a) all available data prior to index date (childbirth)
c) 12 months lookback from Last Menstrual Period Date Plus 2 weeks (LMP2)
d) 3 months lookback from LMP2
e) at index (date of childbirth)
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period
Event: NDD with ASD, Non-Event: No NDD with ASD

15.3.6 Exposure to valproate or lamotrigine/levetiracetam in paternally and maternally matched siblings (Explorative analysis 6)



CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs in Norway

Figure 44. Study population of Primary outcome cohort for Exploratory Analyses 6 in Norway

Table 254. Offspring demographic characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD **Number of offspring**	**Valproate** **N=4**		**Lamotrigine/levetiracetam(composite)** **N=4**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	0	0.00
28-31 (very preterm)	0	0.00	0	0.00
32-36 (moderate to late preterm)	0	0.00	1	25.00
37-41 (at term)	4	100.00	3	75.00
≥42 (post-term)	0	0.00	0	0.00
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	0	0.00
1000-1499 (very low)	0	0.00	0	0.00
1500-2499 (low)	0	0.00	1	25.00
≥2500	4	100.00	3	75.00
Missing	0	0.00	0	0.00
Gender [a]				
Male	2	50.00	0	0.00
Female	2	50.00	4	100.00
Missing	0	0.00	0	0.00
Year of birth				
2005	0	0.00	0	0.00
2006	1	25.00	0	0.00
2007	1	25.00	0	0.00
2008	0	0.00	0	0.00
2009	1	25.00	1	25.00
2010	0	0.00	0	0.00
2011	0	0.00	1	25.00
2012	0	0.00	0	0.00
2013	0	0.00	0	0.00
2014	0	0.00	1	25.00
2015	1	25.00	0	0.00
2016	0	0.00	0	0.00
2017	0	0.00	0	0.00
2018	0	0.00	1	25.00
2019	0	0.00	0	0.00
Total number of years of follow-up	33.7		26.23	
Mean follow-up year	8.43		6.56	

NDD: Neurodevelopmental Disorders
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 255. Offspring clinical characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**	
	N	**%**	**N**	**%**
Comorbidities				
Congenital CMV [a]	0	0.00	0	0.00
Congenital rubella [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00
Foetal alcohol syndrome [a]	0	0.00	0	0.00
Fragile X syndrome [a]	0	0.00	0	0.00
Lejeune/cri du chat syndrome [a]	0	0.00	0	0.00
Tuberous sclerosis [a]	0	0.00	0	0.00
Medication use				
Exposure to AEDs [a]	0	0.00	0	0.00
Outcomes				
ASD (ever, not only as 1st diagnosis)	1	25.00	0	0.00
ASD (as 1st diagnosis)	1	25.00	0	0.00
NDD including ASD	1	25.00	0	0.00
Age at the first diagnosis (years)				
ASD (ever, not only as 1st diagnosis) [b,c]				
0-1	0	0.00	0	0.00
2-3	0	0.00	0	0.00
4-5	1	100.00	0	0.00
6-7	0	0.00	0	0.00
8-9	0	0.00	0	0.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	1	100	0	0.00
NDD including ASD [b,c]				
0-1	0	0.00	0	0.00
2-3	0	0.00	0	0.00
4-5	1	100.00	0	0.00
6-7	0	0.00	0	0.00
8-9	0	0.00	0	0.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	1	100	0	0.00

AED: Antiepileptic Drug; ASD: Autism Spectrum Disorders; CMV: cytomegalovirus; NDD: Neurodevelopmental Disorders
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between index (childbirth) and exit date
b) Categories may be adapted according to the data.
c) Denominator for the percentage is the number of offspring with the outcome.

Table 256. Maternal demographic characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	1	25.00	0	0.00
21-25	0	0.00	0	0.00
26-30	2	50.00	2	50.00
31-35	1	25.00	1	25.00
36-40	0	0.00	1	25.00
>40	0	0.00	0	0.00
Mean (SD)	28.00 (6.27)		31.75 (4.86)	
Median (25^{th} - 75^{th} percentile)	28.5 (23.50, 32.50)		31 (28.00, 35.50)	
Min, max	20.00, 35.00		27.00, 38.00	
Missing	0	0.00	0	0.00

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index (childbirth)

Table 257. Maternal clinical characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder [a]	0	0.00	0	0.00
Diabetes [a]	0	0.00	1	25.00
Epilepsy [a]	0	0.00	0	0.00
Neurotic disorder [a]	0	0.00	0	0.00
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Obesity [b]	0	0.00	0	0.00
CMV [c]	0	0.00	0	0.00
Gestational diabetes [c]	0	0.00	1	25.00
Rubella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	0	0.00
Smoking prior to LMP2 [b]				
Yes	1	25.00	1	25.00
No	2	50.00	3	75.00
Missing	1	25.00	0	0.00
Smoking during pregnancy [c]				
Yes	1	25.00	1	25.00
No	3	75.00	3	75.00
Missing	0	0.00	0	0.00
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AED during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00

Paternal exposure group				
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**	
	N	**%**	**N**	**%**
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K-means cluster prior to LMP2 [d]				
Unexposed	4	100.00	4	100.00
K-means cluster during pregnancy [c]				
Unexposed	4	100.00	4	100.00
Maternal polypharmacy index prior to LMP2 [d]				
0	3	75.00	2	50.00
1-4	1	25.00	2	50.00
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.25 (0.50)		0.50 (0.58)	
Median (25^{th} - 75^{th} percentile)	0 (0.00, 0.50)		0.5 (0.00, 1.00)	
Min, max	0.00, 1.00		0.00, 1.00	
Maternal polypharmacy index during pregnancy [c]				
0	2	50.00	3	75.00
1-4	2	50.00	1	25.00
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.75 (0.96)		0.50 (1.00)	
Median (25^{th} - 75^{th} percentile)	0.5 (0.00, 1.50)		0 (0.00, 1.00)	
Min, max	0.00, 2.00		0.00, 2.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	1	25.00	1	25.00
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	2	50.00	1	25.00
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] - mothers with at least one prescription	3	75.00	4	100.00

Paternal exposure group				
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**	
	N	**%**	**N**	**%**
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	1	25.00	1	25.00

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until index date)
d) 3 months lookback from LMP2

Table 258. Paternal demographic characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD **Number of offspring**	**Valproate** **N=4**		**Lamotrigine/levetiracetam (composite)** **N=4**	
	N	**%**	**N**	**%**
Father's age [a]				
≤20 years	0	0.00	0	0.00
21-25	1	25.00	0	0.00
26-30	1	25.00	2	50.00
31-35	2	50.00	2	50.00
36-40	0	0.00	0	0.00
>40	0	0.00	0	0.00
Mean (SD)	27.75 (4.72)		31.50 (3.00)	
Median (25^{th} - 75^{th} percentile)	29.5 (24.50, 31.00)		32 (29.00, 34.00)	
Min, max	21.00, 31.00		28.00, 34.00	
Missing	-		-	
Year of offspring conception [b]				
2005	1	25.00	0	0.00
2006	0	0.00	0	0.00
2007	1	25.00	0	0.00
2008	0	0.00	1	25.00
2009	1	25.00	0	0.00
2010	0	0.00	1	25.00
2011	0	0.00	0	0.00
2012	0	0.00	0	0.00
2013	0	0.00	0	0.00
2014	1	25.00	1	25.00
2015	0	0.00	0	0.00
2016	0	0.00	0	0.00
2017	0	0.00	1	25.00
2018	0	0.00	0	0.00
2019	0	0.00	0	0.00

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) at mother's LMP2

Table 259. Paternal clinical characteristics by paternal exposure group; primary outcome

Paternal exposure group				
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder excluding bipolar affective disorder and mania [a]	0	0.00	0	0.00
Bipolar affective disorder [a]	0	0.00	0	0.00
Mania [a]	0	0.00	0	0.00
Neurotic disorder [a]	0	0.00	1	25.00
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Lifestyle characteristics				
Substance abuse [c]	0	0.00	0	0.00
Medication use				
AED indication				
Epilepsy	1	25.00	3	75.00
Bipolar affective disorder and mania	0	0.00	0	0.00
Other/unknown	3	75.00	1	25.00
K-means cluster [d]				
Cluster A	4	100.00	2	50.00
Cluster B	0	0.00	2	50.00
Paternal polypharmacy index [d]				
0	3	75.00	1	25.00
1-4	1	25.00	3	75.00
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.25 (0.50)		1.75 (1.26)	
Median (25^{th} - 75^{th} percentile)	0 (0.00, 0.50)		2 (1.00, 2.50)	
Min, max	0.00, 1.00		0.00, 3.00	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	2	50.00	3	75.00
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	3	75.00	4	100.00

Cluster A: constant high exposure; Cluster B: constant low exposure
AED: Antiepileptic Drug; NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2

Table 260. Association between potential offspring risk factors/confounders for NDD by paternal exposure group; primary outcome

	Paternal exposure group				Comparison
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**		**Valproate vs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	
Offspring risk factors/confounders					
Male	2	50.00	0	0.00	-
Female	2	50.00	4	100.00	-
Missing	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.42 (0.4286)*
Congenital CMV [b]	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	-
Foetal alcohol syndrome [b]	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	0	0.00	-

CMV: cytomegalovirus; NDD: Neurodevelopmental Disorders
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
b) between index and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 261. Association between potential maternal risk factors/confounders for NDD by paternal exposure group; primary outcome

Paternal exposure group					**Comparison**
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**		**Valproatevs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	
Maternal risk factors/confounders					
Mother's age [a] (categorical)					
≤20 years	1	25	0	0	-
21-25	0	0	0	0	-
26-30	2	50	2	50	-
31-35	1	25	1	25	-

Paternal exposure group					Comparison
NDD **Number of offspring**	**Valproate** **N=4**		**Lamotrigine/levetiracetam (composite)** **N=4**		**Valproatevs Lamotrigine /levetiracetam** **-**
	N	**%**	**N**	**%**	
36-40	0	0	1	25	-
>40	0	0	0	0	-
Test statistics	-	-	-	-	2.00 (0.5724)
Mother's age [a] (continuous)					
Mean (SD)	28.00 (6.27)		31.75 (4.86)		-0.95 (0.3831)
Median (25^{th} - 75^{th} percentile)	28.5 (23.50, 32.50)		31 (28.00, 35.50)		-
Min, max	20.00, 35.00		27.00, 38.00		-
Missing	0	0	0	0	-
Affective disorder [b]	0	0	0	0	-
Diabetes [b]	0	0	1	25	1.00 (1.0000)*
Gestational diabetes [c]	0	0	1	25	1.00 (1.0000)*
Neurotic disorder [b]	0	0	0	0	-
Schizophrenia, schizotypal and delusional disorders [b]	0	0	0	0	-
Obesity [d]	0	0	0	0	-
CMV [c]	0	0	0	0	-
Rubella [c]	0	0	0	0	-
Alcohol abuse prior to LMP2 [d]	0	0	0	0	-
Alcohol abuse during pregnancy [c]	0	0	0	0	-
Substance abuse prior to LMP2 [d]	0	0	0	0	-
Substance abuse during pregnancy [c]	0	0	0	0	-
Smoking prior to LMP2 [d]					
Yes	1	25	1	25	-
No	2	50	3	75	-
Missing	1	25	0	0	-
Test statistics without 'Missing' category	-	-	-	-	1.00 (1.0000)*
Smoking during pregnancy [c]					
Yes	1	25	1	25	-
No	3	75	3	75	-
Missing	0	0	0	0	-
Test statistics without 'Missing' category	-	-	-	-	1.00 (1.0000)*
Maternal polypharmacy index prior to LMP2 [e](categorical)					
0	3	75	2	50	-
1-4	1	25	2	50	-
5-10	0	0	0	0	-
>10	0	0	0	0	-
Test statistics	-	-	-	-	1.00 (1.0000)*

Paternal exposure group					Comparison
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**		**Valproatevs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	
Maternal polypharmacy index prior to LMP2 [e] (continuous)					
Mean (SD)	0.25 (0.50)		0.50 (0.58)		16.00 (0.6084)*
Median (25th - 75th percentile)	0(0.00, 0.50)		0.5 (0.00, 1.00)		-
Min, max	0.00, 1.00		0.00, 1.00		-
Maternal polypharmacy index during pregnancy [c](categorical)					
0	2	50	3	75	-
1-4	2	50	1	25	-
5-10	0	0	0	0	-
>10	0	0	0	0	-
Test statistics	-	-	-	-	1.00 (1.0000)*
Maternal polypharmacy index during pregnancy[c] (continuous)					
Mean (SD)	0.75 (0.96)		0.50 (1.00)		19.50 (0.7389)*
Median (25th - 75th percentile)	0.5(0.00, 1.50)		0(0.00, 1.00)		-
Min, max	0.00, 2.00		0.00, 2.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	1	25	1	25	1.00 (1.0000)*
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	2	50	1	25	1.00 (1.0000)*
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] -mothers with at least one prescription	3	75	4	100	1.00 (1.0000)*
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	1	25	1	25	1.00 (1.0000)*

Paternal exposure group					Comparison
NDD Number of offspring	Valproate N=4		Lamotrigine/levetiracetam (composite) N=4		Valproatevs Lamotrigine /levetiracetam -
	N	%	N	%	

LMP2: Last Menstrual Period Date Plus 2 weeks; NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

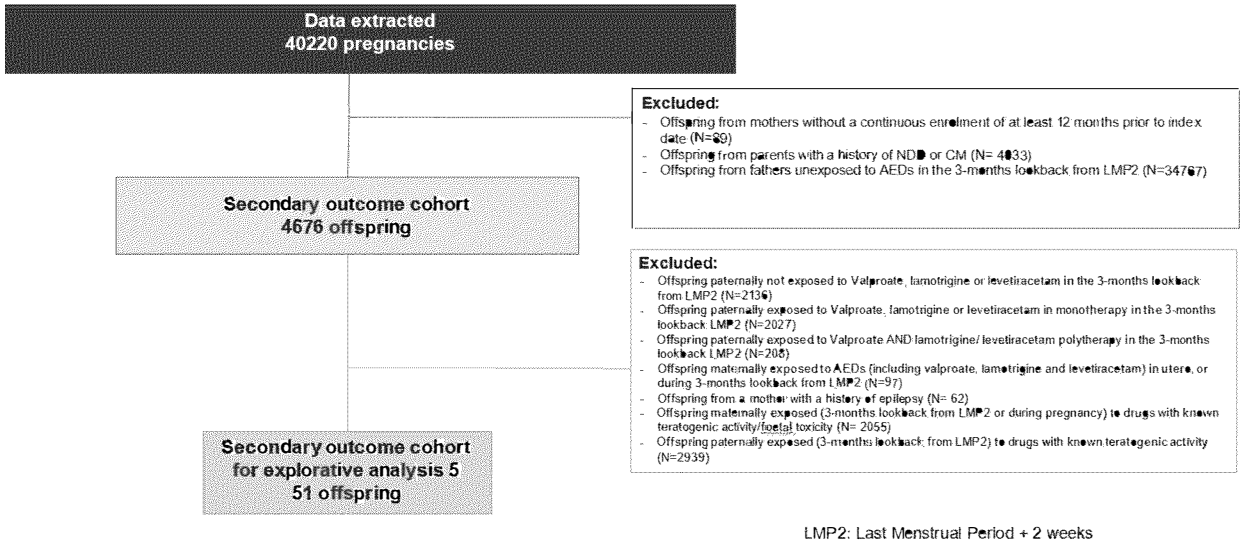
Table 262. Association between potential paternal risk factors/confounders for NDD by paternal exposure group; primary outcome

Paternal exposure group					Comparison
NDD Number of offspring	Valproate N=4		Lamotrigine/levetiracetam (composite) N=4		Valproate vs Lamotrigine /levetiracetam -
	N	%	N	%	
Paternal risk factors/confounders					
Affective disorder [a,b]	0	0.00	0	0.00	-
Bipolar affective disorder [a]	0	0.00	0	0.00	-
Mania [a]	0	0.00	0	0.00	-
Neurotic disorder [a]	0	0.00	1	25.00	1.14 (0.2850)
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00	-
Substance abuse [c]	0	0.00	0	0.00	-
Paternal polypharmacy index [d] (categorical)					
0	3	75.00	1	25.00	-
1-4	1	25.00	3	75.00	-
5-10	0	0.00	0	0.00	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	2.00 (0.1573)
Paternal polypharmacy index [d] (continuous)					
Mean (SD)	0.25 (0.50)		1.75 (1.26)		-2.22 (0.0924)
Median (25^{th} - 75^{th} percentile)	0 (0.00, 0.50)		2 (1.00, 2.50)		-
Min, max	0.00, 1.00		0.00, 3.00		-

Paternal exposure group					Comparison
NDD Number of offspring	**Valproate N=4**		**Lamotrigine/levetiracetam (composite) N=4**		**Valproate vs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	2	50.00	3	75.00	0.53 (0.4652)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	3	75.00	4	100.00	1.14 (0.2850)
Father's age [e] (categorical)					
≤20 years	0	0.00	0	0.00	-
21-25	1	25.00	0	0.00	-
26-30	1	25.00	2	50.00	-
31-35	2	50.00	2	50.00	-
36-40	0	0.00	0	0.00	-
>40	0	0.00	0	0.00	-
Test statistics	-	-	-	-	1.33 (0.5134)
Father's age [e] (continuous)					
Mean (SD)	27.75 (4.72)		31.50 (3.00)		-1.34 (0.2365)
Median (25^{th} - 75^{th} percentile)	29.5 (24.50, 31.00)		32 (29.00, 34.00)		-
Min, max	21.00, 31.00		28.00, 34.00		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [f,g]					
2005-2009	3	75.00	1	25.00	-
2010-2014	1	25.00	2	50.00	-
2015-2019	0	0.00	1	25.00	-
Test statistics	-	-	-	-	2.33 (0.3114)

NDD: Neurodevelopmental Disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) all available data prior to index date (childbirth)
b) excluding bipolar affective disorder and mania
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

15.3.7 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Explorative analysis 5 CM)



An offspring may be present in more than one exclusion criterion

CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 45. Study population of Secondary outcome cohort for Exploratory Analyses 5 in Norway

Table 263. Offspring demographic characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM Number of offspring	**Valproate(polytherapy) N=6**		**Lamotrigine/levetiracetam(polytherapy) N=45**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	1	2.22
28-31 (very preterm)	0	0.00	1	2.22
32-36 (moderate to late preterm)	0	0.00	1	2.22
37-41 (at term)	6	100.00	41	91.11
≥42 (post-term)	0	0.00	1	2.22
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	1	2.22
1000-1499 (very low)	0	0.00	1	2.22
1500-2499 (low)	0	0.00	1	2.22
≥2500	6	100.00	41	91.11

Missing	0	0.00	1	2.22
Gender [a]				
Male	3	50.00	23	51.11
Female	3	50.00	22	48.89
Missing	0	0.00	0	0.00
Year of birth				
2005	0	0.00	1	2.22
2006	2	33.33	4	8.89
2007	0	0.00	4	8.89
2008	1	16.67	4	8.89
2009	0	0.00	2	4.44
2010	0	0.00	4	8.89
2011	2	33.33	0	0.00
2012	0	0.00	5	11.11
2013	0	0.00	2	4.44
2014	1	16.67	6	13.33
2015	0	0.00	4	8.89
2016	0	0.00	3	6.67
2017	0	0.00	4	8.89
2018	0	0.00	2	4.44
2019	0	0.00	0	0.00

CM: Congenital Malformations
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 264. Offspring clinical characteristics paternal exposure group; secondary outcome

	Paternal exposure group			
CM **Number of offspring**	**Valproate(polytherapy)** **N=6**		**Lamotrigine/levetiracetam(polytherapy)** **N=45**	
	N	**%**	**N**	**%**
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital Herpes Simplex	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00
Congenital varicella	0	0.00	0	0.00
Foetal alcohol syndrome	0	0.00	0	0.00
Outcomes				
CM	1	16.67	1	2.22
Major CM (at any time)	0	0.00	1	2.22
Mino r CM (at any time)	1	16.67	1	2.22
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]				
Stillbirth	0	0.00	0	0.00
Spontaneous abortion	0	0.00	0	0.00

Intrauterine growth retardation	0	0.00	1	100.00
Perinatal mortality	0	0.00	0	0.00

CM: Congenital Malformations; CMV: cytomegalovirus
Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date
b) Denominator for the percentage is the number of offspring with CM.

Table 265. Maternal demographic characteristics by paternal exposure group; secondary outcome

Paternal exposure group				
CM Number of offspring	**Valproate(polytherapy) N=6**		**Lamotrigine/levetiracetam(polytherapy) N=45**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	0	0.00	2	4.44
21-25	1	16.67	9	20.00
26-30	2	33.33	15	33.33
31-35	2	33.33	17	37.78
36-40	1	16.67	2	4.44
>40	0	0.00	0	0.00
Mean (SD)	30.17 (6.40)		28.96 (4.72)	
Median (25th - 75th percentile)	31 (26.00, 32.00)		28 (26.00, 33.00)	
Min, max	21.00, 40.00		19.00, 38.00	
Missing	0	0.00	0	0.00

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index (childbirth)

Table 266. Maternal clinical characteristics by paternal exposure group; secondary outcome

Paternal exposure group				
CM Number of offspring	**Valproate(polytherapy) N=6**		**Lamotrigine/levetiracetam(polytherapy) N=45**	
	N	**%**	**N**	**%**
Comorbidities				
Diabetes [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00
Obesity [b]	0	0.00	0	0.00
CMV [c]	0	0.00	0	0.00
Folate deficiency [c]	0	0.00	0	0.00
Gestational diabetes [c]	0	0.00	1	2.22
Herpes simplex virus [c]	0	0.00	0	0.00
Rubella [c]	0	0.00	0	0.00

Paternal exposure group				
CM **Number of offspring**	**Valproate(polytherapy)** **N=6**		**Lamotrigine/levetiracetam(polytherapy)** **N=45**	
	N	**%**	**N**	**%**
Toxoplasmosis [c]	0	0.00	0	0.00
Varicella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	0	0.00
Smoking prior to LMP2 [b]				
Yes	0	0.00	1	2.22
No	4	66.67	29	64.44
Missing	2	33.33	15	33.33
Smoking during pregnancy [c]				
Yes	1	16.67	3	6.67
No	4	66.67	33	73.33
Missing	1	16.67	9	20.00
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AEDs during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K-means cluster prior to LMP2 [d]				

Paternal exposure group				
CM Number of offspring	**Valproate(polytherapy) N=6**		**Lamotrigine/levetiracetam(polytherapy) N=45**	
	N	**%**	**N**	**%**
Unexposed	6	100.00	45	100.00
K-means cluster during pregnancy [c]				
Unexposed	6	100.00	45	100.00
Maternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [d] - mothers with at least one prescription	0	0.00	0	0.00
Maternal exposure to teratogenic activity/foetal toxicity during pregnancy [c] - mothers with atleast one prescription	0	0.00	0	0.00

AED: Antiepileptic Drug; CM: Congenital Malformations; CMV: cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks
Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring.
Percentages were calculated over the total number of offspring.

a) all available data prior to index date (12th week of gestation in Norway, 22nd week of gestation in Denmark)

b) 12 months lookback from LMP2

c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)

d) 3 months lookback from LMP2

e) Oxazolidine derivatives were not sold in Norway during the study period

Table 267. Paternal demographic characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM Number of offspring	**Valproate (polytherapy) N=6**		**Lamotrigine/levetiracetam (polytherapy) N=45**	
	N	**%**	**N**	**%**
Father's age [a]				
≤20 years	0	0.00	0	0.00
21-25	1	16.67	3	6.67
26-30	1	16.67	15	33.33
31-35	3	50.00	18	40.00
36-40	0	0.00	5	11.11
>40	1	16.67	4	8.89
Mean (SD)	31.83 (5.64)		32.11 (5.31)	
Median (25th - 75th percentile)	32 (27.00, 34.00)		32 (28.00, 35.00)	
Min, max	25.00, 41.00		22.00, 50.00	
Year of offspring conception [b]				
2005	0	0.00	2	4.44
2006	2	33.33	3	6.67
2007	0	0.00	4	8.89

	Paternal exposure group			
CM Number of offspring	**Valproate (polytherapy) N=6**		**Lamotrigine/levetiracetam (polytherapy) N=45**	
	N	**%**	**N**	**%**
2008	1	16.67	4	8.89
2009	0	0.00	3	6.67
2010	0	0.00	3	6.67
2011	2	33.33	2	4.44
2012	0	0.00	3	6.67
2013	0	0.00	4	8.89
2014	1	16.67	5	11.11
2015	0	0.00	3	6.67
2016	0	0.00	5	11.11
2017	0	0.00	3	6.67
2018	0	0.00	1	2.22
2019	0	0.00	0	0.00

CM: Congenital Malformations, SD: Standard Deviation, Min: Minimum, Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at index (childbirth)

b) at mother's LMP2

Table 268. Paternal clinical characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM Number of offspring	**Valproate (polytherapy) N=6**		**Lamotrigine/levetiracetam (polytherapy) N=45**	
	N	**%**	**N**	**%**
Medication use				
Exposure to AEDs[a, b]				
Fatty acid derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Barbiturates derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	28	62.22
Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Carboxamide derivatives and other antiepileptics	0	0.00	14	31.11
Fatty acid derivatives and Carboxamide derivatives	5	83.33	0	0.00
Benzodiazepine derivatives and other antiepileptics	0	0.00	1	2.22
Benzodiazepine derivatives and Fatty acid derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives	0	0.00	0	0.00

	Paternal exposure group			
CM Number of offspring	**Valproate (polytherapy) N=6**		**Lamotrigine/levetiracetam (polytherapy) N=45**	
	N	**%**	**N**	**%**
Succinimide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Hydantoin derivatives and Carboxamide derivatives	0	0.00	0	0.00
Hydantoin derivatives and other antiepileptics	0	0.00	1	2.22
Hydantoin derivatives and Succinimide derivatives	0	0.00	0	0.00
Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Fatty acid derivatives	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives	0	0.00	0	0.00
Barbiturates derivatives and Benzodiazepine derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Carboxamide derivatives and Fatty acid derivatives and other antiepileptics	1	16.67	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	1	2.22
Benzodiazepine derivatives and Succinimide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Fatty acid derivatives and Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	0	0.00
AED indication				
Epilepsy	4	66.67	31	68.89
Bipolar affective disorder and mania	0	0.00	0	0.00
Other/unknown	2	33.33	14	31.11
K-means cluster [a]				
Cluster A	4	66.67	36	80.00
Cluster B	2	33.33	9	20.00
Paternal exposure to teratogenic activity/foetal toxicity [a]	0	0.00	0	0.00

AED: Antiepileptic Drug, CM: Congenital Malformations
Cluster A: constant moderate exposure, Cluster B: moderate to low exposure
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) 3 months lookback from LMP2
b) Valproate or lamotrigine/levetiracetam in combination with other AED(s). Each combination found in the data were listed here.

Table 269.Association between potential offspring risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				Comparison
CM Number of offspring	**Valproate (polytherapy) N=6**		**Lamotrigine/levetiracetam (polytherapy) N=45**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
Offspring risk factors/confounders[a]					
Congenital CMV	0	0.00	0	0.00	-
Congenital Herpes Simplex	0	0.00	0	0.00	-
Congenital rubella	0	0.00	0	0.00	-
Congenital toxoplasmosis	0	0.00	0	0.00	-
Congenital varicella	0	0.00	0	0.00	-
Foetal alcohol syndrome	0	0.00	0	0.00	-

Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) between index (12^{th} week of gestation in Norway, 22^{nd} week of gestation in Denmark) and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 270. Association between potential maternal risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				Comparison
CM Number of offspring	**Valproate (polytherapy) N=6**		**Lamotrigine/levetiracetam (polytherapy) N=45**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
Maternal risk factors/confounders Mother´s age [a](categorical)					
≤20 years	0	0.00	2	4.44	-
21-25	1	16.67	9	20.00	-
26-30	2	33.33	15	33.33	-
31-35	2	33.33	17	37.78	-
36-40	1	16.67	2	4.44	-
>40	0	0.00	0	0.00	-
Test statistics	-	-	-	-	1.67 (0.7963)
Mother´s age [a](continuous)					

	Paternal exposure group				Comparison
CM Number of offspring	**Valproate (polytherapy) N=6**		**Lamotrigine/levetiracetam (polytherapy) N=45**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
Mean (SD)	30.17 (6.40)		28.96 (4.72)		0.45 (0.6708)
Median (25th - 75th percentile)	31(26.00, 32.00)		28(26.00, 33.00)		-
Min, max	21.00, 40.00		19.00, 38.00		-
Missing	0	0.00	0	0.00	-
Diabetes [b]	0	0.00	0	0.00	-
Obesity [c]	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [c]	0	0.00	0	0.00	-
Alcohol abuse during pregnancy [d]	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [c]	0	0.00	0	0.00	-
Substance abuse during pregnancy [d]	0	0.00	0	0.00	-
Smoking prior to LMP2 [c]					
No	4	66.67	29	64.44	-
Yes	0	0.00	1	2.22	-
Missing	2	33.33	15	33.33	-
Test statistics without 'Missing' category	-	-	-	-	1.00 (1.0000)*
Smoking during pregnancy [d]					
No	4	66.67	33	73.33	-
Yes	1	16.67	3	6.67	-
Missing	1	16.67	9	20.00	-
Test statistics without 'Missing' category	-	-	-	-	0.41 (0.4183)*
CMV [d]	0	0.00	0	0.00	-
Folate deficiency [d]	0	0.00	0	0.00	-
Gestational diabetes [d]	0	0.00	1	2.22	1.00 (1.0000)*
Herpes simplex virus [d]	0	0.00	0	0.00	-
Rubella [d]	0	0.00	0	0.00	-
Toxoplasmosis [d]	0	0.00	0	0.00	-
Varicella [d]	0	0.00	0	0.00	-

CM: Congenital Malformations; CMV: cytomegalovirus; LMP2: Last Menstrual Period Date Plus 2 weeks
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) at index (12th week of gestation in Norway, 22nd week of gestation in Denmark).
b) all available data prior to index date.
c) 12 months lookback from LMP2.

	Paternal exposure group				Comparison
CM Number of offspring	**Valproate (polytherapy) N=6**		**Lamotrigine/levetiracetam (polytherapy) N=45**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	

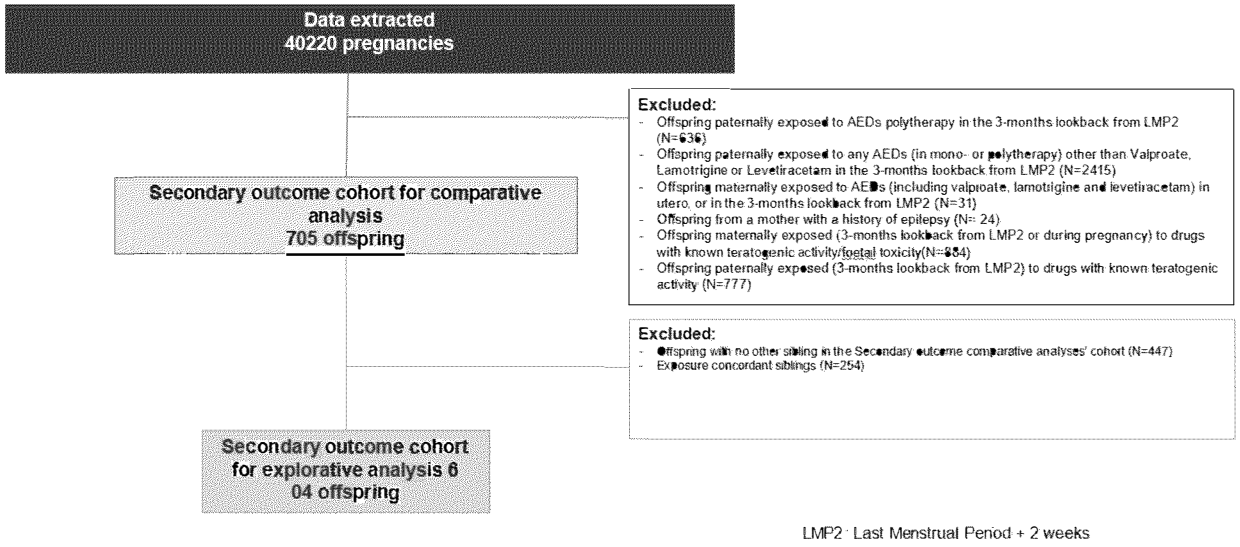
d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy.)
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 271. Association between potential paternal risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				Comparison
CM Number of offspring	**Valproate (polytherapy) N=6**		**Lamotrigine/levetiracetam (polytherapy) N=45**		**Vaproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -**
	N	**%**	**N**	**%**	
Paternal risk factors/confounders Father´s age [a](categorical)					
≤20 years	0	0.00	0	0.00	-
21-25	1	16.67	3	6.67	-
26-30	1	16.67	15	33.33	-
31-35	3	50.00	18	40.00	-
36-40	0	0.00	5	11.11	-
>40	1	16.67	4	8.89	-
Test statistics	-	-	-	-	2.27 (0.6870)
Father´s age [a] (continuous)					
Mean (SD)	31.83 (5.64)		32.11 (5.31)		-0.11 (0.9127)
Median (25^{th} - 75^{th} percentile)	32(27.00, 34.00)		32(28.00, 35.00)		-
Min, max	25.00, 41.00		22.00, 50.00		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [b,c]					
2005-2009	3	50.00	16	35.56	-
2010-2014	3	50.00	17	37.78	-
2015-2019	0	0.00	12	26.67	-
Test statistics	-	-	-	-	2.10 (0.3503)

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring. Difference between categorical variables were tested using Chi-square independence test; however, if the frequency of any of the categories analysed was <5 Fisher's exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (12^{th} week of gestation in Norway, 22^{nd} week of gestation in Denmark).
b) at mother's LMP2.
c) calendar years were grouped in each country according to the length of the study period.
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

15.3.8 Exposure to valproate or lamotrigine/levetiracetam in paternally and maternally matched siblings (Exploratory analysis 6 CM)



AED: antiepileptic drugs; LMP2: Last Menstrual Period Date Plus 2 weeks

Figure 46. Study population of Secondary outcome cohort for Exploratory Analyses 6 in Norway

Table 272. Offspring demographic characteristics by paternal exposure group; secondary outcome

Paternal exposure group				
CM **Number of offspring**	**Valproate** **N=0**		**Lamotrigine/levetiracetam** **N=4**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	0	0.00
28-31 (very preterm)	0	0.00	0	0.00
32-36 (moderate to late preterm)	0	0.00	1	25.00
37-41 (at term)	0	0.00	3	75.00
≥42 (post-term)	0	0.00	0	0.00
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	0	0.00
1000-1499 (very low)	0	0.00	0	0.00
1500-2499 (low)	0	0.00	1	25.00
≥2500	0	0.00	3	75.00
Missing	0	0.00	0	0.00
Gender [a]				
Male	0	0.00	0	0.00
Female	0	0.00	4	100.00
Missing	0	0.00	0	0.00
Year of birth				
2006	0	0.00	0	0.00
2007	0	0.00	0	0.00
2008	0	0.00	0	0.00
2009	0	0.00	1	25.00
2010	0	0.00	0	0.00
2011	0	0.00	2	50.00
2012	0	0.00	1	25.00

Paternal exposure group

CM **Number of offspring**	**Valproate** **N=0**		**Lamotrigine/levetiracetam** **N=4**	
	N	**%**	**N**	**%**
2013	0	0.00	0	0.00
2014	0	0.00	0	0.00
2015	0	0.00	0	0.00
2016	0	0.00	0	0.00
2017	0	0.00	0	0.00
2018	0	0.00	0	0.00
2019	0	0.00	0	0.00

CM: Congenital Malformations.
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth).

Table 273. Offspring clinical characteristics paternal exposure group; secondary outcome

Paternal exposure group				
CM **Number of offspring**	**Valproate** **N=0**		**Lamotrigine/levetiracetam** **N=4**	
	N	**%**	**N**	**%**
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital Herpes Simplex	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00
Congenital varicella	0	0.00	0	0.00
Foetal alcohol syndrome	0	0.00	0	0.00
Outcomes				
CM	0	0.00	1	25.00
Major CM (at any time)	0	0.00	0	0.00
Minor CM (at any time)	0	0.00	1	25.00
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]				
Stillbirth	0	0.00	0	0.00
Spontaneous abortion	0	0.00	0	0.00
Intrauterine growth retardation	0	0.00	0	0.00
Perinatal mortality	0	0.00	0	0.00

CMV: cytomegalovirus; CM: Congenital Malformations
Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date
b) Denominator for the percentage is the number of offspring with CM.

Table 274. Maternal demographic characteristics by paternal exposure group; secondary outcome

Paternal exposure group				
CM **Number of offspring**	**Valproate** **N=0**		**Lamotrigine/levetiracetam** **N=4**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	0	0.00	0	0.00
21-25	0	0.00	1	25.00
26-30	0	0.00	2	50.00
31-35	0	0.00	1	25.00
36-40	0	0.00	0	0.00
>40	0	0.00	0	0.00
Mean (SD)	-		29.00 (3.37)	
Median (25^{th} - 75^{th} percentile)	-		29 (26.50, 31.50)	
Min, max	-		25.00, 33.00	
Missing	0	0.00	0	0.00

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 275. Maternal clinical characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM **Number of offspring**	**Valproate** **N=0**		**Lamotrigine/levetiracetam (composite)** **N=4**	
	N	**%**	**N**	**%**
Comorbidities				
Diabetes [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00

	Paternal exposure group			
CM **Number of offspring**	**Valproate** **N=0**		**Lamotrigine/levetiracetam (composite)** **N=4**	
	N	**%**	**N**	**%**
Obesity [b]	0	0.00	0	0.00
CMV [c]	0	0.00	0	0.00
Folate deficiency [c]	0	0.00	0	0.00
Gestational diabetes [c]	0	0.00	0	0.00
Herpes simplex virus [c]	0	0.00	0	0.00
Rubella [c]	0	0.00	0	0.00
Toxoplasmosis [c]	0	0.00	0	0.00
Varicella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	0	0.00
Smoking prior to LMP2 [b]	0	0.00	0	0.00
Yes	0	0.00	1	25.00
No	0	0.00	3	75.00
Missing	0	0.00	0	0.00
Smoking during pregnancy [c]	0	0.00	0	0.00
Yes	0	0.00	1	25.00
No	0	0.00	3	75.00
Missing	0	0.00	0	0.00
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00

	Paternal exposure group			
CM **Number of offspring**	**Valproate** **N=0**		**Lamotrigine/levetiracetam (composite)** **N=4**	
	N	**%**	**N**	**%**
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AEDs during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K-means cluster prior to LMP2 [d]				
Unexposed	0	0.00	4	100.00
K-means cluster during pregnancy [c]				
Unexposed	0	0.00	4	100.00

	Paternal exposure group			
CM Number of offspring	**Valproate N=0**		**Lamotrigine/levetiracetam (composite) N=4**	
	N	**%**	**N**	**%**
Maternal exposure to teratogenic activity/foetal toxicity prior to LMP2 [d] - mothers with at least one prescription	0	0.00	0	0.00
Maternal exposure to teratogenic activity/foetal toxicity during pregnancy [c] - mothers with atleast one prescription	0	0.00	0	0.00

AED: Antiepileptic Drug; CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: as Menstrual Period Date Plus 2 weeks
Number of offspring represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (12th week of gestation in Norway, 22nd week of gestation in Denmark)
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Norway during the study period

Table 276. Paternal demographic characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM **Number of offspring**	**Valproate** **N=0**		**Lamotrigine/levetiracetam** **N=4**	
	N	**%**	**N**	**%**
Father's age [a]				
≤20 years	0	0.00	0	0.00
21-25	0	0.00	0	0.00
26-30	0	0.00	3	75.00
31-35	0	0.00	1	25.00
36-40	0	0.00	0	0.00
>40	0	0.00	0	0.00
Mean (SD)	-		29.75 (0.96)	
Median (25^{th} - 75^{th} percentile)	-		29.5 (29.00, 30.50)	
Min, max	-		29.00, 31.00	
Year of offspring conception [b]				
2005	0	0.00	0	0.00
2006	0	0.00	0	0.00
2007	0	0.00	0	0.00
2008	0	0.00	1	25.00
2009	0	0.00	0	0.00
2010	0	0.00	2	50.00
2011	0	0.00	0	0.00
2012	0	0.00	1	25.00
2013	0	0.00	0	0.00
2014	0	0.00	0	0.00
2015	0	0.00	0	0.00
2016	0	0.00	0	0.00
2017	0	0.00	0	0.00

2018	0	0.00	0	0.00
2019	0	0.00	0	0.00

CM: Congenital Malformations ; SD: Standard Deviation ; Min: Minimum; Max: Maximum
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
a) at index (childbirth)
b) at mother's LMP2

Table 277. Paternal clinical characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM **Number of offspring**	**Valproate** **N=0**		**Lamotrigine/levetiracetam (composite)** **N=4**	
	N	**%**	**N**	**%**
Medication use				
AED indication				
Epilepsy	0	0.00	3	75.00
Bipolar affective disorder and mania	0	0.00	0	0.00
Other/unknown	0	0.00	1	25.00
K-means cluster [a]				
Cluster A	0	0.00	2	50.00
Cluster B	0	0.00	2	50.00
Paternal exposure to teratogenic activity/foetal toxicity [a]	0	0.00	0	0.00

Cluster A: constant moderate exposure; Cluster B: moderate to low exposure; AED: Antiepileptic Drug
Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) 3 months lookback from Last Menstrual Period Date Plus 2 weeks (LMP2)

15.4 Propensity score models

15.4.1 Propensity score models for the Primary outcome cohort

After the identification of confounders and risk factors associated to the occurrence of NDD, including ASD, in offspring paternally exposed at the time of conception to valproate (monotherapy), and lamotrigine or levetiracetam (composite monotherapy) lamotrigine/levetiracetam, separate propensity score (PS) models were constructed. Methods based on PS are frequently used in non-interventional studies to control for confounding when estimating treatment effects (79). PS methods allow controlling for measured confounding in treatment effects when the measured confounders related with the treatment are correctly modelled in the PS, and thus, allowing comparisons between the 2 populations (80). Each PS model reflects the probability of an offspring being assigned to valproate or the comparator exposure group (lamotrigine/levetiracetam), given a set of observed covariates.

For this study, both risk factors and confounders were included in the PS model. This option was made as the inclusion of confounders addresses confounding bias and risk factors correct for small amounts of chance bias or empirical confounding existing within each realisation of the dataset, thereby improving the precision of the estimator (81). In this study particularly, candidate covariates were considered to enter the PS model if the OR in a single association with the outcome and/or the exposure was higher than 1.1 or lower than 0.9. For categorical variables with more than 2 categories the Wald test was used to assess whether the variable was significantly associated with the outcome.

In this study, 3 different model approaches were used and compared, and the choice of the PS model that was then used as weights in the inverse probability of treatment weights, based on the balance achieved in the "weighted" exposure groups.

The first approach consisted of a logistic regression model with all potential confounders and risk factors associated with the study outcomes and/or exposure. The second modelling approach used of a random decision forest model, and finally, the third modelling approach was a logistic regression informed by the random forest model, that used data-driven identification of interactions identified by the random forest model and then incorporated into the logistic regression model.

In particular, the best model was chosen as the one for which all standardised differences are below 0.1 and variance ratios between 0 and 2, or if none of the model achieved this, the one with the highest number of confounders for which the standardised differences are below 0.1 (82).

Different models were chosen according to these criteria and are described in the Box 2.

Box 2: Selected propensity score models for all cohorts in Denmark, Sweden and Norway

Primary outcome cohort	Analysis	Sweden	Norway	Denmark
NDD including ASD	Comparative analysis	Logistic	Logistic	Logistic
	Sensitivity analysis 1	Logistic	Logistic	Logistic
	Sensitivity analysis 3	Logistic	Logistic	Logistic
	Sensitivity analysis 5 (lamotrigine)	Logistic	Logistic	Logistic
	Sensitivity analysis 5 (levetiracetam)	Logistic	Logistic	Logistic
	Sensitivity analysis 7	Logistic	Logistic	Logistic
	Sensitivity analysis 11	Logistic	Logistic	Logistic*

NDD: neurodevelopmental disorders; ASD: autism spectrum disorder; RF: random forest. *In sensitivity analysis 11, for Denmark, either the logistic informed by RF and logistic models presented the same number of unbalanced variables, and the logistic model was selected for consistency with the main analysis

The PS were then used as weights in the inverse probability of treatment weights approach to balance differences in covariate distribution between offspring paternally exposed to valproate and offspring paternally exposed to lamotrigine/levetiracetam in the adjusted analyses. This statistical approach for estimating the PS models was applied to different populations, specifically by countries, this led to the inclusion of different covariates in the 3 final PS models. The variables included in each of the final PS model can be found in the Box 3, and were usually similar for all countries.

Box 3 Variables included in propensity score models by country and by outcome cohort.

NDD	Sweden	Norway	Denmark
PS models (variables or interaction)			
Offspring risk factors/confounders			
Gender	×	×	×
Maternal risk factors/confounders			
Mother's age		×	×
Affective disorder	×	×	×
Diabetes [d]		×	×
Gestational diabetes	×	×	×
Neurotic disorder	×	×	×
Obesity	×	×	×
Substance abuse during pregnancy			×
Smoking prior to LMP2	×		
Smoking during pregnancy	×	×	×
Maternal polypharmacy index			×
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 - mothers with at least one prescription	×	×	×
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy - mothers with at least one prescription	×	×	×
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 -mothers with at least one prescription		×	×
Concomitant medications associated with neuropsychiatric adverse events during pregnancy - mothers with at least one prescription	×	×	×
Paternal risk factors/confounders			
Affective disorder	×	×	×
Bipolar affective disorder	×	×	×
Mania	×	×	×
Neurotic disorder	×	×	×
Schizophrenia, schizotypal and delusional disorders	×	×	×
Substance abuse	×	×	
Paternal polypharmacy index	×		
Concomitant medications associated with valproate-indicated psychiatric conditions – fathers with at least one prescription		×	
Concomitant medications associated with neuropsychiatric adverse events - fathers with at least one prescription	×	×	×
Year of offspring conception	×	×	×

15.4.2 Propensity score models for the secondary outcome cohort

The approach previously described for the primary outcome was applied for computing the PS models for the Secondary outcome cohort. Thus, and although no risk factors nor confounders were identified as significantly associated to both the exposure and outcome, selected candidate covariates for which association with the outcome and/or the exposure was higher than 1.1 or lower than 0.9 were considered. The best model was chosen also as previously described, and for the secondary outcome analyses the models chosen are described in the Box 4.

Box 4: Selected propensity score models for all cohorts in Denmark, Sweden and Norway

Outcome cohort	Analysis	Sweden	Norway	Denmark
Secondary outcome	Comparative analysis	NA	Logistic	Logistic
	Exploratory analysis 7	Logistic	NA	NA
	Sensitivity analysis 4	NA	Logistic	Logistic
	Sensitivity analysis 5A (lamotrigine)	NA	Logistic	Logistic
	Sensitivity analysis 5B (levetiracetam)	NA	Logistic	Logistic
	Sensitivity analysis 9	NA	Logistic	Logistic

The variables included in each of the final PS model can be found in the Box 5.

Box 5 Variables included in propensity score models by country and by outcome cohort.

CM PS models (variables or interaction)	Denmark	Sweden	Norway
Offspring risk factors/confounders			
Foetal alcohol syndrome	×		
Maternal risk factors/confounders			
Gestational diabetes	×		
Alcohol abuse prior to LMP2	×		
Alcohol abuse during pregnancy	×		
Substance abuse prior to LMP2	×		
Substance abuse during pregnancy	×		×
Smoking prior to LMP2		×	
Smoking during pregnancy		×	×
Varicella during pregnancy			×

15.5 Missing values

15.5.1 Denmark

Table 278. Missing data patterns; primary outcome in Denmark

Group	Offspring risk factors/confounders[a]	Maternal risk factors/confounders[b]		Paternal risk factors/confounders [c]	Frequence	Percentage
	None of the factors over 5% missingness	Smoking prior LMP2	Smoking during pregnancy	None of the factors over 5% missingness		
Group 1		X			1783	91.44
Group 2					88	4.51
Group 3		X	X		79	4.05
Group 4			X		0	0.00

LMP2: Last Menstrual Period Date Plus 2 weeks

a: Gender, Congenital Cytomegalovirus (CMV), Congenital rubella, Fœtal alcohol syndrom, Fragile X syndrome, Lejeune/cri du chat, Tuberous sclerosis

b: Other maternal factors (none was over 5% missingness): Mother's age, Affective disorder, Diabetes, Gestational diabetes, Neurotic disorder, Schizophrenia, schizotypal and delusional disorders, Obesity, CMV, Rubella, Alcohol abuse prior to LMP2, Alcohol abuse during pregnancy, Substance abuse prior to LMP2, Substance abuse during pregnancy, Maternal polypharmacy index prior to LMP2, Maternal polypharmacy index during pregnancy, Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 - mothers with at least one prescription, Concomitant medications associated with valproate -indicated psychiatric conditions during pregnancy - mothers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 - mothers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events during pregnancy - mothers with at least one prescription

c: Bipolar affective disorder, Mania, Affective disorder excluding bipolar affective disoreder and mania, neurotic disorder, Schizophrenia, schizotypal and delusional disorders, Substance abuse, Paternal polypharmacy index, Concomitant medications associated with valproate -indicated psychiatric conditions - fathers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events - fathers with at least one prescription, Father's age, Year of offspring conception

The 4 groups represent 4 subgroups of offspring with the following patterns:
Group 1. Only maternal smoking prior to LMP2 missing
Group 2. No risk factors or confounders missing
Group 3. Maternal smoking prior to LMP2 AND during pregnancy missing
Group 4. Only maternal smoking during pregnancy missing

Table 279. Missing data patterns; secondary outcome in Denmark

	Offspring risk factors/confounders[a]	Maternal risk factors/confounders[b]		Paternal risk factors/confounders [c]		
Group	None of the factors over 5% missingness	Smoking prior LMP2	Smoking during pregnancy	None of the factors over 5% missingness	Frequence	Percentage
Group 1		X			605	93.36
Group 2					32	4.94
Group 3		X	X		11	1.70
Group 4			X		0	0.00

LMP2: Last Menstrual Period Date Plus 2 weeks

a: Congenital Cytomegalovirus (CMV), Congenital Herpes Simplex, Congenital rubella, Congenital toxoplasmosis, Congenital varicella, Foetal alcohol syndrome

b: Other maternal factors (none was over 5% missingness): Mother´s age , Diabetes, Obesity, Alcohol abuse prior to LMP2, Alcohol abuse during pregnancy, Substance abuse prior to LMP2, Substance abuse during pregnancy, CMV, Folate deficiency, Gestational diabetes, Herpes simplex virus, Rubella, Toxoplasmosis, Varicella

c: Father´s age, Year of offspring conception

The 4 groups represent 4 subgroups of offspring with the following patterns:
Group 1. Only maternal smoking prior to LMP2 missing
Group 2. No risk factors or confounders missing
Group 3. Maternal smoking prior to LMP2 AND during pregnancy missing
Group 4. Only maternal smoking during pregnancy missing

15.5.2 Sweden

Table 280. Missing data patterns; primary outcome in Sweden

	Offspring risk factors/confounders[a]	Maternal risk factors/confounders[b]		Paternal risk factors/confounders		
Group	None of the factors over 5% missingness	Smoking prior LMP2	Smoking during pregnancy	None of the factors over 5% missingness	Frequence	Percentage
Group 1		X			2239	95.07
Group 2					67	2.85
Group 3		X	X		49	2.08
Group 4			X		0	0.00

LMP2: Last Menstrual Period Date Plus 2 weeks

a: Gender, Congenital Cytomegalovirus (CMV), Congenital rubella, Fœtal alcohol syndrom, Fragile X syndrome, Lejeune/cri du chat, Tuberous sclerosis

b: Other maternal factors (none was over 5% missingness): Mother's age, Affective disorder, Diabetes, Gestational diabetes, Neurotic disorder, Schizophrenia, schizotypal and delusional disorders, Obesity, CMV, Rubella, Alcohol abuse prior to LMP2, Alcohol abuse during pregnancy, Substance abuse prior to LMP2, Substance abuse during pregnancy, Maternal polypharmacy index prior to LMP2, Maternal polypharmacy index during pregnancy, Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 - mothers with at least one prescription, Concomitant medications associated with valproate -indicated psychiatric conditions during pregnancy - mothers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 - mothers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events during pregnancy - mothers with at least one prescription

c: Affective disorder excluding bipolar affective disorder and mania, Bipolar affective disorder, Mania, neurotic disorder, Schizophrenia, schizotypal and delusional disorders, Substance abuse, Paternal polypharmacy index, Concomitant medications associated with valproate -indicated psychiatric conditions - fathers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events - fathers with at least one prescription, Father's age, Year of offspring conception

The 4 groups represent 4 subgroups of offspring with the following patterns:
Group 1. Only maternal smoking prior to LMP2 missing
Group 2. No risk factors or confounders missing
Group 3. Maternal smoking prior to LMP2 AND during pregnancy missing
Group 4. Only maternal smoking during pregnancy missing

Table 281. Missing data patterns; secondary outcome in Sweden

	Offspring risk factors/confounders[a]	Maternal risk factors/confounders[b]		Paternal risk factors/confounders		
Group	None of the factors over 5% missingness	Smoking prior LMP2	Smoking during pregnancy	None of the factors over 5% missingness	Frequence	Percentage
Group 1		X			854	96.17
Group 2					21	2.36
Group 3		X	X		13	1.46
Group 4			X		0	0.00

LMP2: Last Menstrual Period Date Plus 2 weeks

a: Congenital Cytomegalovirus (CMV), Congenital Herpes Simplex, Congenital rubella, Congenital toxoplasmosis, Congenital varicella, Foetal alcohol syndrome

b: Other maternal factors (none was over 5% missingness): Mother´s age , Diabetes, Obesity, Alcohol abuse prior to LMP2, Alcohol abuse during pregnancy, Substance abuse prior to LMP2, Substance abuse during pregnancy, CMV, Folate deficiency, Gestational diabetes, Herpes simplex virus, Rubella, Toxoplasmosis, Varicella

c: Father´s age, Year of offspring conception

The 4 groups represent 4 subgroups of offspring with the following patterns:

Group 1. Only maternal smoking prior to LMP2 missing

Group 2. No risk factors or confounders missing

Group 3. Maternal smoking prior to LMP2 AND during pregnancy missing

Group 4. Only maternal smoking during pregnancy missing

15.5.3 Norway

Table 282. Missing data patterns; primary outcome in Norway

Group	Offspring risk factors/confounders[a]	Maternal risk factors/confounders[b]		Paternal risk factors/confounders[c]	Freq	Perc
	None of the factors over 5% missingness	Smoking prior LMP2	Smoking during pregnancy	None of the factors over 5% missingness		
Group 1					1488	76.58
Group 2		X	X		239	12.30
Group 3		X			209	10.76
Group 4			X		7	0.36

LMP2: Last Menstrual Period Date Plus 2 weeks

a: Gender, Congenital Cytomegalovirus (CMV), Congenital rubella, Fœtal alcohol syndrome, Fragile X syndrome, Lejeune/cri du chat syndrome, Tuberous sclerosis

b: Other maternal factors (none was over 5% missingness): Mother's age, Affective disorder, Diabetes, Gestational diabetes, Neurotic disorder, Schizophrenia, schizotypal and delusional disorders, Obesity, CMV, Rubella, Alcohol abuse prior to LMP2, Alcohol abuse during pregnancy, Substance abuse prior to LMP2, Substance abuse during pregnancy, Maternal polypharmacy index prior to LMP2, Maternal polypharmacy index during pregnancy, Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 - mothers with at least one prescription, Concomitant medications associated with valproate -indicated psychiatric conditions during pregnancy - mothers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 - mothers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events during pregnancy - mothers with at least one prescription

c: Bipolar affective disorder, Mania, Affective disorder excluding bipolar affective disoreder and mania, neurotic disorder, Schizophrenia, schizotypal and delusional disorders, Substance abuse, Paternal polypharmacy index, Concomitant medications associated with valproate -indicated psychiatric conditions - fathers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events - fathers with at least one prescription, Father's age, Year of offspring conception

The 4 groups represent 4 subgroups of offspring with the following patterns:

Group 1. No risk factors or confounders missing

Group 2. Maternal smoking prior to LMP2 AND during pregnancy missing

Group 3. Only maternal smoking prior to LMP2 missing

Group 4. Only maternal smoking during pregnancy missing

Table 283. Missing data patterns; secondary outcome in Norway

	Offspring risk factors/confounders[a]	Maternal risk factors/confounders[b]		Paternal risk factors/confounders[c]		
Group	None of the factors over 5% missingness	Smoking prior LMP2	Smoking during pregnancy	None of the factors over 5% missingness	Freq	Perc
Group 1					542	76.88
Group 2		X	X		88	12.48
Group 3		X			73	10.35
Group 4			X		2	0.28

LMP2: Last Menstrual Period Date Plus 2 weeks
a: Congenital Cytomegalovirus (CMV), Congenital Herpes Simplex, Congenital rubella, Congenital toxoplasmosis, Congenital varicella, Foetal alcohol syndrome

b: Other maternal factors (none was over 5% missingness): Mother's age, Diabetes, Obesity, Alcohol abuse prior to LMP2, Alcohol abuse during pregnancy, Substance abuse prior to LMP2, Substance abuse during pregnancy, CMV, Folate deficiency, Gestational diabetes, Herpes simplex virus, Rubella, Toxoplasmosis, Varicella

c:Father's age, Year of offspring conception

The 4 groups represent 4 subgroups of offspring with the following patterns:

Group 1. No risk factors or confounders missing

Group 2. Maternal smoking prior to LMP2 AND during pregnancy missing

Group 3. Only maternal smoking prior to LMP2 missing

Group 4. Only maternal smoking during pregnancy missing

Signature: [redacted]
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