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

Date: 02 October 2023

Addendum v2.0 to VALNAC09345 Final Study Report V1.1

Prepared For:

Valproate marketing authorisation holders being part of study consortium.

Addendum to the Final Study Report Approval and Sign-off

I confirm that I have read the contents of this Addendum to the final report V1.1

Statistician	[redacted]		
	Print name here	Signature	Date
Epidemiologist	[redacted]		
	Print name here	Signature	Date
Principal Investigator	Florent Rich y		
	Print name here	Signature	Date

POST-AUTHORISATION SAFETY STUDY (PASS)

Addendum to the Final Study Report

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
Date of last version of the final study report	27 March 2023 (submission date)
EU PAS/ENCePP register number	EUPAS34201
Active substance	Antiepileptic drugs (AEDs) including valproate Anatomical Therapeutic Chemical (ATC) (World Health Organisation) WHO code: N03A
Medicinal product	AEDs including valproate
Product reference	EMEA/H/A-31/1454
Procedure number	NA
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 CONSILIENT HEALTH LIMITED; CRESCENT PHARMA LIMITED; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG; LUPIN HEALTHCARE LIMITED; VIATRIS GX BV/SRL: BE; VIATRIS SANTE (LYON): FR; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; 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 (composite monotherapy) treatment at the time of conception from data in Denmark, Sweden and Norway. **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 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, 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/levetiracetam, 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 (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 (composite monotherapy) at the time of conception.
Country(-ies) of study	The study was conducted in Denmark, Sweden, and Norway.
Authors	[redacted] On behalf of IQVIA and the Consortium

This study was conducted in accordance with all relevant regulatory requirements, including, where applicable, the Declaration of Helsinki (and its amendments), the guideline on good pharmacovigilance practices (GVP) Module VIII – post-authorisation safety studies, and the guidelines for good pharmacoepidemiology practice (GPP) (ISPE).

1. MARKETING AUTHORISATION HOLDER(S)

Marketing authorisation holder(s)	APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA LIMITED; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG; LUPIN HEALTHCARE LIMITED; VIATRIS GX BV/SRL: BE; VIATRIS SANTE (LYON): FR; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; SANOFI AVENTIS GROUP; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROP and; WOCKHARDT UK LIMITED
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2. ABSTRACT

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
Keywords	Valproate; paternal exposure; autism; congenital malformations; post-authorisation safety study
Rationale and background	Valproate-containing medicines are used for epilepsy and bipolar disorders, but due to increased risks of neurodevelopmental disorders (NDD) and congenital malformations (CM) in offspring after valproate exposure during pregnancy, its use has been restricted to cases with no other alternative treatment 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 autism spectrum disorder (ASD), or CM in offspring following paternal exposure to antiepileptic drugs (AEDs) at the time of conception. Following the Pharmacovigilance Risk Assessment Committee (PRAC) request dated 08 February 2018, a post-authorisation safety study (PASS) 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. **This PASS was conducted from 3 Nordic countries registries: Sweden, Denmark and Norway.** Due to identified data outages in the Norwegian dataset, the findings in this updated addendum supersede those reported in the previous submitted addendum v1.0. Briefly, the original study period in Norway began in 2006. However, due to the fact that the Norwegian Patient Registry, which provided diagnostic codes, can be linked to other registries only from 2008, a revised study period starting in 2010 was used instead. This decision was made to ensure a 24-month lookback period for the study variables,

	particularly for fathers. Specifically, only pregnancies that ended in 2010 and onward were considered, to ensure an adequate and sufficient lookback period for the study variables. Hence, the analysis of Norwegian data has been rerun. For this reason, the meta-analysis, reported in the final study report v1.1, updated in the corrigendum v1.0, and summarized below, has also been rerun and the results updated accordingly. In this study, after pooling the propensity score (PS) weighted adjusted hazard ratio (HR) from Denmark (HR: 1.34, 95% confidence interval [CI]: 0.79, 2.25), Sweden (HR: 1.54, 95% CI: 0.95, 2.51), and Norway (HR: 1.76, 95% CI: 0.83, 3.71), a significantly higher risk of NDD, including ASD, was observed among offspring from fathers exposed to valproate when compared to lamotrigine/levetiracetam group (HR: 1.50, 95% CI: 1.09, 2.07). Besides the main analyses, several sensitivity analyses were performed, to assess the robustness and allow a better understanding of the results. Some analyses (namely sensitivity analyses 2 in Denmark and in Norway, and exploratory analysis 8) were not presented in the final study report. In the present addendum, we report and discuss the results for **sensitivity analysis 2**, which focused on ASD ignoring all other NDD diagnoses, and **exploratory analysis 8**, where the spectrum of CM sub-types by organ class was described, with stratification as major or minor CM whenever it was feasible. Sensitivity analysis 2 was performed in Denmark, Sweden, and Norway. Exploratory analysis 8 was performed in Denmark and Norway.
Research question and objectives	***Sensitivity analysis 2*** To investigate the risk of ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment (composite monotherapy) in the 3 months lookback from last menstrual period date plus 2 weeks (LMP2).

	Exploratory analysis 8 To describe the spectrum of CM sub-types by target organ class, with stratification as major or minor CM where feasible, in live and non-live offspring paternally exposed to valproate (monotherapy), and to lamotrigine/levetiracetam treatment (composite monotherapy).
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 to investigate the risk of NDD, including ASD, as the primary outcome of interest and the risk of CM (as composite of major and/or minor CM) as secondary outcome.
Setting	The study period began on 01 January 1997 (01 April 2004 for the secondary outcome) in Denmark, 01 January 2007 in Sweden and 01 January 2010 in Norway, based on the availability of information from national registries. The study time period ended on 31 December 2018 for Denmark and 31 December 2019 for Sweden and Norway.
Subjects and study size	The study population comprised live births, stillbirths and spontaneous abortions for whom medical record linkage to mother and father was known within the registries. The population for analysing ASD (sensitivity analysis 2) was limited to live births with available medical record linkage to both mother and father. The population for analysing CM (exploratory analysis 8) included live births, stillbirths, and spontaneous abortions[1] during the 2nd and 3rd trimesters of gestation with available medical record linkage to both parents.

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

	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%. To observe a HR of 2.0 (ie, doubling of risk in offspring paternally exposed to valproate) with 5% significance and 80% power, a sample size of 3,253 children within the family linked unit would be needed across all 3 countries. This requires a minimum of 1,627 offspring within a family linked unit with paternal exposure to valproate (monotherapy), and a minimum of 1,627 offspring within a family linked unit with paternal exposure to lamotrigine/levetiracetam (composite monotherapy).
Variables and data sources	The primary outcome of interest in the main analyses (presented in the main report, not in this addendum) 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. For sensitivity analysis 2, the outcome of interest was specifically ASD diagnosis (ever, not only as 1st NDD diagnosis) and for exploratory 8, spectrum of CM sub-types by organ class were described. 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, 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.
Results	**Sensitivity analysis 2** • *Characteristics of the cohorts for ASD*

	A total of 1,948 offspring in Denmark, 2,354 in Sweden, and 1,416 in Norway were included for descriptive analysis. ASD was observed in 1.4%, 2.0%, and 1.0% of offspring paternally exposed to valproate, and in 1.8%, 0.8% and 0.4% of offspring paternally exposed to lamotrigine/levetiracetam, respectively in Denmark, Sweden and Norway. With regard to maternal characteristics, the most frequent maternal comorbidities diagnosed prior to childbirth were neurotic disorders (6.5% in Denmark [5.6% in the valproate group vs. 7.2% in the lamotrigine/levetiracetam group], 11.0% in Sweden [9.1% vs. 12.2% in respective groups], and 13.2% in Norway [12.6% vs. 13.4% in respective groups]), affective disorder (3.8% in Denmark [2.4% vs. 4.8% respectively], 9.0% in Sweden [8.4% vs. 9.4% respectively], and 8.9% in Norway [5.8% vs. 10.1% respectively]), and gestational diabetes (3.8% in Denmark [3.5% vs. 4.0% respectively], 3.0% in Sweden [2.5% vs. 3.3% respectively], and 6.1% in Norway [5.0% vs. 6.6% respectively]). Maternal smoking during pregnancy was recorded for 16.0% of mothers in Denmark (16.6% vs. 15.7% respectively), for 6.2% of mothers in Sweden (7.6% vs. 5.2% respectively), and for 4.9% of mothers in Norway (6.8% vs. 4.2% respectively). The proportion of maternal concomitant medications during pregnancy associated with neuropsychiatric adverse events was high in all countries: 43.9% in Denmark (38.3% vs. 47.7% respectively), 44.6% in Sweden (42.2% vs. 46.2% respectively), and 42.5% in Norway (40.8% vs. 43.2% respectively). With regard to paternal characteristics, the most frequent paternal comorbidities diagnosed prior to childbirth in Denmark, Sweden, and Norway were neurotic disorders (9.1% in Denmark [6.1% in the valproate group vs. 11.2% in the lamotrigine/levetiracetam group], 21.9% in Sweden [13.7% vs. 27.3% in respective groups], and 13.2% in Norway [7.6% vs. 15.4% respectively]) and affective disorder excluding bipolar disorder and mania (9.2% in Denmark [3.8% vs. 13.0% respectively], 22.5% in Sweden

	[11.2% vs. 29.9% respectively], and 18.2% in Norway [7.8% vs. 22.3% respectively]). In the 3 countries, the most common indication for AEDs was epilepsy, both among fathers exposed to valproate (70% in Denmark; 70.7% in Sweden; 57.9% in Norway) and lamotrigine/levetiracetam (59.0% in Denmark; 46.1% in Sweden; 41.0% in Norway). In the 3 countries, a higher proportions of offspring paternally exposed to valproate were conceived in the earlier years of the study inclusion, in contrast to the lamotrigine/levetiracetam group where the highest proportions were observed in the more recent years of study inclusion, leading to quite longer follow-up periods among offspring paternally exposed to valproate compared to those paternally exposed to lamotrigine/levetiracetam in Denmark and Sweden: mean follow-up periods were 9.5 and 6.7 years in the respective groups in Denmark, 6.8 and 5.1 years in Sweden). In Norway, though, the follow-up period was quite similar in both groups (5.0 years vs. 4.8 years, respectively). *Effect estimation for ASD* In Denmark, in the PS-weighted Cox regression model, an adjusted HR of 0.76 (95% CI: 0.30, 1.89) for ASD was observed in the offspring of fathers exposed to valproate compared to offspring of fathers exposed to lamotrigine/levetiracetam. Maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy remained imbalanced after the inverse probability of treatment weights (IPTW). Therefore, this variable was further adjusted in the PS-weighted Cox regression and remained significantly associated with the risk of ASD (HR: 10.04, 95% CI: 4.04, 24.97). In Sweden, a higher risk of ASD was observed in offspring from fathers exposed to valproate when compared to offspring from fathers exposed lamotrigine/levetiracetam group: PS-weighted adjusted HR of 2.70, (95% CI: 1.19, 6.17). In Norway, the PS-weighted adjusted HR could not be produced due to the low number of ASD events (<10).

	Exploratory analysis 8 In Denmark, a total of 111 CM were observed, 34 (24 major, 10 minor) and 77 (61 major, 16 minor) in the valproate and the lamotrigine levetiracetam groups respectively. The most frequent CM diagnoses were in limbs in offspring paternally exposed to valproate (17.7%), whereas in offspring paternally exposed to lamotrigine/levetiracetam the most frequent CM diagnoses were congenital heart defects (26.0%). In Norway, a total of 105 CM were observed, 40 (25 major, 15 minor) and 65 (31 major, 34 minor) in the valproate and the lamotrigine levetiracetam groups respectively. CM in digestive system was the most frequently reported target body organ class, with the proportion of most of the CM diagnoses being similar in offspring paternally exposed to valproate (32.5%) and those paternally exposed to lamotrigine/levetiracetam (30.8%). The second most common target body system organ class for CM was the limb, with 25.0% of the CM events in the valproate group, and 24.6% in the lamotrigine/levetiracetam group.
Discussion	The present addendum reports the results of sensitivity analysis 2 and exploratory analysis 8 of the PASS paternal exposure to valproate. In sensitivity analysis 2, the results regarding risk of ASD in offspring paternally exposed to valproate compared to lamotrigine/levetiracetam were not similar to that observed for NDD including ASD (ie, the primary analysis) in Denmark and Sweden. The adjusted HR for ASD from the PS-weighted Cox model were 0.76 (95% CI: 0.30, 1.89) in Denmark, 2.70 (95% CI: 1.19, 6.17) in Sweden. In Norway, it was not possible to provide PS-weighted adjusted HR due to the low number of ASD events (<10). Nevertheless, for Denmark and Sweden, the estimated relative risks for ASD were subject to lower precision, as shown by the wider CI when compared to the main analysis. One of the main limitations was the difference in the length of follow-up between countries, with Danish and Swedish data having the highest and lowest mean length of follow-up, respectively. There were also differences in the length of follow-up within each country between the 2 compared groups in these 2 countries. The low number of ASD outcomes in both exposure groups may have

	led to instability in the estimation of HR and made the risk comparison less reliable. Furthermore, the study did not consider family history of ASD or paternal behaviors, which may have an impact on the risk of ASD in offspring. Lastly, the degree to which confounding was controlled differed across the countries, and the Danish results were potentially affected by the presence of confounders. Exploratory analysis 8 described the spectrum of CM sub-types by target body system organ class with stratification as major or minor in offspring paternally exposed to either valproate or lamotrigine/levetiracetam in Denmark and Norway. The results showed that the most frequent target body system organ classes affected by CM were digestive system, limb, congenital heart defects, and genital in both Denmark and Norway. Additionally, most of the CM reported were considered major. In Denmark, limb and congenital heart defects were the most frequent CM diagnoses in valproate and lamotrigine/levetiracetam exposure groups, respectively. In Norway, digestive system was the most frequent target body organ class, and the proportion of most of the CM diagnoses was similar in both exposure groups. However, 3 exceptions to this similar reporting trend across the 2 exposure groups were observed: genital CMs were almost exclusively reported in offspring paternally exposed to lamotrigine/levetiracetam; chromosomal CM were exclusively reported in offspring paternally exposed to valproate; in Denmark, the number of CM diagnoses for congenital heart defects represented 26.0% of the observed CMs in the lamotrigine/levetiracetam group, but the number was masked (5 or less) in the valproate group, which prevented drawing any conclusions.
Conclusion	The sensitivity analysis 2 and exploratory analysis 8 were conducted to examine the risk of ASD and the frequency of CM by body organ class in offspring paternally exposed to valproate compared to lamotrigine/levetiracetam in Norway, Denmark, and Sweden. Due to the low number of ASD events (<10), it was not possible to produce an estimate for the risk of ASD in Norway. In Denmark and Sweden, the risk of ASD, from the multivariate

	analysis, was found not to be similar to the primary analysis (risk of NDD), with a significant increase in the risk of ASD observed in offspring paternally exposed to valproate in Sweden. The most frequent target body system organ classes affected by CM were digestive system, limb, congenital heart defect, and genital in both countries, and most of the CM reported were considered major. Overall, due to methodological limitations, and low frequency of events that could affect the reliability and accuracy of the results, these findings should be interpreted with caution.
Marketing authorization holder (MAH)	APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA LIMITED; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG; LUPIN HEALTHCARE LIMITED*; VIATRIS GX BV/SRL: BE; VIATRIS SANTE (LYON): FR;* NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; SANOFI AVENTIS GROUP; STADA ARZNEIMITTEL AG; TECNIFAR S.A.; TEVA PHARMACEUTICALS EUROPE and; WOCKHARDT UK LIMITED
Name(s) and affiliation(s) of principal investigator(s)	Florent Richy, PhD, MPH Director, Global Epidemiology IQVIA [redacted]

3. LIST OF ABBREVIATIONS

AED	Antiepileptic Drug
ASD	Autism Spectrum Disorders
CI	Confidence Interval
CM	Congenital Malformations
DDD	Defined Daily Dose
EU	European Union
HR	Hazard Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IPTW	Inverse Probability of Treatment Weights
IQR	Interquartile Range
LMP2	Last Menstrual Period Date Plus 2 weeks
MAH	Marketing Authorization Holder
NA	Not Applicable
NDD	Neurodevelopmental Disorders
OR	Odds ratio
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity Score
PY	Person Years
RMST	Restricted Mean Survival Analysis
SSRI	Selective Serotonin Reuptake Inhibitors

4. INVESTIGATORS

Principal Investigator: Florent Richy Director, Global Epidemiology, IQVIA

5. OTHER RESPONSIBLE PARTIES

This study was performed by IQVIA, a contract research organisation (CRO), with guidance, input, review, and approval of Valproate European Union (EU) consortium.

Project Manager: [redacted]

Epidemiological Oversight: [redacted]

Biostatistical Oversight: [redacted]

External Medical and Methods Advisers: [redacted]

6. MILESTONES

Not applicable (NA)

7. RATIONALE AND BACKGROUND

Please, see Section 6 in the final study report v1.1.

8. 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 neurodevelopmental disorders (NDD), including autism spectrum disorder (ASD), as well as congenital malformations (CM) in offspring. Paternal exposure to valproate was compared to paternal exposure to lamotrigine/levetiracetam, which was considered a safer treatment (1–4). In women, these drugs were generally associated with lower risk of teratogenicity, CM and neurodevelopmental disorder including ASD, for their offspring exposed during pregnancy compared to valproate, but it is unknown whether the effect is the same in fathers.

In the present addendum, we report and discuss the results for sensitivity analysis 2, which focused on ASD, and exploratory analysis 8, where the spectrum of CM sub-types by organ class was described, with stratification as major or minor CM whenever it was feasible. Sensitivity analysis 2

was performed in Denmark, Sweden, and Norway. Exploratory analysis 8 was performed in Denmark and Norway but not in Sweden since data on non-live offspring was not available.

On 19 January 2023 and 27 March 2023, the marketing authorization holders (MAHs) submitted a final study report to the Pharmacovigilance Risk Assessment Committee (PRAC) (please see final study report v1.0 and v1.1) as part of the post-authorization safety study (PASS) to evaluate the paternal exposure to valproate and the risk of NDD including ASD, as well as CM, in offspring. The original submission included a description of the study methodology, statistical data analysis, findings, discussion, and interpretation. In a subsequent investigation, the MAHs identified the presence of unforeseen outages in the Norwegian data, which compromised the reliability and accuracy of the initial findings:

- the diagnostic codes from the Norwegian Patient Registry were only available from 2008 onward, as explained in more detail in Section 2 Erratum and 2.1. Norway Summary of the corrigendum to the final study report v1.1, the analysis of Norway's data has been completely rerun using an updated study period starting in 2010. Specifically, only pregnancies that ended in 2010 have been considered, ensuring an adequate and sufficient lookback period of 24 months for the study variables.

The MAHs acknowledge the importance of maintaining the highest standards of scientific integrity, and presenting reliable correct results, which are essential to decision making for patients' safety. For that reason, every step of the research process has been meticulously re-examined, the data collection protocols reassessed, the analytical techniques refined, and stringent quality control measures applied to properly evaluate and mitigate the impact of the identified outages. Through this meticulous approach, the MAHs aimed to provide a more reliable and refined representation of the findings to address the significant limitations and biases arising from the identified outages in Norway. Therefore, in the present updated addendum, only the results for Norway supersede those reported in the previous submitted addendum v1.0.

The complete description of the study objectives is available in the final study report v1.1 (please see Section 7).

9. AMENDMENTS AND UPDATES

NA

10. RESEARCH METHODS

10.1 Study Design

Please see Section 9.1 in the final study report v1.1.

10.2 Setting

Please see Section 9.2.1 in the study protocol v7.0 and Section 2 in the corrigendum v1.0 to the final study report v1.1.

10.3 Subjects

10.3.1 Inclusion Criteria

Please see Section 9.3.1 in the final study report v1.1.

10.3.2 Exclusion Criteria

Please see Section 9.3.1 in the final study report v1.1.

10.4 Variables

10.4.1 Exposure Definition and Measures

Please see Section 9.4.1 in the final study report v1.1.

10.4.2 Outcome Definition and Measures

During the observation period, which spanned from the index date to the exit date for each offspring, outcome events were identified based on International Statistical Classification of Diseases and Related Health Problems 10th Revision (ICD-10) codes recorded in-patient registries.

ASD

The **index date** was defined as the birth date of the offspring from which offspring were observed for occurrence of the outcome of interest[2].

The **exit date/end of follow-up** was defined as the end of the study period (31 December 2018 in Denmark and 31 December 2019 in Sweden and Norway), death, emigration (where available), reaching the age of

[2] 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

12 years for Denmark and Sweden and the age of 10 years for Norway, or date of first diagnosis of ASD, whichever was the soonest.

ASD was defined as a diagnosis of at least one ICD-10 code reported in the categories below:

- F84.0 Childhood autism
- F84.1 Atypical autism
- F84.2 Rett's syndrome
- F84.3 Other childhood disintegrative disorder
- F84.5 Asperger syndrome
- F84.8 Other pervasive developmental disorders
- F84.9 Pervasive developmental disorder, unspecified

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 (5). However, a sensitivity analysis (sensitivity analysis 4) was performed in Denmark and Norway, to address this concern.

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 (31 December 2018 for Denmark and 31 December 2019 for Norway), death, emigration (where available), reaching the age of 12 years for Denmark and the age of 10 years for Norway, 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)

The diagnoses include, but are not limited to:

- Q00-07 Congenital malformations of the nervous system
- Q10-18 Congenital malformations of eye, ear, face and neck
- Q20-28 Congenital malformations of the circulatory system
- Q30-34 Congenital malformations of the respiratory system
- Q35-37 Cleft lip and cleft palate
- Q38-45 Other congenital malformations of the digestive system
- Q50-56 Congenital malformations of genital organs
- Q60-64 Congenital malformations of the urinary system
- Q65-79 Congenital malformations and deformations of the musculoskeletal system
- Q80-89 Other congenital malformations
- Q90-99 Chromosomal abnormalities, not elsewhere classified

10.4.3 Case Assessment

NA in sensitivity analysis 2 nor in exploratory analysis 8.

10.4.4 Potential Confounders/Risk Factors

Please see Section 9.4.4 in the final study report v1.1.

10.5 Data Sources and Measurement

Please see Section 9.5 in the final study report v1.1.

10.6 Bias

Please see Section 9.6 in the final study report v1.1.

10.7 Study Size

Please see Section 9.7 in the final study report v1.1.

Complete details can be found in the Study Protocol v6.0.

10.8 Data Transformation

Please see Section 9.8 in the final study report v1.1.

10.9 Statistical Methods

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

All statistical tests used a 0.05 significance level and are double-sided. All analyses for this addendum report were conducted and presented separately for Denmark, Sweden and Norway.

Please see Section 9.9 in the final study report v1.1.

10.9.1 Main Summary Measures

For more details please see Section 9.9.1 of the final study report v1.1.

10.9.2 Main Statistical Measures

Please see Section 9.9.2 of the final study report v1.1.

10.9.3 Missing Values

Regression models for sensitivity analysis 2 were estimated on complete cases only, and the number of cases included in each analysis was reported. Missing values were not imputed.

Please see Section 9.9.3 of the final study report v1.1.

10.9.4 Sensitivity Analyses

Please see Section 9.9.4 of the final study report v1.1.

10.9.4.1 Sensitivity analysis 2 – Focus on ASD

A sensitivity analysis was conducted to assess the risk of ASD in offspring paternally exposed to valproate compared to lamotrigine/levetiracetam (composite monotherapy) treatment in the 3 months lookback from last menstrual period date plus 2 weeks (LMP2). The population used in this analysis was the Primary Outcome Cohort for Comparative Analyses (please see Section 9.3.1.1.2 in the final report v1.1); however, due to the change in the outcome definition (and subsequently exit date for offspring experiencing this specific ASD outcome), additional offspring were excluded when applying the following post data extraction exclusion criteria: offspring maternally exposed to antiepileptic drugs (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, and offspring exposed to AEDs and/ or diagnosed with epilepsy after birth.

In this analysis, events for NDD other than ASD were ignored; instead, only diagnoses for ASD were considered as events of interest (both in the descriptive analyses as well as in the comparative ones); offspring not experiencing ASD were followed up until the earliest of 12 years of age in Denmark and Sweden, 10 years of age in Norway, end of study time period, death or emigration.

The cohort characteristics, incidence, univariate and multivariate analyses were repeated on this population. Propensity score (PS) estimation and weighting were repeated since this analysis focused on ASD alone as the outcome. The approach outlined in main study report was followed for the PS estimation and weighting. Multivariate analyses followed the approach described in the main report; however, the definition of the outcome was different since only ASD offspring were considered to have experienced the outcome of interest.

For sensitivity analysis 2 the effect of paternal exposure to valproate (compared with lamotrigine/levetiracetam) on ASD was evaluated through multivariate Cox proportional hazard models. Propensity score weighted Cox regression models were estimated. The adjusted hazard ratio (HR) (with 95% confidence interval [CI]) of ASD in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam were presented.

10.9.5 Exploratory Analyses

10.9.5.1 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 it was feasible. The number and percentage of CM cases by sub-type were presented, overall and by paternal exposure group (valproate, levetiracetam/lamotrigine composite monotherapy and separately).

The population used in this analysis was the secondary outcome cohort for Explorative Objective 8.

Post data extraction exclusion criteria were applied to the secondary outcome cohort (please see Section 9.3.1.2 in the final study report v1.1) as follows: offspring not experiencing the secondary outcome (CM) during their follow-up, offspring paternally unexposed to AEDs in the 3-months lookback from LMP2, offspring paternally exposed to AEDs 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, offspring maternally exposed to AEDs (including valproate, lamotrigine and levetiracetam) in utero, or during 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, offspring paternally exposed (3-months lookback from LMP2) to drugs with known teratogenic activity, as based on literature for maternal exposure.

Only offspring experiencing the secondary outcome were included in this analysis; for these offspring, the number and percentage of each CM sub-type was presented. All records of minor and major CM during the entire follow-up were considered, including multiple different records for the same offspring. In this analysis, the percentage of each CM sub-type was calculated over the total number of CM diagnoses detected among offspring included in the population.

10.9.6 Amendments to the Statistical Analysis Plan

NA

10.10 Quality Control

NA

11. RESULTS

In this updated addendum v2.0 to the updated final study report version 1.1, we present only the results related to ASD as outcome for sensitivity analysis 2 in Denmark, Sweden, and Norway, and to the secondary outcome (CM) for Denmark and Norway (see Box 1, summary of analysis). **Only the results for Norway supersede those reported in the previous submitted addendum v1.0.** Furthermore, minor editorial changes have been implemented throughout the document to ensure alignment of table legends in both Denmark and Sweden, and correction of formatting issues including cross-references and typographical errors.

Note that for Sweden, the analyses relevant to the secondary outcome, CMs, are not presented, since data on non-live offspring was not available, precluding the creation of the secondary outcome cohort.

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

	Denmark		Sweden		Norway	
Analysis description	ASD	CM	ASD	CM	ASD	CM
Sensitivity analysis 2	X	NA	X	NA	X	NA
Exploratory analysis 8	NA	X	NA	NA	NA	X

ASD: autism spectrum disorder cohort; CM: congenital malformation cohort; NA: not applicable; "X" indicates the analysis was performed and is presented in this addendum; NA: not applicable.

11.1 Sensitivity Analysis 2 - Focus on ASD as Outcome

Table 1 shows the summary of the main results for ASD as outcome, by country. The overall cumulative incidence proportion (0-12 years of follow-up for Denmark and Sweden; 0-10 years of follow-up for Norway), overall incidence rate of ASD (0-12 years of follow-up for Denmark and Sweden; 0-10 years of follow-up for Norway), and adjusted Cox regression models in Denmark and Sweden are presented. Due to the low event count (<10) in Denmark and Sweden, it was not possible to provide crude Cox regression models. Likewise, in Norway, it was not possible to provide the crude and adjusted Cox regression models due to the low event count (<10). Please see Section 10.9.4 for further details.

Table 1 Summary results by country for ASD

Summary of results of Autism Spectrum Disorders (ASD) as outcome	Denmark	Sweden	Norway
Overall Cumulative incidence proportion of ASD (0-12 years DK and SE; 0-10 years NO)			
N (Overall)	1948	2354	1416
n	32	31	8
Overall population	1.65 (1.08, 2.21)	1.32 (0.86, 1.78)	0.56 (0.17, 0.96)
N (Valproate)	791	930	397
n	11	19	4
Valproate	1.39 (0.57, 2.21)	2.04 (1.13, 2.95)	1.01 (0.03, 1.99)
N (Lamotrigine/levetiracetam)	1157	1424	1019
n	21	12	4
Lamotrigine/levetiracetam	1.82 (1.05, 2.58)	0.84 (0.37, 1.32)	0.39 (0.01, 0.78)
Overall Cumulative incidence rate of ASD (0-12 years DK and SE; 0-10 years NO)			
n	32	31	8
Overall population	2.11 (1.44, 2.98)	2.3 (1.56, 3.26)	1.16 (0.50, 2.28)
n (Valproate)	11	19	4
Valproate	1.47 (0.73, 2.63)	3.01 (1.81, 4.70)	2.00 (0.55, 5.13)
n (Lamotrigine/levetiracetam)	21	12	4
Lamotrigine/levetiracetam	2.72 (1.69, 4.16)	1.67 (0.86, 2.92)	0.81 (0.22, 2.08)
Adjusted Cox regression model			
N (Valproate)	671	848	NA
n	9	19	NA
Valproate – HR (95% CI)	0.76 (0.30, 1.89)	2.70 (1.19, 6.17)	—
N (Lamotrigine/levetiracetam)	1115	1334	NA
n	17	9	NA
Lamotrigine/levetiracetam	Ref	Ref	—

ASD: Autism Spectrum Disorders; CI: confidence interval; HR: hazard ratio; N: number of offspring in the considered subgroup; n: number of ASD in the considered subgroup; Ref: Reference; NA: Not applicable; DK: Denmark; SE: Sweden; NO: Norway.

11.1.1 Denmark

The study population for sensitivity analysis 2 in Denmark included 1,948 offspring, of whom 791 were paternally exposed to valproate and 1,157 were paternally exposed to lamotrigine/levetiracetam.

Table 2, showing the results of the effect estimation for ASD, is provided in Section 11.1.1.7; all the other tables are presented in Appendix (Section 16.1.1).

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

Overall, the majority of offspring were male (52.2%), born at term between 37-41 weeks of gestational age (89.7%) and weighing ≥2,500g (96.6%). The total offspring-years of follow-up was 15,181.4 (7,473.0 for valproate and 7,708.4 for lamotrigine/levetiracetam group) and the mean follow-up in years per offspring was 9.5 for the valproate group and 6.7 for the lamotrigine/levetiracetam group (Table 6). The highest proportions of offspring paternally exposed to valproate were born in the earlier years (from 2001 to 2006)

of the study period, in contrast to the lamotrigine/levetiracetam group where the highest proportions were observed in the more recent years (from 2009 to 2016) of the study period.

Any ASD diagnosis, (ie, ever and not only as a first NDD diagnosis), outcome of interest of this sensitivity analysis, were observed in 1.4% of offspring paternally exposed to valproate and in 1.8% of offspring paternally exposed to lamotrigine/levetiracetam (Table 7).

ASD as the first NDD diagnosis, was observed in 1.4% of offspring paternally exposed to valproate and in 1.4% of offspring paternally exposed to lamotrigine/levetiracetam (Table 7).

Overall, the median (Interquartile Range [IQR]) age of mothers for sensitivity analysis 2 at childbirth was 30 (27, 34) years (Table 8). The most prevalent maternal clinical characteristics prior to childbirth were neurotic disorder observed in 5.6% and 7.2% of mothers of offspring paternally exposed to valproate and lamotrigine/levetiracetam, gestational diabetes observed in 3.5% and 4.0%, and affective disorder observed in 2.4% and in 4.8% of mothers, respectively (Table 9).

Proportion of smoking during pregnancy was approximately 16% in total (16.6% in the valproate group, and 15.6% in the lamotrigine/levetiracetam group). Regarding the concomitant medications associated with neuropsychiatric adverse events prior to LMP2, this was similar among the exposed groups. For the concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy and prior to LMP2, these proportions were lower in the valproate group compared to the lamotrigine/levetiracetam group: respectively 2.6% vs 5.5% during pregnancy and. 5.4% vs 8.4% prior to LMP2 (Table 9).

Regarding paternal demographic characteristics, the overall median (IQR) age of fathers at childbirth was 33 (29, 36.5) years. The highest proportions of offspring paternally exposed to valproate were conceived in the earlier years of the study follow-up, in contrast to the lamotrigine/ levetiracetam group where the highest proportions were observed in the more recent years of study follow-up (Table 10).

Among fathers exposed to valproate, 6.1% presented neurotic disorder, 3.8% affective disorder excluding bipolar disorder and mania, and 2.7% presented bipolar affective disorder. Among fathers exposed to lamotrigine/levetiracetam, proportions were generally higher with 11.2% neurotic disorder, 13% affective disorder excluding bipolar disorder and mania, and 7.3% bipolar affective disorder (Table 11).

The most frequent indication[3] for AED treatment was epilepsy in both groups (69.5% in the valproate group, 59.2% in the lamotrigine/levetiracetam group) (Table 11).

The K-means algorithm, analysing Defined Daily Dose (DDD) trajectories in fathers exposed to AEDs 3 months prior to conception (ie prior to LMP2) identified 2 different clusters A, B, one with constant high exposure (A) and one with constant low exposure (B). In the valproate group, 52.6% were in cluster A, 47.4% were in cluster B. In the lamotrigine/levetiracetam group, 57.5% were in cluster A, 42.5% were in cluster B (Table 11).

11.1.1.2 Cumulative incidence proportion

Crude cumulative incidence proportions (risk) of ASD by paternal exposure group are presented in Table 12-Table 14 stratified by gender. There were 57.0% of offspring paternally exposed to valproate followed up for 12 years versus 20.7% of the offspring paternally exposed to lamotrigine/levetiracetam. The crude cumulative incidence proportions of ASD for 0-12 years of follow-up appeared to be lower in offspring paternally exposed to valproate (1.4, 95% CI: 0.6, 2.2) than in offspring paternally exposed to lamotrigine/levetiracetam (1.8, 95% CI: 1.1, 2.6), although the 95% CI overlapped (Table 38).

Considering the group exposed to valproate, the crude cumulative incidence proportion for 0-12 years of follow-up also appeared to be higher in male offspring (1.5, 95% CI: 0.3, 2.6) than female offspring (1.3, 95% CI: 0.2, 2.5). Due to a small number of cases, result in the lamotrigine/levetiracetam by gender was masked. The reported proportions should be interpreted with caution since these are crude estimates, and no adjustments were made (Table 13-Table 14).

11.1.1.3 Cumulative incidence rate and time to ASD diagnosis

Cumulative incidence rates of ASD by paternal exposure group are presented in Table 15, Table 16, and Table 17, overall and stratified by gender, respectively. Considering the overall study follow-up, a lower incidence rate of ASD was observed among offspring paternally exposed to valproate (1.5, 95% CI: 0.7, 2.6 per 1,000 Person Years [PY]) than among those exposed to lamotrigine/levetiracetam (2.7, 95% CI: 1.7, 4.2 per 1,000 PY), although the 95% CIs for the 2 groups were overlapping. When considering the overall period of follow-up, the cumulative incidence rate in male offspring was higher than in female offspring in the valproate group.

[3] 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".

Regarding time to first diagnosis of ASD, the crude estimate for both exposure groups is presented as Kaplan-Meier curves in Figure 3. 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 possible to estimate the upper bound of the 95% CI. The 5th percentile of the time to ASD was 145.8, 95% CI: 123.5, - months for the lamotrigine/levetiracetam paternal exposure group. It was not possible to estimate for the valproate paternal exposure group due to low number of events.

11.1.1.4 Association between potential risk factors/confounders for ASD and paternal exposure group

Association between potential covariates (risk factors and confounders) for ASD and paternal exposure group was assessed in the cohort for sensitivity analysis 2. Results of the crude associations are shown in Table 20, Table 21, and Table 22.

For the offspring, none of the characteristics considered were associated with paternal exposure (Table 20).

Maternal characteristics (Table 21) that were significantly associated with paternal exposure were:

- Age (p=0.0039), lower mean maternal age in the valproate paternal exposure group
- Affective disorder (p=0.0077), lower percentage in the valproate exposure group
- Maternal polypharmacy index prior to LMP2 (p=0.0002) and during pregnancy (p<0.0001), lower mean index in the valproate paternal exposure group
- Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 (p=0.0134), concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy (p=0.0023), concomitant medications associated with neuropsychiatric adverse events during pregnancy (p<0.0001), lower percentage in the valproate paternal exposure group

Paternal characteristics (Table 22) that were 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), lower 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=0.00017), lower percentage in the valproate exposure group
- Age (p=0.0084), 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.

11.1.1.5 Association between potential risk factors/confounders and ASD

Association between covariates (potential risk factors / confounders) and occurrence of ASD was assessed in the cohort for sensitivity analysis 2. Results of the crude associations are shown in Table 23 to Table 25.

For offspring characteristics, gender (Odds ratios [OR]: 0.30, 95% CI: 0.13, 0.70; p=0.0052) was associated with occurrence of ASD (Table 23); the proportion of events among females was lower than the proportion of events among males.

For maternal characteristics considered as risk factors, affective disorder (OR: 4.96, 95% CI: 1.85, 13.26), schizophrenia, schizotypal and delusional disorders (OR: 12.71, 95% CI: 2.67, 60.49; absolute numbers were masked), substance abuse prior to LMP2 (OR: 30.87, 95% CI: 2.73, 349.47; absolute numbers were masked), smoking during pregnancy (OR: 2.55, 95%: CI 1.18, 5.51; absolute numbers were masked), concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 (OR: 4.51, 95% CI: 1.99, 10.22; numbers were: 8 ASD among the 140 offspring of mother using this concomitant medication *vs* 24 ASD among the 1,808 offspring of mother not using it) and during pregnancy (OR: 7.96, 95% CI: 3.46, 18.29; numbers were: 8 ASD among the 85 offspring of mother using this concomitant medication *vs* 24 ASD among the 1,863 offspring of mother not using it), were significantly associated with the offspring having an ASD event (Table 24).

For paternal characteristics considered as risk factors or confounders (Table 25), the following variables were significant associated with offspring having an ASD event: substance abuse (OR: 10.27 95% CI: 1.20, 87.85), concomitant medications associated with valproate-indicated psychiatric conditions (OR: 2.28, 95% CI: 1.11, 4.64), and year of offspring conception (p=0.0309), offspring conceived in 2002-2007 had a higher odds (OR: 1.62, 95% CI: 0.59, 4.48) of having an ASD event, however after 2008 the odds of having an ASD event was lower compared to the reference category of 1996-2001.

11.1.1.6 Variable estimates from propensity score

Variables found to be associated with the outcome whose OR was >1.1 or <0.9, irrespective of statistical association, were included in the PS models for the analysis of the ASD comparative 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. 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 26), gender of the offspring was not associated with paternal exposure to valproate or lamotrigine/levetiracetam (OR: 1.03, 95% CI: 0.83, 1.29, p=0.7852). Offspring with mothers with concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy (OR: 0.33, 95% CI: 0.12, 0.89, p=0.0285) had lower probability of being in the valproate exposure group. Offspring with fathers with affective disorders (OR: 0.41, 95% CI: 0.21, 0.80, p=0.0089), bipolar affective disorder (OR: 0.08, 95% CI: 0.01, 0.44, p=0.0042), concomitant medications associated with valproate-indicated psychiatric conditions (OR: 0.32, 95% CI: 0.22, 0.45, p<0.0001), and offspring conceived at later years (p<0.0001), had a lower probability of being in the valproate exposure group.

The PS model that best achieved a balance in the weighted exposure groups after using inverse probability of treatment weights (IPTW) was the PS model estimated from logistic regression. Table 27 shows the balance results obtained after using this regression model. Thus, the logistic regression model was used to apply IPTW in the effect estimation analysis (presented in Section 11.1.1.7).

11.1.1.7 Effect estimation for ASD

The effect estimation for ASD using a PS-weighted Cox regression model was assessed in a total of 1,786 offspring (671 in the valproate group and 1,115 in the lamotrigine/levetiracetam group).

Maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy remained imbalanced after the IPTW. Therefore, this variable was further adjusted in the PS-weighted Cox regression. Other covariates remained imbalanced after IPTW (Table 27) but could not be added in the model due to small number of events.

In the PS-weighted Cox regression model, an HR of 0.76 (95% CI: 0.30, 1.89) for ASD was observed in offspring of fathers exposed to valproate compared to offspring of fathers exposed to lamotrigine/levetiracetam (Table 2). In the PS-weighted Cox regression model, valproate-indicated psychiatric conditions during pregnancy remained significantly associated with the risk of ASD (HR of 10.04, 95% CI: 4.04, 24.97).

Table 2 Effect estimation for ASD using PS-weighted Cox model (PS scores obtained using logistic regression); ASD as the outcome for sensitivity analysis 2

Variable	Total (N)	Number of events (N)	Model estimates		
			HR	95% CI	P-value
Valproate	671	9			
Lamotrigine/levetiracetam	1115	17			
Paternal exposure: valproate vs lamotrigine/levetiracetam	1786	26	0.76	(0.30, 1.89)	0.5509
Maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy - mothers with at least one prescription	-		10.04	(4.04, 24.97)	<.0001

ASD: autism spectrum disorders; CI: confidence interval; HR: hazard ratio; PS: propensity score, LMP2: last menstrual period date plus 2 weeks.

The model was weighted for the following variables included in the PS model: Offspring risk factors/confounders: Gender (Male/Female); Maternal risk factors/confounders: Affective disorder, Gestational diabetes, Neurotic disorder, Obesity, Substance abuse prior to LMP2, Smoking during pregnancy (No/Yes), 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. Concomitant medications associated with valproate-indicated psychiatric conditions (fathers with at least one prescription), and year of offspring conception (see Table 26).

11.1.2 Sweden

The study population of sensitivity analysis 2 consisted of 2,354 offspring, of whom 930 were paternally exposed to valproate, and 1,424 were paternally exposed to lamotrigine/levetiracetam.

Table 3, showing the results of the effect estimation for ASD, is provided in Section 11.1.2.7; all the other tables are presented in Appendix (Section 16.1.2).

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

Overall, the majority of offspring were male (51.2%), born at term between 37-41 weeks of gestational age (88.8%) and weighing ≥2,500 g (96.6%). The total offspring-years of follow-up was 13,500.1 (6,311.6 for valproate and 7,188.5 for lamotrigine/levetiracetam group) and the mean follow-up in years per offspring was 6.8 for the valproate group and 5.1 for the lamotrigine/levetiracetam group (Table 32). The proportions of offspring paternally exposed to valproate born per year oscillated between 7% and 10% over the period 2007 and 2017, before declining to 5% in 2018 and 2019. In contrast, in the lamotrigine/levetiracetam group the lowest proportions of offspring born per year were observed at the beginning of the study period between 2007 (2.7%) and 2010 (5.4%), to increase then over the period 2011 (7%) and 2019 (13%).

Regarding clinical characteristics of offspring, the diagnosis of NDD including ASD, occurred in 5.3% of offspring paternally exposed to valproate and 2.8% of offspring paternally exposed to lamotrigine/levetiracetam (Table 33)

Any ASD diagnosis (ie, ever and not only as a first NDD diagnosis), outcome of interest of this sensitivity analysis, was observed in 2.0% of offspring paternally exposed to valproate and in 0.8% of offspring paternally exposed to lamotrigine/levetiracetam.

ASD as the first NDD diagnosis, during the full study period, was observed in 1.6% of offspring paternally exposed to valproate and in 0.6% of offspring paternally exposed to lamotrigine/levetiracetam.

Overall, the median (IQR) age of mothers at childbirth was 31 (27, 35) years (Table 34). The most prevalent maternal clinical characteristics prior to childbirth were neurotic disorder observed in 9.1% and 12.2% of mothers of offspring paternally exposed to valproate and lamotrigine/levetiracetam, affective disorder observed in 8.4% and in 9.4% of mothers, and gestational diabetes observed in 2.5% and 3.3%, respectively (Table 35).

Overall, 13.9% had a record of smoking in the 3 months before LMP2 (16.2% in the valproate group, and 12.4% in the lamotrigine/levetiracetam group) and 6.2% of smoking during pregnancy (7.6% in the valproate group, and 5.2% in the lamotrigine/levetiracetam group).

Regarding the concomitant medications associated with neuropsychiatric adverse events during pregnancy and during the period prior to LMP2, this was similar among the exposed groups: respectively 42.2% and 61.4% of mothers of offspring paternally exposed to valproate, and respectively 46.2% and 61.1% of mothers of offspring paternally exposed to lamotrigine/levetiracetam had at least one prescription (Table 35).

Regarding paternal demographic characteristics, the overall median (IQR) age of fathers at childbirth was 34 (30, 38) years. The proportions of offspring paternally exposed to valproate conceived per year oscillated between 7% and 9% over the study follow-up, except for the year 2017 (<5%) and 2019 (<1%). In the lamotrigine/ levetiracetam group the highest proportions were observed in the more recent years of study follow-up (Table 36).

Among fathers exposed to valproate, 13.7% presented neurotic disorder, 13.1% presented bipolar affective disorder and 11.2% bipolar affective disorder excl. bipolar disorder and mania. Among fathers exposed to lamotrigine/levetiracetam, proportions were generally higher with 29.9% presenting bipolar affective disorder excl. bipolar disorder and mania, 29.4% presenting bipolar affective disorder and 27.3% neurotic disorder (Table 37).

The most frequent indication[4] for AED treatment was epilepsy in both exposure groups (70.4% in the valproate group; 46.6% in the lamotrigine/levetiracetam group) (Table 37).

The K-means algorithm, analysing DDD trajectories in fathers exposed to AEDs 3 months prior to conception (ie, prior to LMP2) identified 3 different clusters A, B, and C, one with constant high exposure (A), one with low-to-high exposure (B), and one with high-to-low exposure (C). In the valproate group, 41.6% were in cluster A, 30.9% were in cluster B, and 27.5% 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 37).

11.1.2.2 Cumulative incidence proportion

Crude cumulative incidence proportions (risk) of ASD by paternal exposure group are presented in Table 38 overall and Table 39-Table 40 stratified by gender. A proportion of 16.7% of offspring paternally

[4] 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".

exposed to valproate were followed up for 12 years versus 6.4% of offspring paternally exposed to lamotrigine/levetiracetam.

The crude cumulative incidence proportions of ASD for 0-12 years of follow-up appeared to be higher in offspring paternally exposed to valproate (2.0, 95% CI: 1.1, 3.0) than in offspring paternally exposed to lamotrigine/levetiracetam (0.8, 95% CI: 0.4, 1.3), although the 95% CI overlapped (Table 38).

The crude cumulative incidence proportion for 0-12 years of follow-up also appeared to be higher in male (1.83, 95% CI: 1.07, 2.58) than female offspring (0.78, 95% CI: 0.27, 1.29) in both exposure groups. However, these proportions should be interpreted with caution since these are crude estimates, and no adjustments were made (Table 39 and Table 40).

11.1.2.3 Cumulative incidence rate and time to ASD diagnosis

Cumulative incidence rates of ASD by paternal exposure group are presented in Table 41, Table 42, and Table 43, overall and stratified by gender, respectively. Considering the overall study follow-up, a higher incidence rate of ASD was observed among offspring paternally exposed to valproate (3.0, 95% CI: 1.8, 4.7 per 1,000 PY) than among those exposed to lamotrigine/levetiracetam (1.7, 95% CI: 0.9, 2.9 per 1,000 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 time to first diagnosis of ASD, the crude estimate for both exposure groups is presented as Kaplan-Meier curves in Figure 4. 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 possible to estimate the upper bound of the 95% CI. The 5th percentile of the time to ASD was 144.2, 95% CI: 120.6, - months for the valproate paternal exposure group. It was not possible to estimate this for the lamotrigine/levetiracetam paternal exposure group due to low number of events.

11.1.2.4 Association between potential risk factors/confounders for ASD and paternal exposure group

Association between potential covariates (risk factors and confounders) for ASD and paternal exposure group was assessed in the cohort for sensitivity analysis 2. Results of the crude associations are shown in Table 46, Table 47, and Table 48.

For the offspring, none of the characteristics considered were associated with paternal exposure (Table 46).

Maternal characteristics (Table 47) that were significantly associated with paternal exposure in the offspring were:

- Age (p=0.0015), lower mean maternal age in the valproate paternal exposure group
- Neurotic disorder (p=0.0196), 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=0.0120) and during pregnancy (p=0.0158), higher percentage in the valproate paternal exposure group
- Maternal polypharmacy index during pregnancy (p=0.0427), lower mean index in the valproate paternal exposure group
- Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 (p=0.0298), lower percentage in the valproate paternal exposure group

Paternal characteristics (Table 48) that were 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=0.0125), 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.

11.1.2.5 Association between potential risk factors/confounders and ASD

Association between covariates (potential risk factors / confounders) and occurrence of ASD was assessed in the cohort for sensitivity analysis 2. Results of the crude associations are shown in Table 49 to Table 51.

For offspring characteristics, only gender (OR: 0.42, 95% CI: 0.19, 0.93; p=0.0313) was associated with occurrence of ASD (Table 49); the proportion of events among females was lower than the proportion of events among males.

For maternal characteristics considered as risk factors, mother's age (p=0.0458), smoking during pregnancy (OR: 3.02, 95% CI: 1.14, 8.02, p=0.0261), and affective disorder (OR: 3.01, 95% CI: 1.28, 7.08; p=0.0114) were significantly associated with the offspring having an ASD event (Table 50).

For paternal characteristics considered as risk factors or confounders (Table 51), the following variables were significantly associated with offspring having an ASD event: schizophrenia, schizotypal and delusional disorders (OR: 3.90, 95% CI: 1.34, 11.40), concomitant medications associated with valproate-indicated psychiatric conditions (OR: 2.18, 95% CI: 1.07, 4.45), year of offspring conception (p<0.0154), offspring conceived between 2011-2015 had a lower odds of having an ASD event (OR: 0.33, 95% CI: 0.15, 0.70), compared to the reference category of 2006-2010, paternal polypharmacy index (p=0.0439), offspring from fathers with the polypharmacy index from 5-10 had a higher odds (OR: 5.28, 95% CI: 1.67, 16.75) of having an ASD event compared with the reference category of 0.

11.1.2.6 Variable estimates from propensity score

Variables found to be associated with the outcome whose OR was >1.1 or <0.9, irrespective of statistical association, were included in the PS models for the analysis of the ASD comparative 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. 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 52), gender of the offspring was not associated with paternal exposure to valproate or lamotrigine/levetiracetam (OR: 1.06, 95% CI: 0.88, 1.28, p=0.5462). Offspring with mothers with gestational diabetes (OR: 0.29, 95% CI: 0.14, 0.61, p<0.0011) had lower probability of being in the valproate exposure group. Offspring with fathers with affective disorders (OR: 0.42, 95% CI: 0.30, 0.58, p<0.0001), bipolar affective disorder (OR: 0.57, 95% CI: 0.43, 0.77, p=0.0003), paternal polypharmacy 1-4 (OR: 0.74, 95% CI: 0.57, 0.97, p=0.0286), and offspring conceived in 2011-2015 (OR: 0.56, 95% CI: 0.45, 0.70, p<0.0001) or 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. In contrast, offspring with fathers with paternal schizophrenia, schizotypal and delusional disorders (OR: 2.82, 95% CI: 1.64, 4.85, p<0.0002), had a higher probability of being in the valproate exposure group.

The PS model that best achieved a balance in the weighted exposure groups after using IPTW was the PS model estimated from logistic regression. Table 53 shows the balance results obtained after using this

logistic regression model. Thus, the logistic regression model was used to apply IPTW in the effect estimation analysis (presented in Section 11.1.2.7).

11.1.2.7 Effect estimation for ASD

The effect estimation for ASD using a PS-weighted Cox regression model was assessed in a total of 2,182 offspring (848 in the valproate group and 1,334 in the lamotrigine/levetiracetam group).

In the PS-weighted Cox regression model, a higher risk of ASD was observed in offspring of fathers exposed to valproate compared to offspring of fathers exposed lamotrigine/levetiracetam group (HR: 2.70, 95% CI: 1.19, 6.17) (Table 3).

Table 3 Effect estimation for ASD using PS-weighted Cox model; ASD as outcome for sensitivity analysis 2

Variable	Total (N)	Number of events (N)	Model estimates		
			HR	95% CI	P-value
Valproate	848	19			
Lamotrigine/levetiracetam	1334	9			
Paternal exposure: valproate vs lamotrigine/levetiracetam	2182	28	2.70	(1.19, 6.17)	0.0180

ASD: autism spectrum disorders; CI: confidence interval; HR: hazard ratio; PS: propensity score; LMP2: last menstrual period date plus 2 weeks.

The model was weighted for the following variables included in the PS model: offspring risk factors/confounders, gender (male/female), maternal risk factors/confounders, mother's age (categorical): affective disorder, gestational diabetes, neurotic disorder, obesity, substance abuse prior to LMP2, smoking prior to LMP2 (no/yes), smoking during pregnancy (no/yes), 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 (categorical): 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), and year of offspring conception (see Table 52).

11.1.3 Norway

The study population of the sensitivity analysis 2 consisted of 1,416 offspring, of whom 397 were paternally exposed to valproate, and 1,019 were paternally exposed to lamotrigine/levetiracetam.

Due to the low event count (<10), it was not possible to provide the Cox regression models results. As reported in the Statistical Analysis Plan v2.0 (see Section 7.2.2) for both the primary and the secondary outcome, to ensure the validity of the model, the 10 events per variable rule is observed. Therefore, the results of the effect estimation for ASD, are not provided; all the other tables are presented in Appendix (Section 16.1.3).

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

Overall, the majority of offspring were male (52.1%), born at term between 37-41 weeks of gestational age (90.0%), and weighing ≥2,500 g (96.4%). The total offspring-years of follow-up was 6,917.1 (1,997.8 for valproate and 4,919.3 for lamotrigine/levetiracetam group), and the mean follow-up in years per offspring was 5.0 for the valproate group and 4.8 for the lamotrigine/levetiracetam group (Table 58). In the valproate exposure group, a majority of offspring (51.9%) were born before 2015. In the lamotrigine/levetiracetam group, the distributions over time were the other way round, with a majority of the offspring (52.1%) were born from 2015 and after (Table 58).

Regarding clinical characteristics of offspring by paternal exposure group, diagnosis of NDD including ASD, occurred in 3.5% of offspring paternally exposed to valproate and 2.2% of offspring paternally exposed to lamotrigine/levetiracetam (Table 59).

Any ASD diagnoses, ie, ever, and not only as a first NDD diagnosis, were observed in 1.0% of offspring paternally exposed to valproate and in 0.4% of offspring paternally exposed to lamotrigine/levetiracetam (Table 59).

ASD as the first NDD diagnosis was observed in 0.5% of offspring paternally exposed to valproate and in 0.3% of offspring paternally exposed to lamotrigine/levetiracetam.

Overall, the median (IQR) age of mothers at childbirth was 31.0 (27.0, 34.0) years (Table 60). The most prevalent clinical characteristics recorded in mothers prior to childbirth were neurotic disorder which was observed in 12.6% of mothers of offspring paternally exposed to valproate and in 13.4% of mothers of offspring paternally exposed to lamotrigine/levetiracetam; affective disorder which was observed in 5.8% of mothers of offspring paternally exposed to valproate and in 10.1% of mothers of offspring paternally exposed to lamotrigine/levetiracetam; and gestational diabetes which was observed in 5.0% of mothers of

offspring paternally exposed to valproate and in 6.6% of mothers of offspring paternally exposed to lamotrigine/levetiracetam (Table 61).

Regarding maternal characteristics of the 1,416 offspring included for sensitivity analysis 2, 4.9% had a record of smoking during pregnancy (6.8% in valproate exposure group and 4.2% in lamotrigine/levetiracetam exposure group). Correspondingly, the proportion of mothers smoking prior to LMP2 was 12.6% (14.6% and 11.9% in the valproate and lamotrigine/levetiracetam exposure groups, respectively), although a high proportion of missingness (13.5%) was observed (Table 61).

Regarding the use of concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy, 3.0% of mothers of offspring paternally exposed to valproate and 6.1% of mothers of offspring paternally exposed to lamotrigine/levetiracetam had at least one prescription (Table 61).

Regarding paternal demographic characteristics, the overall median (IQR) age of fathers at childbirth was 33.0 (30.0, 38.0) years. Higher proportions of offspring paternally exposed to valproate were conceived in the earlier years of the study inclusion (2010-2015), in contrast to the lamotrigine/levetiracetam group where higher proportions were observed in the latest years of study inclusion (2014-2018) (Table 62).

Regarding clinical characteristics of the fathers, in the group of offspring paternally exposed to valproate, 14.1% of fathers presented bipolar affective disorder, 7.8% presented affective disorder excluding bipolar disorder and mania, and 7.6% presented neurotic disorder. Among offspring paternally exposed to lamotrigine/levetiracetam, proportions were generally higher with 27.8% of fathers presenting bipolar affective disorder, 22.3% of fathers presenting affective disorder excluding bipolar disorder and mania, and 15.4% presenting neurotic disorder (Table 63).

The most frequent indication[5] for AED treatment was epilepsy in both groups (57.9% in the valproate group, 41.0% in the lamotrigine/levetiracetam group) (Table 63). Regarding the use of concomitant medications associated with neuropsychiatric adverse events, 56.7% of fathers of offspring paternally exposed to valproate, and 64.5% 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 in the 3 months prior to conception (ie, prior to LMP2) identified 2 different clusters A and B one with constant low exposure (cluster B) and one with constant higher exposure to AEDs (cluster A). A larger proportion of fathers were

[5] 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 were found in the medical history, the indication was considered "other/unknown".

in cluster A (70.0%) than in cluster B (30.0%) both in the valproate group, and in the lamotrigine/levetiracetam group (76.8% in cluster A and 23.2% in cluster B) (Table 63).

11.1.3.2 Cumulative incidence proportion

The crude cumulative incidence proportions (risk) of ASD by paternal exposure group are presented in Table 64 overall and in Table 65 and Table 66 stratified by gender. There were 7.1% of offspring paternally exposed to valproate followed up for 10 years versus 8.2% of offspring paternally exposed to lamotrigine/levetiracetam.

The crude cumulative incidence proportions of ASD for 0-10 years of follow-up appeared to be higher in offspring paternally exposed to valproate (1.0%, 95% CI: 0.0, 2.0) than in offspring paternally exposed to lamotrigine/levetiracetam (0.4%, 95% CI: 0.0, 0.8), although the 95% CI overlapped (Table 64).

The crude cumulative incidence proportion for overall 0-10 years of follow-up was similar in male (0.5%, 95% CI: 0.0, 1.1) and female offspring (0.6%, 95% CI: 0.0, 1.2), though in female, it was higher in the valproate group compared to the lamotrigine/levetiracetam. However, these proportions should be interpreted with caution since these are crude estimates, no adjustments were made (Table 65 and Table 66).

11.1.3.3 Cumulative incidence rate and time to ASD diagnosis

Cumulative incidence rates of ASD by paternal exposure group are presented in Table 67, Table 68 and Table 69 overall and stratified by gender, respectively. Considering the overall study follow-up, a higher incidence rate of ASD was observed among offspring paternally exposed to valproate (2.0, [95% CI: 0.6, 5.1] per 1,000 PY) than among those paternally exposed to lamotrigine/levetiracetam (0.8, [95% CI: 0.2, 2.1] per 1,000 PY), although the 95% CIs for the 2 groups were overlapping. When stratifying by gender, higher cumulative incidence rates were observed in females in the valproate group compared to the lamotrigine/levetiracetam group, as opposed to males.

Regarding time to first diagnosis of ASD, the crude estimates for both exposure groups are presented as Kaplan-Meier curves Figure 5. Over the study period, the frequency of events was lower than 5% in the cohort; therefore, percentiles of the time to diagnosis could not be estimated.

11.1.3.4 Association between potential risk factors/confounders for ASD and paternal exposure group

Association between potential covariates (risk factors and confounders) for ASD and paternal exposure group was assessed in the cohort for sensitivity analysis 2. Results of the crude associations are shown in Table 72 to Table 74.

For the offspring, none of the characteristics considered were associated with paternal exposure (Table 72).

Maternal characteristics (Table 73) that were significantly associated with paternal exposure were:

- Affective disorder (p=0.0104), lower percentage in the valproate paternal exposure group
- Smoking during pregnancy (p=0.0288), higher percentage in the valproate paternal exposure group
- Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy (p=0.0201), lower percentage in the valproate paternal exposure group.

Paternal characteristics (Table 74) that were 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), 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 (p=0.0065), a lower percentage in the valproate exposure group
- Age (p=0.0037), younger fathers in the valproate group

11.1.3.5 Association between potential risk factors/confounders and ASD

These results could not be produced due to the low number of ASD events (<10), as shown in Section 16.1.3.2 (Table 64) and Section 16.1.3.3 (Table 67).

11.1.3.6 Variable estimates from propensity score

These results could not be produced due to the low number of ASD events (<10), as shown in Section 16.1.3.2 (Table 64) and Section 16.1.3.3 (Table 67).

11.1.3.7 Effect estimation for ASD

These results could not be produced due to the low number of ASD events (<10), as shown in 16.1.3.2 (Table 64) and Section 16.1.3.3 (Table 67).

11.2 Exploratory Analysis 8

The analysis was performed to describe the spectrum and frequency of CMs according to the target body system organ class in live and non-live offspring by paternal exposure group (valproate vs. lamotrigine/levetiracetam).

11.2.1 Denmark

Results from exploratory analysis 8 are presented in Table 4.

For the exploratory analyses 8, the inclusion criterion was all offspring from the secondary outcome cohort (N=3,777) (Figure 1).

After additional exclusions, a total of 76 offspring with a CM diagnosis were included. Since offspring may have more than one distinct CM diagnosis, a total of 111 records (ie CM diagnoses with distinct ICD-10 codes among the 76 offspring) were included in this analysis (Figure 1).

Among the 111 CM records reported for the cohort, 34 were in the valproate group and 77 in the lamotrigine/levetiracetam group. Of these events, major CM accounted for 76.6% (n=85) and minor CM accounted for 23.4% (n=26). Stratified by exposure group, 70.6% (n=24) of the CM events in the valproate group were major and 29.4% (n=10) were minor. In the lamotrigine/levetiracetam group, 79.2% (n=61) of the CM events were major and 20.8% (n=16) were minor.

Twenty-two events in total were observed in the limb (19.8%) and of these, 16 were reported in the lamotrigine/levetiracetam group, accounting for 20.8% of all CM in this group, whereas 6 occurred in the valproate group, accounting for 17.7% of all CM in this group.

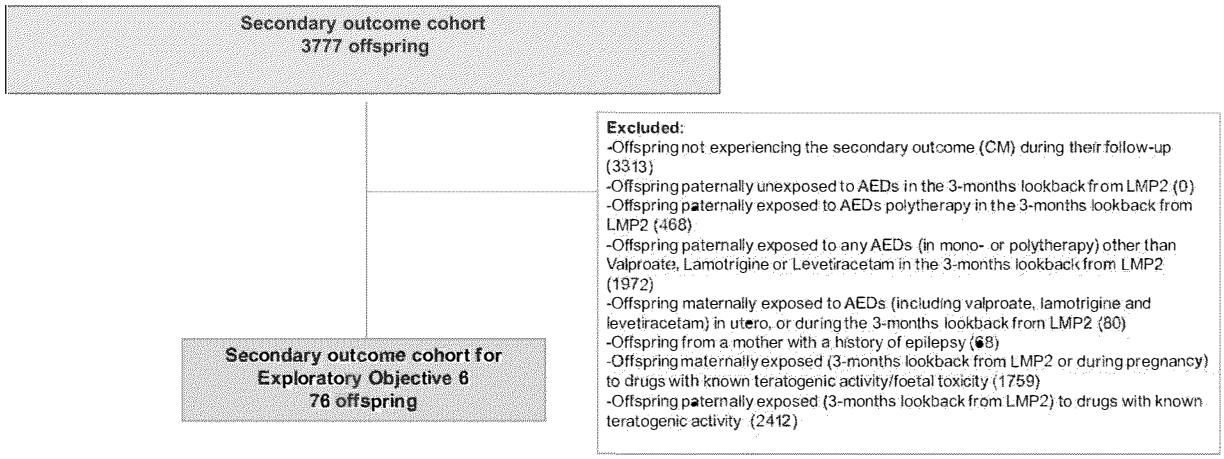
There were 20 events reported congenital heart defects (26.0%) in the lamotrigine/levetiracetam group, all major CM. Results on congenital heart defects in the valproate group were masked[6].

The class of chromosomal CM accounted for 6 events (5.4%) in total, all major CM. Due to the low number of events in both the valproate group and the lamotrigine/levetiracetam group, frequencies by exposure category are masked [6].

[6] 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).

The number of CM diagnoses in the eye was 5 (4.5%), all major CM. Due to the low number of events in both the valproate group and the lamotrigine/levetiracetam group, frequencies by exposure category are masked.

For other target body systems and organ classes, frequencies are either zero or masked.



An offspring may be present in more than one exclusion criterion
AED: antiepileptic drugs; CM: Congenital Malformation; LMP2: Last menstrual period date plus 2 weeks.

Figure 1 Study population for secondary outcome exploratory analysis 8 in Denmark

Table 4 Spectrum of CMs according to the target body system organ class by paternal exposure group; CM secondary outcome

CM Number of CM diagnoses	Paternal exposure group									
	Valproate N=34		Lamotrigine/ levetiracetam N=77		Lamotrigine N=67		Levetiracetam N=10		Total (valproate + lamotrigine/ levetiracetam) N=111	
	N	%	N	%	N	%	N	%	N	%
Major	24	70.59	61	79.22	***	***	***	***	85	76.58
Minor	10	29.41	16	20.78	***	***	***	***	26	23.42
Nervous System	***	***	***	***	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***
Eye	***	***	***	***	***	***	***	***	5	4.50
Major	***	***	***	***	***	***	***	***	5	4.50
Minor	***	***	***	***	***	***	***	***	0	0.00
Ear, face and neck	***	***	***	***	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***
Congenital Heart Defects	***	***	20	25.97	***	***	***	***	***	***
Major	***	***	20	25.97	***	***	***	***	***	***
Minor	***	***	0	0.00	***	***	***	***	***	***
Respiratory	***	***	***	***	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***
Oro-facial clefts	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Digestive system	***	***	***	***	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***
Abdominal wall defects	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM Number of CM diagnoses	Paternal exposure group									
	Valproate N=34		Lamotrigine/ levetiracetam N=77		Lamotrigine N=67		Levetiracetam N=10		Total (valproate + lamotrigine/ levetiracetam) N=111	
	N	%	N	%	N	%	N	%	N	%
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Urinary	***	***	***	***	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***
Genital	***	***	14	18.18	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***
Limb	6	17.65	16	20.78	***	***	***	***	22	19.82
Major	***	***	11	14.29	***	***	***	***	***	***
Minor	***	***	5	6.49	***	***	***	***	***	***
Chromosomal	***	***	***	***	***	***	***	***	6	5.41
Major	***	***	***	***	***	***	***	***	6	5.41
Minor	***	***	***	***	***	***	***	***	0	0.00
Other anomalies/syndromes	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Skeletal dysplasias	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Craniosynostosis	***	***	***	***	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***
Congenital constriction bands/amniotic band	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM Number of CM diagnoses	Paternal exposure group									
	Valproate N=34		Lamotrigine/ levetiracetam N=77		Lamotrigine N=67		Levetiracetam N=10		Total (valproate + lamotrigine/ levetiracetam) N=111	
	N	%	N	%	N	%	N	%	N	%
Situs inversus	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Conjoined twins	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital skin disorders	***	***	***	***	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***
Valproate syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Genetic syndromes + microdeletions	***	***	***	***	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***
Genetic syndromes + sequences	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Musculoskeletal	***	***	10	12.99	***	***	***	***	***	***
Major	***	***	***	***	***	***	***	***	***	***
Minor	***	***	***	***	***	***	***	***	***	***

CM: congenital malformations.
*** Masked values indicating that data was calculated but not disclosed.
Legend: Number and percentage of CM diagnoses by sub-type with stratification to major and minor CM are presented. Percentage is calculated over the total number of CM diagnoses, ie, n/N.

11.2.2 Norway

Results from exploratory analysis 8 are presented in Table 5.

For the exploratory analyses 8, the inclusion criterion was all offspring from the secondary outcome cohort (N=3,315) (Figure 2).

After additional exclusions, a total of 70 offspring with a CM diagnosis were included in this analysis. Since offspring may have more than one distinct CM diagnosis, a total of 105 records (ie CM diagnoses with distinct ICD-10 codes among the 70 offspring) were included in this analysis (Figure 2).

Among the 105 CM reported for the cohort, 40 were in the valproate group and 65 in the lamotrigine/levetiracetam group. Of these events, major CM accounted for 53.3% (n=56) and minor CM accounted for 46.7% (n=49). Stratified by exposure group, 62.5% (n=25) of the CM in the valproate group were major and 37.5% (n=15) were minor. In the lamotrigine/levetiracetam group, 47.7% (n=31) of the CM were major and 52.3% (n=34) were minor.

The most common target body system organ class for CM was the digestive system (total 33 [31.4%], major CM 12 [11.4%], and minor CM 21 [20.0%]). Stratified by exposure group, 13 (32.5%) of the CM of the digestive system were in the valproate group, of which 15.0% (n=6) were major CM and 17.5% (n=7) were minor CM. In the lamotrigine/levetiracetam group, of the 30.8% (n=20) of the CM of the digestive system 9.2% (n=6) were major and 21.5% (n=14) were minor.

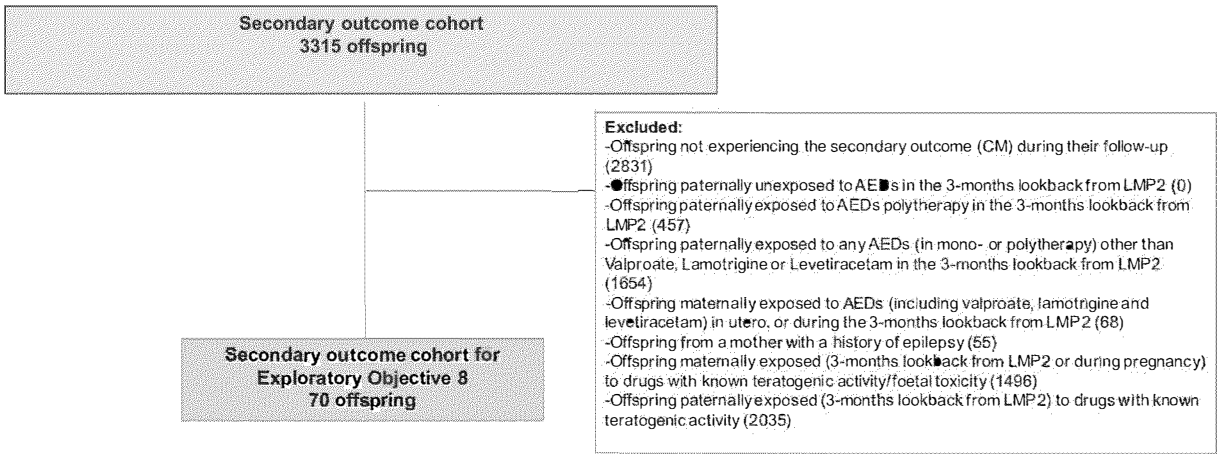
The second most common target body system organ class for CM was the limb, with 26 events (24.8%), 14 (13.3%) major CM, and 12 (11.4%) minor CM. Stratified by exposure group, 25.0% (n=10) of the CM of the limb were in the valproate group, of which 15.0% (n=6) were major CM and 10.0% (n=4) were minor CM. In the lamotrigine/levetiracetam group, of the 24.6% (n=16) of the CM of the limb, 12.3% (n=8) were major CM, and 12.3% (n=8) were minor CM.

The number of congenital heart defects was 14 (13.3%), of whom 11 (10.5%) were major CM and 3 (2.9%) were minor CM. Stratified by exposure group, 12.5% (n=5) of the congenital heart defects were in the valproate group, of which 10.0% (n=4) were major CM and 2.5% (n=1) were minor CM. In the lamotrigine/levetiracetam group, of the 13.9% (n=9) of the congenital heart defects, 10.8% (n=7) were major CM, and 3.1% (n=2) were minor CM.

The number of CM diagnoses for genital was 9 (8.6%), including major (5.7%) and minor (2.9%) CM. Of these, only 1 major CM (2.5%) occurred in the valproate group and 8 (12.3%, of which n=5, 7.7% were major CM, and n=3, 4.6% were minor CM) in the lamotrigine/levetiracetam group. Likewise, the number and percentage of chromosomal anomalies were 6 (5.7%), all of which occurred in the valproate group. These anomalies were all major.

Number and percentages are also presented for the classes eye (total n=4, 3.8%; valproate group, n=1, 2.5%; and lamotrigine/levetiracetam group, n=3, 4.6%); urinary (total n=3, 2.9%; all in the lamotrigine/levetiracetam group, n=3, 4.6%); congenital skin disorders (total n=3, 2.9%; valproate group, n=1, 2.5%; and lamotrigine/levetiracetam group, n=2, 3.1%); ear, face and neck (total n=2, 1.9%; all in the lamotrigine/levetiracetam group, n=2, 3.1%); respiratory system (total n=2, 1.9%; all in the valproate group, n=2, 5.0%); musculoskeletal (total n=2, 1.9%; valproate group, n=1, 2.5%; and lamotrigine/levetiracetam group, n=1, 1.5%); and, nervous system (total n=1, 1.0%; all in the lamotrigine/levetiracetam group, n=1, 1.5%).

For further details see Table 5.



An offspring may be present in more than one exclusion criterion
AED: antiepileptic drugs; CM: Congenital Malformation; LMP2: last menstrual period date plus 2 weeks.

Figure 2 Study population of Secondary outcome cohort for Exploratory Analyses 8 in Norway

Table 5 Spectrum of CMs according to the target body system organ class by paternal exposure group; CM as secondary outcome

CM Number of CM diagnoses	Paternal exposure group									
	Valproate N=40		Lamotrigine/ levetiracetam N=65		Lamotrigine N=55		Levetiracetam N=10		Total (valproate + lamotrigine/ levetiracetam) N=105	
	N	%	N	%	N	%	N	%	N	%
Major	25	62.50	31	47.69	25	45.45	6	60.00	56	53.33
Minor	15	37.50	34	52.31	30	54.55	4	40.00	49	46.67
Nervous System	0	0.00	1	1.54	1	1.82	0	0.00	1	0.95
Major	0	0.00	1	1.54	1	1.82	0	0.00	1	0.95
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Eye	1	2.50	3	4.62	3	5.45	0	0.00	4	3.81
Major	0	0.00	1	1.54	1	1.82	0	0.00	1	0.95
Minor	1	2.50	2	3.08	2	3.64	0	0.00	3	2.86
Ear, face and neck	0	0.00	2	3.08	2	3.64	0	0.00	2	1.90
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	2	3.08	2	3.64	0	0.00	2	1.90
Congenital Heart Defects	5	12.50	9	13.85	9	16.36	0	0.00	14	13.33
Major	4	10.00	7	10.77	7	12.73	0	0.00	11	10.48
Minor	1	2.50	2	3.08	2	3.64	0	0.00	3	2.86
Respiratory	2	5.00	0	0.00	0	0.00	0	0.00	2	1.90
Major	1	2.50	0	0.00	0	0.00	0	0.00	1	0.95
Minor	1	2.50	0	0.00	0	0.00	0	0.00	1	0.95
Oro-facial clefts	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM Number of CM diagnoses	Paternal exposure group									
	Valproate N=40		Lamotrigine/ levetiracetam N=65		Lamotrigine N=55		Levetiracetam N=10		Total (valproate + lamotrigine/ levetiracetam) N=105	
	N	%	N	%	N	%	N	%	N	%
Digestive system	13	32.50	20	30.77	18	32.73	2	20.00	33	31.43
Major	6	15.00	6	9.23	6	10.91	0	0.00	12	11.43
Minor	7	17.50	14	21.54	12	21.82	2	20.00	21	20.00
Abdominal wall defects	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Urinary	0	0.00	3	4.62	3	5.45	0	0.00	3	2.86
Major	0	0.00	2	3.08	2	3.64	0	0.00	2	1.90
Minor	0	0.00	1	1.54	1	1.82	0	0.00	1	0.95
Genital	1	2.50	8	12.31	5	9.09	3	30.00	9	8.57
Major	1	2.50	5	7.69	3	5.45	2	20.00	6	5.71
Minor	0	0.00	3	4.62	2	3.64	1	10.00	3	2.86
Limb	10	25.00	16	24.62	11	20.00	5	50.00	26	24.76
Major	6	15.00	8	12.31	4	7.27	4	40.00	14	13.33
Minor	4	10.00	8	12.31	7	12.73	1	10.00	12	11.43
Chromosomal	6	15.00	0	0.00	0	0.00	0	0.00	6	5.71
Major	6	15.00	0	0.00	0	0.00	0	0.00	6	5.71
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other anomalies/syndromes	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM Number of CM diagnoses	Paternal exposure group									
	Valproate N=40		Lamotrigine/ levetiracetam N=65		Lamotrigine N=55		Levetiracetam N=10		Total (valproate + lamotrigine/ levetiracetam) N=105	
	N	%	N	%	N	%	N	%	N	%
Skeletal dysplasias	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Craniosynostosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital constriction bands/amniotic band	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Situs inversus	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Conjoined twins	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital skin disorders	1	2.50	2	3.08	2	3.64	0	0.00	3	2.86
Major	1	2.50	1	1.54	1	1.82	0	0.00	2	1.90
Minor	0	0.00	1	1.54	1	1.82	0	0.00	1	0.95
Valproate syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM Number of CM diagnoses	Paternal exposure group									
	Valproate N=40		Lamotrigine/ levetiracetam N=65		Lamotrigine N=55		Levetiracetam N=10		Total (valproate + lamotrigine/ levetiracetam) N=105	
	N	%	N	%	N	%	N	%	N	%
Genetic syndromes + microdeletions	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Genetic syndromes + sequences	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Musculoskeletal	1	2.50	1	1.54	1	1.82	0	0.00	2	1.90
Major	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Minor	1	2.50	1	1.54	1	1.82	0	0.00	2	1.90

CM: congenital malformations.
Legend: Number and percentage of CM diagnoses by sub-type with stratification to major and minor CM are presented. Percentage is calculated over the total number of CM diagnoses, ie, n/N.

12. DISCUSSION

In the present addendum, only results for sensitivity analysis 2 and exploratory analysis 8 of the PASS – paternal exposure to valproate – are reported.

They are discussed in conjunction with the results from the main analyses and not as isolated findings.

However, due to outages identified in the Norwegian data, in the present updated addendum, only the results for Norway supersede those reported in the previous submitted addendum v1.0.

The analysis of Norway's data has been completely rerun due to the following reasons: first, the Norwegian Patient Registry, which provided diagnostic codes, can only be linked to other registries from 2008 onward; second, the original study period in Norway started in 2006. To ensure a 24 month lookback period for the study variables, the decision was made to use an updated study period beginning in 2010. This approach specifically considered pregnancies that ended in 2010, which provided an appropriate and comprehensive lookback for the study variables, particularly for fathers.

Sensitivity analysis 2 was conducted, to assess the risk of ASD (ever, not only as 1st NDD diagnosis) in offspring paternally exposed to valproate compared to lamotrigine/levetiracetam composite monotherapy treatment in the 3 months lookback from LMP2, in Denmark, Sweden and Norway. This sensitivity analysis consisted in repeating the primary analysis but restricting the outcome of interest to ASD specifically.

The exploratory analysis 8 aimed to describe, among offspring diagnosed with CM, the spectrum of CM sub-types by target body system organ class with stratification as major or minor in Denmark and Norway. Only offspring experiencing a CM were included in this analysis; for these offspring, the number and percentage of each CM sub-type were presented, 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.

12.1 Key Results

12.1.1 Sensitivity Analysis 2 – Risk of ASD

In sensitivity analysis 2, the risk of ASD in offspring paternally exposed to valproate compared to lamotrigine/levetiracetam was not similar to the one observed for NDD, including ASD (ie, in the primary analysis) in Denmark and Sweden. In Norway, it was not possible to provide the risk of ASD in offspring paternally exposed to valproate compared to those exposed to lamotrigine/levetiracetam due to the low number of events (<10).

The adjusted HRs for ASD from the PS-weighted Cox model were 0.76 (95% CI: 0.30, 1.89) in Denmark, and 2.70 (95% CI: 1.19, 6.17) in Sweden. The reported risks in sensitivity analysis 2 are subject to lower

precision, as showed by the wider 95% CI, than those from primary analysis (respective adjusted HRs for NDD were 1.34 (95% CI: 0.79, 2.25) in Denmark and 1.54 (95% CI: 0.95, 2.51) in Sweden. The wider CIs in the sensitivity analysis are due to the lower number of events – with a total of 26 ASD (*vs*. 74 NDD) events in Denmark and 28 ASD (*vs*. 81 NDD) events in Sweden. In Norway there were a total of 8 ASD (*vs*. 34 NDD) events thereby precluding the production of the Cox models. The description of the ASD events according to age at diagnosis showed a different pattern for Denmark compared to Sweden. In Denmark, 6 of the 21 ASD diagnoses in offspring paternally exposed to lamotrigine/levetiracetam were observed at 10-11 years of age (versus 0 ASD diagnoses in the valproate group) with 20.7% of the offspring followed up for 12 years (versus 57.0% in the valproate group). In Norway, it was not possible to observe diagnoses of ASD at 10-11 years due to the shorter study period. However, 7.1% of the offspring were followed up for 10 years in the valproate group (versus 8.2% in the lamotrigine or levetiracetam group). In Norway, 3 out of 4 (75%) ASD diagnoses in the valproate group were observed between 3-4 years of age and 1 at 4-5 years of age. In contrast, in the lamotrigine and levetiracetam groups, the 4 ASD diagnoses were equally distributed from 3-4 years of age to 8–9 years of age.

In Sweden, a reverse trend was observed, where offspring paternally exposed to lamotrigine/levetiracetam experienced ASD diagnoses at younger ages when compared to those paternally exposed to valproate.

In Sweden, 5 of the 19 ASD diagnoses in offspring paternally exposed to the valproate group were observed between 8 and 9 years of age (versus 1 of the 12 ASD diagnoses in the lamotrigine/levetiracetam group), with 39.8% of offspring followed up for 9 years (versus 22.9% in the lamotrigine/levetiracetam group). Besides, 3 of the 19 ASD diagnoses in offspring paternally exposed to valproate group were observed between 10 and 11 years (versus none of the 12 ASD diagnoses in the lamotrigine/levetiracetam group), with 16.7% of offspring followed up for 12 years (versus 6.4% in the lamotrigine/levetiracetam group).

Overall, in Sweden, offspring paternally exposed to valproate were followed up for a longer period than those exposed to the lamotrigine/levetiracetam group. Additionally, 40% of all ASD diagnoses (8 of 19) were observed between 8 and 11 years of age versus 8.3% of all ASD diagnoses (1 of 12) in the lamotrigine/levetiracetam group.

This discrepancy shows an imbalance in the follow-up between the groups and could potentially bias the results, as longer follow-up periods allow for more time to detect developmental outcomes such as ASD. As already underlined in the study report, there was a greater mean length of follow-up in offspring paternally exposed to valproate compared to those paternally exposed to lamotrigine/levetiracetam, consistent across the 3 studied countries, but the difference between the 2 groups and global length of follow-up were not similar across the countries. The difference in follow-up duration between the 2 exposure groups was the highest in Denmark (9.5 years in the valproate group versus 6.7 in the lamotrigine/levetiracetam group), followed by Sweden (6.8 years in the valproate group versus 5.1 in the lamotrigine/levetiracetam group), and minimally in Norway (5.0 years in the valproate group versus 4.8 in the lamotrigine/levetiracetam group). Besides, the longest follow-up in the lamotrigine/levetiracetam group

is in Denmark. These findings highlight the potential impact of the length of follow-up which may have been underestimated in the main analysis.

The degree to which confounding was controlled also differed across the countries included in the study. The Danish results were potentially affected by the presence of risk factors or confounders, that remained unbalanced after PS weighting. Particularly, the maternal characteristic "concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", that was twice as prevalent in the lamotrigine/levetiracetam group compared to the valproate group (5.5% *vs* 2.7%, respectively). After further adjustment for this variable in the final PS-weighted Cox regression model, it remained strongly associated with ASD (HR: 10.04; 95% CI: 4.04, 24.97).

12.1.2 Exploratory Analysis 8 – Congenital Malformation by Target Body System Organ Class

Exploratory analysis 8 was performed in Denmark and Norway but not in Sweden since data on non-live offspring was not available. This analysis showed that the most frequent target body system organ classes affected by CM were digestive system, limb, congenital heart defects, and genital in offspring paternally exposed to either valproate or lamotrigine/levetiracetam and that most of the CM reported were considered as major in both Denmark and Norway. In Denmark, major CM accounted for 76.6% (n=85) and minor CM accounted for 23.4% (n=26) of these events; in Norway, major CM accounted for 53.3% (n=56) and minor CM accounted for 46.7% (n=49) of these events.

In Denmark, in offspring paternally exposed to valproate, all results except for CM in limbs (representing 17.7% of the observed CMs), were masked, meaning 5 or less events, or to preclude recalculation of values that lead to a small number of observations. In offspring paternally exposed to lamotrigine/levetiracetam, the most frequent CM diagnoses were congenital heart defects, representing 26.0% (*versus* 'masked' in the valproate group), then limbs representing 20.8% (*versus* 17.7% in the valproate group). Due to the very low number of reported CM, for most of the target body system organ classes and for the stratification by major/minor, results were masked in both exposure groups. These masked results in either one or both exposure groups prevented drawing any conclusions.

In Norway, CM in digestive system was the most frequently reported target body organ class in both groups, followed by CM in limbs. The proportion of most of the digestive system CM diagnoses was similar in offspring paternally exposed to valproate and in those paternally exposed to lamotrigine/levetiracetam (32.5% and 30.8%, respectively). Likewise, the proportion of the limbs CM diagnoses was similar in offspring paternally exposed to valproate and in those paternally exposed to lamotrigine/levetiracetam (25.0% and 24.6%, respectively). Three exceptions to this similar reporting trend across the 2 exposure groups were observed: genital CMs were almost exclusively reported in offspring paternally exposed to lamotrigine/levetiracetam (12.3% vs. 2.5% in the valproate group); chromosomal CMs were exclusively reported in offspring paternally exposed to valproate (15.0% vs. 0.0% in the lamotrigine/levetiracetam group).

12.2 Limitations

This study was primarily designed to address the specific objectives presented in Section 8. Thus, study limitations may significantly have impacted the sensitivity analysis 2 and exploratory analysis 8 results and must be acknowledged. Nevertheless, all the limitations identified in this addendum also apply to the main results presented in the final study report v1.1. These limitations are described in more detail below.

An insufficient length of follow-up may lead to a reduced capture of ASD 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 countries. The follow-up in the Danish data was about 2 years longer than that in the Swedish data (7.8 and 5.7 years, respectively). This may explain the different estimates of the risk of ASD observed in these 2 countries.

There were also differences in the length of follow-up within each country between the 2 compared groups, with a greater mean length of follow-up observed in offspring paternally exposed to valproate compared to those paternally exposed to lamotrigine/levetiracetam. While the impact of year of conception was considered when constructing the PS, it might still affect the robustness of the estimates in the 2 exposure groups, impairing the comparison of the ASD risk between the 2 exposure groups.

The very low number of ASD outcomes observed in both exposure groups in each country may have led to instability in the estimation of HRs due to an increased variability and to a stronger influence of outliers/extreme values, making the results of the risk comparison less reliable. In Norway, the shorter study time period prevented the estimation of the HRs due to the low number of events.

In addition to the already mentioned limitations, this sensitivity analysis may be further affected by the fact that no information on the incidence of ASD in the siblings from the mother and father were available. Previous results showed the importance of considering family history when assessing the risk of ASD in offspring. In a large cohort of 847,732 children, 1.55% of the children were diagnosed with ASD and having a sibling with ASD increased the risk of the offspring developing ASD. The relative risk of ASD in offspring of mothers with siblings diagnosed with ASD was 3.05 (95% CI: 2.52, 3.64); the one observed for fathers with siblings with ASD was 2.08 (95% CI: 1.53, 2.67) (6).

Additionally, in this sensitivity analysis there were limited information available on fathers' behaviours (such as alcohol consumption, smoking, and other lifestyle factors), which may have an impact on the risk of ASD in offspring. Results from a cohort of 36,731 singleton births showed that paternal demographic characteristics was associated to adverse outcomes, such as paternal education and paternal race/ethnicity, highlighting the importance of considering paternal factors (7). Another potential limitation of the study is the lack of information on the type of epilepsy in each exposure group. This is particularly relevant given that epilepsy is more common AED indication in Sweden, than in the other investigated countries and that the valproate group had a higher prevalence of epilepsy than the lamotrigine/levetiracetam group. 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 NDD and is 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 (8).

Exploratory analysis 8 was also affected by the small number of CM diagnoses which, combined with the masking rules, strongly limited the description by target body organ class and by the major/minor nature of the CM in each group of paternal exposure of interest, especially in Denmark.

12.3 Interpretation

In Denmark, the risk of ASD in offspring paternally exposed to valproate (1.3%) was lower than those exposed to lamotrigine/levetiracetam (1.5%), and the adjusted HR was not statistically significant (0.76, 95% CI: 0.30, 1.89). In Sweden, the risk of ASD was higher in offspring paternally exposed to valproate (2.2%) compared to those exposed to lamotrigine/levetiracetam (0.7%), and adjusted HR of 2.70 (95% CI: 1.19, 6.17).

In Denmark, maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy in offspring was associated to paternal exposure to AEDs. This could be explained by non-random mating among psychiatric patient populations which has been shown previously (9) and could potentially influence confounding. This covariate remained unbalanced after PS weighting and was added to the PS-weighted Cox outcome model. Additionally, other variables were still unbalanced after PS weighting, but due to the small number of events it was not possible to include these covariates in the final model. Therefore, the presence of residual confounding in the estimation of the HR cannot be ruled out.

Results from a Danish national register study found that there may be an increased risk of ASD in the offspring of fathers who used Selective Serotonin Reuptake Inhibitors (SSRIs) before conception, with a 1.62-fold greater risk compared to those who did not (10). The risk was reduced after controlling for possible confounders, particularly fathers' mental disorders (HR: 1.43; 95% CI: 1.18, 1.74). 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 (10).

Also, in the Swedish results for sensitivity analysis 2, an increased risk of ASD was observed in offspring paternally exposed to valproate, compared to those paternally exposed to lamotrigine/levetiracetam. When compared to the main analysis, the magnitude of this effect was even stronger. The median age of ASD diagnosis vs. NDD including ASD diagnosis was similar in offspring paternally exposed to valproate (6.3 vs. 6.2 years respectively) while it differed in offspring paternally exposed to lamotrigine/levetiracetam (4.5 vs. 5.2 years, respectively). This lower median age of ASD diagnosis vs. NDD, including ASD diagnosis in the lamotrigine/levetiracetam group, may reflect the under-capture of ASD diagnoses at later

ages due to reduced follow-up time. The valproate group seems less affected by this due to longer follow-up time (6.8 vs. 5.1 years on average). As a result, the difference in the probability of observing an event in offspring paternally exposed to valproate compared to those exposed to lamotrigine/levetiracetam is larger when the outcome is ASD vs. NDD including ASD. In a study performed in Sweden between 2006-2016, 1.7% of offspring paternally exposed to valproate were diagnosed with an ASD vs. 1.3% of offspring paternally unexposed (11). In our study between 2007-2019, 1.6% of offspring paternally exposed to valproate and 0.6% of offspring paternally exposed to lamotrigine/levetiracetam were diagnosed with ASD as the first NDD diagnosis. ASD diagnoses (not only as a first diagnosis) were observed in 2.0% of offspring paternally exposed to valproate and in 0.8% of offspring paternally exposed to lamotrigine/levetiracetam during the same period. The comparison with the Tomson et al. study is difficult, not only because no information about lamotrigine or levetiracetam was available in the latter but also because methods of diagnosis may have changed over time.

However, important insights into the improvement of ASD detection over time happened in Sweden, Denmark, and Norway. These countries have progressively implemented screening campaigns resulting in the detection of ASD at a younger age. In 2012, the Swedish Child Health Care Services gradually implemented an early screening program for children as young as 2.5 years old to detect ASD (12). Denmark has also implemented a similar program, decreasing the age at which children are diagnosed with ASD since 1997 (13). Norway began implementing early diagnosis measures in 1999 with the MoBA nationwide cohort study (14). However, recent studies have shown that early ASD screening with a parent checklist has low sensitivity and primarily identifies individuals with significant developmental delays (15). A more recent Norwegian study (16) utilizing a questionnaire to identify developmental concerns in children at 18 months of age found that scoring in the "at risk" range was associated with lower IQ and greater severity of autism symptoms, regardless of whether or not the child had ASD. Besides the detection at a younger age also the definition of ASD evolved over time. For instance, Asperger Syndrome now considered part of the broader ASD category (17), may have impacted the observed estimates, potentially biasing the HR observed in our study.

Besides, due to the lower number of events considered for the ASD outcome when compared to the NDD, including ASD outcome, the precision of the estimates was also affected, leading to instability in the HR making it less reliable. Additionally, HR were estimated using Cox proportional hazards models, which assume a constant HR over time. When there are few events, the estimated HR may be highly sensitive to the timing and the number of events, also leading to instability of the estimates.

In addition, informative censoring may occur when time-to-event and time to censoring are dependent, either directly or through covariates (18). 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. In sensitivity analysis 2, offspring not experiencing the event (ASD) were censored at the earliest of: 12 years of age (for Denmark and Sweden only), end of study time period, death or emigration. It is expected that year of birth will be

associated with censoring, because for example one of the censoring mechanisms (reaching the age of 12) only applies to offspring who were born at least 12 years prior to the end of the study time period. It is noteworthy that, with the exception of Norway, follow-up was the shortest in Sweden, with 23.3% of the offspring in the lamotrigine/levetiracetam group followed up more than 8 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 valproate group). This may explain the lower rate of ASD captured in the lamotrigine/levetiracetam in Sweden compared to Denmark and highlight the follow-up duration's impact on the results.

The study findings also indicate that the risk of ASD might not be constant during follow-up from date of birth to event/censoring, due to peaks of events around specific ages, likely due to screening programmes in school-aged children and clinical practice.

For example, in Norway, 3 events (75% of the total ASD events) were observed in the 3-4 years age group for the valproate group, and 1 event (25% of the total ASD events) was observed in this same age group in the lamotrigine/levetiracetam group. In Sweden, 9 out of 31 events (almost 30% of the total ASD events) were observed at 8+ years of age, although this was mainly driven by events observed in the valproate group (8 events occurring in the 8-9 or 10-11 years age groups). In Denmark, small number masking prevented observation of the frequency of ASD events for all age groups; however, almost 30% of ASD events in the lamotrigine/levetiracetam group occurred in the 10-11 years age group.

These findings suggest that year of birth could be associated with the outcome, if offspring born later are more likely to be censored before some of these peaks can occur. In addition, the distribution of year of birth shows differences between the 2 exposure groups; while this confounder has been adjusted for using PS weighting, its association with censoring might still affect the robustness of the estimates in the 2 exposure groups, and their comparison. As this trend in the detection of ASD diagnosis was not anticipated when designing the study, the statistical approach used to compare the risk of experiencing ASD in the 2 exposure groups did not specifically account for this bias.

For example, regarding follow-up time and age at diagnosis of ASD, the following considerations should be noted: in Sweden, 721 offspring out of 2,354 were born on or before 2011; 389 belonged to the valproate group (42% of this cohort) and 332 belonged to the lamotrigine/levetiracetam group (23% of this cohort). In Denmark, 1,165 offspring out of 1,948 were born on or before 2011; 616 of them belonged to the valproate group (78% of this cohort) and 549 belonged to the lamotrigine/levetiracetam group (47% of this cohort).

Several methods could have been considered to mitigate this bias and account for the association between covariates such as year of birth, and censoring time. Some examples include the use of restricted mean survival analysis (RMST) (19). This method consists of estimating the average survival time of patients within a pre-specified time period, ie, up to a specified time point. The time point should be chosen to obtain

a RMST that reflects a clinically relevant time horizon (20); for example, this time horizon could be driven by clinical knowledge on onset/diagnosis of ASD, as well as data availability to be able to observe this diagnosis. Several methods have been proposed to adjust the difference in RMST for potential confounders (21,22). Alternatively, inverse probability of censoring weights (18) also aims to address this issue: in this approach, the censoring mechanism is modeled and used to create subject level weights (that can be used in addition to weights obtained by PS models). In this approach, a first time-to-event model is estimated where the event of interest is censoring, and subject level covariates are used to estimate the probability of each subject remaining uncensored at each time. This conditional probability is then used to create weights (with subjects not censored having higher weights) which can be incorporated into the final model. Assuming, for example, that year of birth is most likely associated with both lifetime/outcome (23) and censoring, this variable could be used in the censoring model to create censoring weights. While this issue might be more evident in this sensitivity analysis, some of the limitations identified might also apply more broadly to other study objectives assessing association between paternal exposure and NDD including ASD. The identified outage in the Norwegian results resulted in a shorter follow-up time. Although this actually made the 2 exposure groups comparable, it also significantly reduced the number of events, which had a major impact on the statistical power. As a result, it was not possible to provide any estimate. Overall, an inadequate sample size in sensitivity analysis 2 can hinder the ability to detect actual effects or differences in the results, even if there are fundamental differences between countries. Furthermore, outliers or extreme values can influence the sensitivity analysis results, causing opposite directions of results by countries. Inadequate sample size can lead to unreliable, unstable, and potentially misleading results.

12.4 Generalizability

As the results of both sensitivity analysis 2 and exploratory analysis 8 rely on a very limited number of events, their generalizability appears limited. The results may not be representative of the real-world situation in the investigated countries.

13. OTHER INFORMATION

None.

14. CONCLUSION

In sensitivity analysis 2, the risk of ASD in offspring paternally exposed to valproate compared to lamotrigine/levetiracetam was not similar to the one observed for NDD including ASD (ie, in the primary analysis) in Denmark and Sweden. In Norway, due to the shorter follow-up time, it was not possible to provide any estimate of the risk of ASD in offspring paternally exposed to valproate compared to those exposed to lamotrigine/levetiracetam because the number of events was <10. A significant increased risk of ASD was observed in offspring paternally exposed to valproate compared to those exposed

lamotrigine/levetiracetam in Sweden, but not in Denmark. However, a shorter follow-up was consistently observed in offspring paternally exposed to lamotrigine/levetiracetam compared to the valproate group. This may have resulted in a length of follow-up not allowing to adequately capture ASD diagnosis.

Exploratory analysis 8 showed that the most frequent target body system organ classes affected by CM were digestive system, limb, congenital heart defect, and genital in offspring paternally exposed to either valproate or lamotrigine/levetiracetam and most of the CM reported were considered as major in both Denmark and Norway.

The observed difference in the effect estimates for the different countries could be attributed to differences in sample size, follow-up duration, exposure time, or other factors that could have influenced the study results such as differences in treatment indication. Considering that the study was not originally designed to address the outcomes evaluated in sensitivity analysis 2 and exploratory analysis 8, it is important to acknowledge that the results are affected by various methodological limitations and low frequency of events that could affect the reliability and accuracy of the findings. Therefore, the conclusions drawn from the results of sensitivity analysis 2 and exploratory analysis 8 should be interpreted with caution.

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16. APPENDICES

16.1 Sensitivity Analysis 2

16.1.1 Denmark

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

Table 6 Offspring demographic characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/levetiracetam) N=1948**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Gestational age (weeks)										
<28 (extremely preterm)	***	***	***	***	***	***	***	***	***	***
28-31 (very preterm)	***	***	***	***	***	***	***	***	***	***
32-36 (moderate to late preterm)	46	5.82	36	3.11	***	***	***	***	82	4.21
37-41 (at term)	683	86.35	1064	91.96	960	91.95	104	92.04	1747	89.68
≥42 (post-term)	56	7.08	52	4.49	***	***	***	***	108	5.54
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	***	***	***	***	***	***	***	***	***	***
1000-1499 (very low)	***	***	***	***	***	***	***	***	***	***
1500-2499 (low)	15	1.90	35	3.03	***	***	***	***	50	2.57
≥2500	767	96.97	1114	96.28	1007	96.46	107	94.69	1881	96.56
Missing	***	***	***	***	***	***	***	***	9	0.46
Gender [a]										

ASD Number of offspring	Paternal exposure group									
	Valproate N=791		Lamotrigine/levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/levetiracetam) N=1948	
	N	%	N	%	N	%	N	%	N	%
Male	411	51.96	606	52.38	545	52.20	61	53.98	1017	52.21
Female	380	48.04	551	47.62	499	47.80	52	46.02	931	47.79
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of birth										
1997	30	3.79	6	0.52	6	0.57	0	0.00	36	1.85
1998	24	3.03	9	0.78	9	0.86	0	0.00	33	1.69
1999	32	4.05	7	0.61	7	0.67	0	0.00	39	2.00
2000	28	3.54	7	0.61	7	0.67	0	0.00	35	1.80
2001	54	6.83	18	1.56	18	1.72	0	0.00	72	3.70
2002	51	6.45	13	1.12	***	***	***	***	64	3.29
2003	58	7.33	27	2.33	***	***	***	***	85	4.36
2004	43	5.44	25	2.16	25	2.39	0	0.00	68	3.49
2005	56	7.08	41	3.54	***	***	***	***	97	4.98
2006	55	6.95	47	4.06	47	4.50	0	0.00	102	5.24
2007	44	5.56	54	4.67	***	***	***	***	98	5.03
2008	31	3.92	65	5.62	56	5.36	9	7.96	96	4.93
2009	43	5.44	70	6.05	64	6.13	6	5.31	113	5.80
2010	39	4.93	76	6.57	***	***	***	***	115	5.90
2011	28	3.54	84	7.26	***	***	***	***	112	5.75
2012	29	3.67	92	7.95	***	***	***	***	121	6.21
2013	29	3.67	88	7.61	78	7.47	10	8.85	117	6.01
2014	31	3.92	101	8.73	89	8.52	12	10.62	132	6.78
2015	35	4.42	95	8.21	83	7.95	12	10.62	130	6.67
2016	26	3.29	102	8.82	86	8.24	16	14.16	128	6.57
2017	19	2.40	72	6.22	54	5.17	18	15.93	91	4.67
2018	6	0.76	58	5.01	45	4.31	13	11.50	64	3.29

ASD Number of offspring	Paternal exposure group									
	Valproate N=791		Lamotrigine/levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/levetiracetam) N=1948	
	N	%	N	%	N	%	N	%	N	%
Total number of years of follow-up	7473. 02		7708. 41		7206. 52		501. 89		15181. 44	
Mean follow-up year	9. 45		6. 66		6. 9		4. 44		7. 79	

ASD: autism spectrum disorders; g: grams.
*** Masked values indicating 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 will be 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 7 Offspring clinical characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

ASD Number of offspring	Paternal exposure group									
	Valproate N=791		Lamotrigine/Levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/ levetiracetam) N=1948	
	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	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Foetal alcohol syndrome	***	***	***	***	***	***	***	***	***	***
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	0	0.00	0	0.00	0	0.00	0	0.00
Medication use										
Exposure to AEDs [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Outcomes										
ASD (ever, not only as 1st NDD diagnosis)	11	1.39	21	1.82	***	***	***	***	32	1.64
ASD (as 1st NDD diagnosis)	11	1.39	16	1.38	***	***	***	***	27	1.39
NDD including ASD	41	5.18	41	3.54	***	***	***	***	82	4.21
Age at the first diagnosis (years)										
ASD (ever, not only as 1st NDD diagnosis) [b,c]										
0-1	***	***	***	***	***	***	***	***	***	***
2-3	***	***	5	0.43	***	***	***	***	***	***
4-5	***	***	***	***	***	***	***	***	5	0.26
6-7	***	***	***	***	***	***	***	***	7	0.36
8-9	***	***	***	***	***	***	***	***	5	0.26
10-11	0	0.00	6	0.52	6	0.57	0	0.00	6	0.31
Total (offspring with the outcome)	11	1.4	21	1.82	19	1.81	***	***	32	1.65

ASD Number of offspring	Paternal exposure group									
	Valproate N=791		Lamotrigine/Levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/ levetiracetam) N=1948	
	N	%	N	%	N	%	N	%	N	%
NDD including ASD [b,c]										
0-1	***	***	***	***	***	***	***	***	7	0.36
2-3	5	0.63	8	0.69	***	***	***	***	13	0.67
4-5	***	***	***	***	***	***	0	0.00	13	0.67
6-7	11	1.39	6	0.52	***	***	***	***	17	0.87
8-9	12	1.52	7	0.61	***	***	***	***	19	0.98
10-11	7	0.88	6	0.52	6	0.57	0	0.00	13	0.67
Total (offspring with the outcome)	41	5.18	41	3.55	***	***	***	***	82	4.22

AED: antiepileptic drug; ASD: autism spectrum disorders; CMV: cytomegalovirus; 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 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 might be adapted according to the data.

Table 8 Maternal demographic characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

ASD Number of offspring	Paternal exposure group									
	Valproate N=791		Lamotrigine/levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/ levetiracetam) N=1948	
	N	%	N	%	N	%	N	%	N	%
Mother's age [a]										
≤20 years	10	1.26	19	1.64	***	***	***	***	29	1.49
21-25	136	17.19	156	13.48	***	***	***	***	292	14.99
26-30	287	36.28	399	34.49	356	34.10	43	38.05	686	35.22
31-35	259	32.74	391	33.79	345	33.05	46	40.71	650	33.37
36-40	87	11.00	160	13.83	152	14.56	8	7.08	247	12.68
>40	12	1.52	32	2.77	32	3.07	0	0.00	44	2.26
Mean (SD)	30.01 (4.70)		30.69 (4.99)		30.78 (5.07)		29.90 (4.07)		30.41 (4.88)	
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

ASD: autism spectrum disorders; Max: maximum; Min: minimum; SD: standard deviation.
*** Masked values indicating 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 will be 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 9 Maternal clinical characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

ASD	Paternal exposure group									
Number of offspring	Valproate N=791		Lamotrigine/ levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/ levetiracetam) N=1948	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Affective disorder [a]	19	2.40	55	4.75	***	***	***	***	74	3.80
Diabetes [a]	9	1.14	25	2.16	***	***	***	***	34	1.75
Epilepsy [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Neurotic disorder [a]	44	5.56	83	7.17	***	***	***	***	127	6.52
Schizophrenia, schizotypal and delusional disorders [a]	***	***	9	0.78	***	***	***	***	***	***
Obesity [b]	10	1.26	18	1.56	***	***	***	***	28	1.44
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gestational diabetes [c]	28	3.54	46	3.98	41	3.93	5	4.42	74	3.80
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	0.31
Alcohol abuse during pregnancy [c]	***	***	***	***	***	***	***	***	***	***
Substance abuse prior to LMP2 [b]	***	***	***	***	***	***	***	***	***	***
Substance abuse during pregnancy [c]	***	***	***	***	***	***	***	***	6	0.31
Smoking prior to LMP2 [b]										
Yes	***	***	16	1.38	16	1.53	0	0.00	***	***
No	25	3.16	43	3.72	37	3.54	6	5.31	68	3.49
Missing	***	***	1098	94.90	991	94.92	107	94.69	***	***
Smoking during pregnancy [c]										
Yes	131	16.56	180	15.56	***	***	***	***	311	15.97
No	604	76.36	954	82.45	857	82.09	97	85.84	1558	79.98

ASD Number of offspring	Paternal exposure group Valproate N=791		Lamotrigine/ levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/ levetiracetam) N=1948	
	N	%	N	%	N	%	N	%	N	%
Missing	56	7.08	23	1.99	***	***	***	***	79	4.06
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	0	0.00	0	0.00	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00	0	0.00	0	0.00	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	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	0	0.00	0	0.00	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
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	0	0.00	0	0.00	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00	0	0.00	0	0.00	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	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	0	0.00	0	0.00	0	0.00	0	0.00

ASD Number of offspring	Paternal exposure group Valproate N=791		Lamotrigine/ levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/ levetiracetam) N=1948	
	N	%	N	%	N	%	N	%	N	%
Carboxamide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
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	791	100.00	1157	100.00	1044	100.00	113	100.00	1948	100.00
K-means cluster during pregnancy [c]										
unexposed	791	100.00	1157	100.00	1044	100.00	113	100.00	1948	100.00
Maternal polypharmacy index prior to LMP2 [d]										
0	548	69.28	716	61.88	629	60.25	87	76.99	1264	64.89
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
Mean (SD)	0.48 (0.89)		0.68 (1.13)		0.72 (1.16)		0.35 (0.74)		0.60 (1.04)	
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]										
0	435	54.99	535	46.24	***	***	***	***	970	49.79
1-4	345	43.62	596	51.51	542	51.92	54	47.79	941	48.31
5-10	***	***	***	***	***	***	***	***	***	***
>10	***	***	***	***	***	***	***	***	***	***
Mean (SD)	0.75 (1.07)		0.99 (1.29)		1.01 (1.32)		0.81 (1.03)		0.90 (1.21)	
Median (25^{th} - 75^{th} percentile)	0 (0.00, 1.00)		1 (0.00, 2.00)		1 (0.00, 2.00)		0 (0.00, 1.00)		1 (0.00, 1.00)	

ASD Number of offspring	Paternal exposure group Valproate N=791		Lamotrigine/ levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/ levetiracetam) N=1948	
	N	%	N	%	N	%	N	%	N	%
Min, max	***		***		***		***		***	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	43	5.44	97	8.38	***	***	***	***	140	7.19
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
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] - mothers with at least one prescription	555	70.16	819	70.79	748	71.65	71	62.83	1374	70.53
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	303	38.31	552	47.71	501	47.99	51	45.13	855	43.89

AED: antiepileptic drug; ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period plus 2 weeks; Max: Maximum; Min: Minimum; 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) 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 10 Paternal demographic characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD **Number of offspring**	**Valproate N=791**		**Lamotrigine/levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/levetiracetam) N=1948**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Father's age [a]										
≤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	28.95	269	23.25	245	23.47	24	21.24	498	25.56
31-35	299	37.80	408	35.26	352	33.72	56	49.56	707	36.29
36-40	144	18.20	253	21.87	237	22.70	16	14.16	397	20.38
>40	65	8.22	129	11.15	123	11.78	6	5.31	194	9.96
Mean (SD)	32.69 (5.33)		33.39 (5.89)		33.52 (5.98)		32.24 (4.88)		33.11 (5.68)	
Median	32		33		33		32		33	
(25th - 75th percentile)	(29.00, 36.00)		(29.00, 37.00)		(29.00, 37.00)		(30.00, 35.00)		(29.00, 36.50)	
Min, max	***		***		***		***		***	
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of offspring conception [b]										
1996	***	***	***	***	***	***	***	***	30	1.54
1997	21	2.65	8	0.69	8	0.77	0	0.00	29	1.49
1998	31	3.92	7	0.61	7	0.67	0	0.00	38	1.95
1999	31	3.92	7	0.61	7	0.67	0	0.00	38	1.95
2000	44	5.56	14	1.21	14	1.34	0	0.00	58	2.98
2001	54	6.83	18	1.56	***	***	***	***	72	3.70
2002	48	6.07	19	1.64	***	***	***	***	67	3.44
2003	47	5.94	28	2.42	28	2.68	0	0.00	75	3.85
2004	56	7.08	40	3.46	***	***	***	***	96	4.93
2005	59	7.46	44	3.80	***	***	***	***	103	5.29
2006	43	5.44	45	3.89	45	4.31	0	0.00	88	4.52
2007	34	4.30	66	5.70	58	5.56	8	7.08	100	5.13
2008	42	5.31	75	6.48	67	6.42	8	7.08	117	6.01
2009	42	5.31	68	5.88	***	***	***	***	110	5.65
2010	36	4.55	79	6.83	74	7.09	5	4.42	115	5.90

	Paternal exposure group									
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/levetiracetam) N=1948**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
2011	20	2.53	89	7.69	***	***	***	***	109	5.60
2012	33	4.17	92	7.95	83	7.95	9	7.96	125	6.42
2013	26	3.29	100	8.64	89	8.52	11	9.73	126	6.47
2014	34	4.30	104	8.99	92	8.81	12	10.62	138	7.08
2015	35	4.42	94	8.12	80	7.66	14	12.39	129	6.62
2016	19	2.40	80	6.91	63	6.03	17	15.04	99	5.08
2017	9	1.14	55	4.75	40	3.83	15	13.27	64	3.29
2018	***	***	***	***	***	***	***	***	22	1.13

ASD: autism spectrum disorders: LMP2: last menstrual period plus 2 weeks; Max: Maximum; Min: Minimum; SD: standard deviation.
*** Masked values indicating 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 will be 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 11 Paternal clinical characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/ levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/ levetiracetam) N=1948**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Comorbidities										
Bipolar affective disorder excl. bipolar disorder and mania [a]	30	3.79	150	12.96	***	***	***	***	180	9.24
Bipolar affective disorder [a]	21	2.65	84	7.26	84	8.05	0	0.00	105	5.39
Mania [a]	6	0.76	9	0.78	9	0.86	0	0.00	15	0.77
Neurotic disorder [a]	48	6.07	130	11.24	123	11.78	7	6.19	178	9.14
Schizophrenia, schizotypal and delusional disorders [a]	16	2.02	25	2.16	25	2.39	0	0.00	41	2.10
Lifestyle characteristics										
Substance abuse [b]	5	0.63	***	***	***	***	***	***	***	***
Medication use										
AED indication										
Epilepsy	550	69.53	685	59.20	583	55.84	102	90.27	1235	63.40
Bipolar affective disorder and mania	22	2.78	84	7.26	84	8.05	0	0.00	106	5.44
Other/unknown	219	27.69	388	33.54	377	36.11	11	9.73	607	31.16
K-means cluster prior to LMP2 [c]										
cluster A	416	52.59	665	57.48	588	56.32	77	68.14	1081	55.49
cluster B	375	47.41	492	42.52	456	43.68	36	31.86	867	44.51
Paternal polypharmacy index [c]										
0	545	68.90	653	56.44	568	54.41	85	75.22	1198	61.50
1-4	234	29.58	480	41.49	452	43.30	28	24.78	714	36.65
5-10	12	1.52	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
Mean (SD)	0.54 (1.13)		0.81 (1.23)		0.86 (1.27)		0.32 (0.63)		0.70 (1.20)	
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	***		***		***		***		***	

	Paternal exposure group									
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/ levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/ levetiracetam) N=1948**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Concomitant medications associated with valproate-indicated psychiatric conditions [b] – fathers with at least one prescription	96	12.14	360	31.11	***	***	***	***	456	23.41
Concomitant medications associated with neuropsychiatric adverse events [b] - fathers with at least one prescription	386	48.80	648	56.01	600	57.47	48	42.48	1034	53.08

AED: antiepileptic drug; ASD: autism spectrum disorders; LMP2: last menstrual period plus 2 weeks; Min: minimum, Max: maximum; SD: standard deviation.
*** Masked values indicating 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 will be described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
Cluster A: constant high exposure, cluster B: constant low exposure.
a) all available data prior to index date (childbirth); b) 12-months lookback from LMP2; c) 3-months lookback from LMP2.

16.1.1.2 Cumulative incidence proportion

Table 12 Cumulative incidence proportion (risk) of ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	791	1157	1044	113	1948
0-1 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	782	1092	992	100	1874
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	760	1014	933	81	1774
2-3 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	732	911	847	64	1643
3-4 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	695	808	757	51	1503
4-5 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	662	709	670	39	1371
5-6 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	630	617	587	30	1247
6-7 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	596	530	***	***	1126
7-8 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	565	444	422	22	1009
8-9 years	n	***	***	***	***	***

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	n/N*100	***	***	***	***	***
	N	525	372	***	***	897
9-10 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	481	303	292	11	784
10-11 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	451	239	234	5	690
11-12 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	791	1157	1044	113	1948
Overall (0-12 years)	n	11	21	***	***	32
	n/N*100	1.39 (0.57, 2.21)	1.82 (1.05, 2.58)	***	***	1.64 (1.08, 2.21)

ASD: autism spectrum disorder.
*** Masked values indicating 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) will be presented.

Table 13 Cumulative incidence proportion (risk) of ASD by paternal exposure group for male offspring

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	411	606	545	61	1017
0-1 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	***	574	518	56	***
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	395	526	483	43	921
2-3 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	381	472	437	35	853
3-4 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	360	421	394	27	781
4-5 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	346	369	349	20	715
5-6 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	327	323	***	***	650
6-7 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	309	285	271	14	594
7-8 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	298	239	***	***	537
8-9 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	276	203	***	***	479
9-10 years	n	***	***	***	***	***

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	n/N*100	***	***	***	***	***
	N	247	167	161	6	414
10-11 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	227	131	***	***	358
11-12 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	411	606	545	61	1017
Overall (0-12 years)	n	6	***	***	***	***
	n/N*100	1.46 (0.30,2.62)	***	***	***	***

ASD: autism spectrum disorder.
Legend: Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which will be 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) will be presented.

Table 14 Cumulative incidence proportion (risk) of ASD by paternal exposure group for female offspring

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	380	551	499	52	931
0-1 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	***	518	474	44	***
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	365	488	450	38	853
2-3 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	351	439	410	29	790
3-4 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	335	387	363	24	722
4-5 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	316	340	321	19	656
5-6 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	303	294	***	***	597
6-7 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	287	245	233	12	532
7-8 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	267	205	***	***	472
8-9 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	249	169	***	***	418
9-10 years	n	***	***	***	***	***

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	380	551	499	52	931
	n/N*100	***	***	***	***	***
	N	234	136	131	5	370
10-11 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	224	108	***	***	332
11-12 years	n	***	***	***	***	***
	n/N*100	***	***	***	***	***
	N	380	551	499	52	931
Overall (0-12 years)	n	5	***	***	***	***
	n/N*100	1.32 (0.17,2.46)	***	***	***	***

ASD: autism spectrum disorder.
Legend: Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which will be 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) will be presented.

16.1.1.3 Cumulative incidence rate and time to ASD diagnosis

Table 15 Cumulative incidence rate of ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	787.19	1120.28	1014.78	105.49	1907.47
0-1 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	1559.05	2173.87	1978.5	195.37	3732.93
0-2 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	2305.97	3138.93	2870.96	267.97	5444.9
0-3 years	n	***	***	***	***	5
	n/PY*1000	***	***	***	***	0.92 (0.30, 2.14)
	PY	3017.25	4002.25	3677.79	324.47	7019.51
0-4 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	3694.38	4758.72	4390.68	368.04	8453.1
0-5 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	4340.5	5418.67	5015.87	402.81	9759.17
0-6 years	n	5	9	***	***	14
	n/PY*1000	1.15 (0.37, 2.69)	1.66 (0.76, 3.15)	***	***	1.43 (0.78, 2.41)
	PY	4951.87	5991.42	5560.72	430.7	10943.29
0-7 years	n	***	9	***	***	***
	n/PY*1000	***	1.5 (0.69, 2.85)	***	***	***
	PY	5536.74	6477.32	6022.76	454.56	12014.07
0-8 years	n	***	***	***	***	21
	n/PY*1000	***	***	***	***	1.75 (1.08, 2.67)
	PY	6079.73	6887.24	6413.24	474	12966.96
0-9 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	787.19	1120.28	1014.78	105.49	1907.47
	PY	6582.58	7225.8	6736.06	489.75	13808.39
0-10 years	n	11	15	***	***	26
	n/PY*1000	1.67 (0.83, 2.99)	2.08 (1.16, 3.42)	***	***	1.88 (1.23, 2.76)
	PY	7046.2	7495.21	6997.37	497.84	14541.41
0-11 years	n	11	***	***	***	***
	n/PY*1000	1.56 (0.78, 2.79)	***	***	***	***
	PY	7473.02	7708.41	7206.52	501.89	15181.44
0-12 years	n	11	21	***	***	32
	n/PY*1000	1.47 (0.73, 2.63)	2.72 (1.69, 4.16)	***	***	2.11 (1.44, 2.98)

ASD: autism spectrum disorder; PY: person years.
*** Masked values indicating 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) will be presented.

Table 16. Cumulative incidence rate of ASD by paternal exposure group for males

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	410.24	588.66	530.17	58.49	998.9
0-1 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	812.92	1142.08	1034.39	107.69	1955.01
0-2 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	1201.12	1643.3	1496.07	147.23	2844.42
0-3 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	1570	2091.44	1914.15	177.28	3661.44
0-4 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	1921.56	2485.42	2285.48	199.94	4406.98
0-5 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	2256.87	2830.17	2611.93	218.24	5087.04
0-6 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	2573.02	3130.41	2897.84	232.57	5703.43
0-7 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	2878.81	3392.34	3146.76	245.58	6271.15
0-8 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	3163.12	3614.41	3357.9	256.51	6777.53
0-9 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	3423.19	380116	3535.56	265.6	7224.35
0-10 years	n	6	***	***	***	***

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	410.24	588.66	530.17	58.49	998.9
	n/PY*1000	1.75 (0.64, 3.82)	***	***	***	***
	PY	3657.96	3950.56	3680.47	270.09	7608.52
0-11 years	n	6	***	***	***	***
	n/PY*1000	1.64 (0.60, 3.57)	***	***	***	***
	PY	3872.05	4065.14	3792.05	273.09	7937.19
0-12 years	n	6	***	***	***	***
	n/PY*1000	1.55 (0.57, 3.37)	***	***	***	***

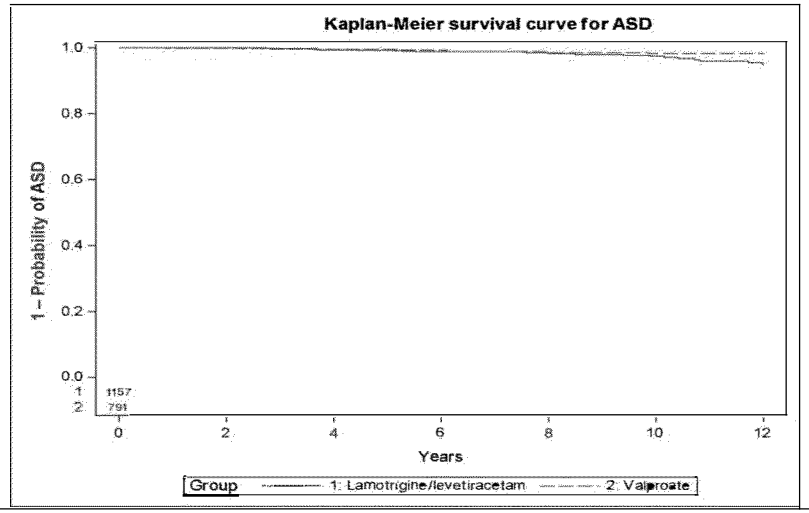
ASD: autism spectrum disorder; PY: person years.
*** Masked values indicating that data was calculated but not disclosed.
Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which will be determined based on the results of the univariate 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) will be presented.

Table 17 Cumulative incidence rate of ASD by paternal exposure group for females

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	376.95	531.62	484.61	47	908.57
0-1 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	746.13	1031.79	944.11	87.68	1777.92
0-2 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	1104.85	1495.62	1374.89	120.73	2600.47
0-3 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	1447.25	1910.82	1763.64	147.18	3358.07
0-4 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	1772.82	2273.3	2105.2	168.1	4046.12
0-5 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	2083.62	2588.5	2403.94	184.56	4672.13
0-6 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	2378.85	2861.02	2662.88	198.13	5239.86
0-7 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	2657.93	3084.98	2875.99	208.99	5742.91
0-8 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	2916.6	3272.83	3055.34	217.49	6189.43
0-9 years	n	***	***	***	***	***
	n/PY*1000	***	***	***	***	***
	PY	3159.39	3424.64	3200.5	224.15	6584.03
0-10 years	n	5	***	***	***	***

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	n/PY*1000	1.58 (0.51, 3.69)	***	***	***	***
	PY	3388.24	3544.65	3316.9	227.75	6932.89
0-11 years	n	5	***	***	***	***
	n/PY*1000	1.48 (0.48, 3.44)	***	***	***	***
	PY	3600.98	3643.27	3414.47	228.81	7244.25
0-12 years	n	5	***	***	***	***
	n/PY*1000	1.39 (0.45, 3.24)	***	***	***	***

ASD: autism spectrum disorder; PY: person years.
*** Masked values indicating that data was calculated but not disclosed.
Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which will be 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) will be presented.



ASD	Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Number of events	11	21	***	***	32
Number of censor	780	1136	***	***	1916
Survival time					
5th percentile	- (-,-)	145.77 (123.53, -)	- (-,-)	120.27 (34.83, -)	- (-,-)
10th percentile	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
25th percentile	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
median	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
75th percentile	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)

ASD: autism spectrum disorder.
Legend: Due to low number of events the median time-to-event could not be calculated.

Figure 3 Kaplan-Meier survival curve for Autism Spectrum Disorder (ASD) and distribution of time to ASD in Denmark

Table 18 Time to ASD by paternal exposure group for male offspring

	Paternal exposure group				
ASD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (Valproate + lamotrigine /levetiracetam)**
Number of events	6	***	***	***	***
Number of censor	405	***	***	***	***
Survival time					
5th percentile	- (-,-)	126.67 (91.37, -)	130.40 (92.33, -)	120.27 (34.83, -)	- (-,-)
10th percentile	- (-,-)	- (-,-)	- (-,-)	120.27 (34.83, -)	- (-,-)
25th percentile	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
median	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
75th percentile	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)

ASD: autism spectrum disorder.
*** Masked values indicating that data was calculated but not disclosed.
Legend: Time-to-event analysis may be stratified according to relevant strong risk factors (such as age or gender) which will be determined based on the results of the univariate analyses. As an example, this table and the table below present stratification by gender.

Table 19 Time to ASD by paternal exposure group for female offspring

	Paternal exposure group				
ASD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	5	***	***	***	***
Number of censor	375	***	***	***	***
Survival time					
5th percentile	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
10th percentile	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
25th percentile	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
median	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)
75th percentile	- (-,-)	- (-,-)	- (-,-)	- (-,-)	- (-,-)

ASD: autism spectrum disorder.
*** Masked values indicating that data was calculated but not disclosed.
Legend: Time-to-event analysis may be stratified according to relevant strong risk factors (such as age or gender) which will be determined based on the results of the univariate analyses. As an example, this table and the table above present stratification by gender.

16.1.1.4 Association between potential risk factors/confounders for ASD and paternal exposure group

Table 20 Association between potential offspring risk factors/confounders for ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group										Comparison
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/ levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/ levetiracetam) N=1948**		**Valproate vs Lamotrigine /levetiracetam-**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Offspring risk factors/confounders											
Gender [a]											
Male	411	51.96	606	52.38	545	52.20	61	53.98	1017	52.21	-
Female	380	48.04	551	47.62	499	47.80	52	46.02	931	47.79	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	0.03 (0.8563)
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]	***	***	***	***	***	***	***	***	***	***	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	-

ASD: autism spectrum disorders; CMV: cytomegalovirus.
*** Masked values indicating that data was calculated but not disclosed.
* 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 used.
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 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.

Table 21 Association between potential maternal risk factors/confounders for ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group										Comparison
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/ levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/ levetiracetam) N=1948**		**Valproate vs 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	17.19	156	13.48	***	***	***	***	292	14.99	-
26-30	287	36.28	399	34.49	356	34.10	43	38.05	686	35.22	-
31-35	259	32.74	391	33.79	345	33.05	46	40.71	650	33.37	-
36-40	87	11.00	160	13.83	152	14.56	8	7.08	247	12.68	-
>40	12	1.52	32	2.77	32	3.07	0	0.00	44	2.26	-
Test statistics	-	-	-	-	-	-	-	-	-	-	11.56 (0.0413)
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)	-	735708.00 (0.0039)*
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	3.80	7.11 (0.0077)
Diabetes [b]	9	1.14	25	2.16	***	***	***	***	34	1.75	2.87 (0.0904)
Gestational diabetes [c]	28	3.54	46	3.98	41	3.93	5	4.42	74	3.80	0.24 (0.6211)
Neurotic disorder [b]	44	5.56	83	7.17	***	***	***	***	127	6.52	2.00 (0.1572)
Schizophrenia, schizotypal and delusional disorders [b]	***	***	9	0.78	***	***	***	***	***	***	0.38 (0.3803)*

	Paternal exposure group										Comparison
ASD **Number of offspring**	**Valproate N=791**		**Lamotrigine/ levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/ levetiracetam) N=1948**		**Valproate vs Lamotrigine /levetiracetam** -
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Obesity [d]	10	1.26	18	1.56	***	***	***	***	28	1.44	0.28 (0.5955)
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]	***	***	***	***	***	***	***	***	6	0.31	1.00 (1.0000)*
Alcohol abuse during pregnancy [c]	***	***	***	***	***	***	***	***	***	***	1.00 (1.0000)*
Substance abuse prior to LMP2 [d]	***	***	***	***	***	***	***	***	***	***	0.27 (0.2761)*
Substance abuse during pregnancy [c]	***	***	***	***	***	***	***	***	6	0.31	1.00 (1.0000)*
Smoking prior to LMP2 [d]											
No	25	3.16	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	604	76.36	954	82.45	857	82.09	97	85.84	1558	79.98	-
Yes	131	16.56	180	15.56	***	***	***	***	311	15.97	-
Missing	56	7.08	23	1.99	***	***	***	***	79	4.06	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	1.22 (0.2688)
Maternal polypharmacy index prior to LMP2 [e] (categorical)											
0	548	69.28	716	61.88	629	60.25	87	76.99	1264	64.89	-
1-4	***	***	424	36.65	398	38.12	26	23.01	***	***	-
5-10	***	***	17	1.47	17	1.63	0	0.00	***	***	-

	Paternal exposure group										Comparison
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/ levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/ levetiracetam) N=1948**		**Valproate vs Lamotrigine /levetiracetam**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	13.72 (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)	-	731967.50 (0.0002)*
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] (categorical)											
0	435	54.99	535	46.24	***	***	***	***	970	49.79	-
1-4	345	43.62	596	51.51	542	51.92	54	47.79	941	48.31	-
5-10	***	***	***	***	***	***	***	***	***	***	-
>10	***	***	***	***	***	***	***	***	***	***	-
Test statistics	-	-	-	-	-	-	-	-	-	-	15.49 (0.0014)
Maternal polypharmacy index during pregnancy[c] (continuous)											
Mean (SD)	0.75 (1.07)	-	0.99 (1.29)	-	1.01 (1.32)	-	0.81 (1.03)	-	0.90 (1.21)	-	724617.00 (<.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	43	5.44	97	8.38	***	***	***	***	140	7.19	6.12 (0.0134)

	Paternal exposure group										Comparison
ASD Number of offspring	Valproate N=791		Lamotrigine/ levetiracetam N=1157		Lamotrigine N=1044		Levetiracetam N=113		Total (valproate + lamotrigine/ levetiracetam) N=1948		Valproate vs Lamotrigine /levetiracetam -
	N	%	N	%	N	%	N	%	N	%	
prior to LMP2 [d] - mothers with at least one prescription											
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	9.32 (0.0023)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription	555	70.16	819	70.79	748	71.65	71	62.83	1374	70.53	0.09 (0.7674)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	303	38.31	552	47.71	501	47.99	51	45.13	855	43.89	16.87 (<.0001)

ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; Max: maximum; Min: minimum; SD: standard deviation.
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
* 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.
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 (ASD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, ie row percentage). The association between each characteristics and the outcome were 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 22 Association between potential paternal risk factors/confounders for ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group										Comparison
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/ levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/ levetiracetam) N=1948**		**Valproate vs Lamotrigine /levetiracetam**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	-
Paternal risk factors/confounders											
Affective disorder excluding bipolar affective disorder and mania [a]	30	3.79	150	12.96	***	***	***	***	180	9.24	47.13 (<.0001)
Bipolar affective disorder [a]	21	2.65	84	7.26	84	8.05	0	0.00	105	5.39	19.54 (<.0001)
Mania [a]	6	0.76	9	0.78	9	0.86	0	0.00	15	0.77	0.00 (0.9618)
Neurotic disorder [a]	48	6.07	130	11.24	123	11.78	7	6.19	178	9.14	15.11 (0.0001)
Schizophrenia, schizotypal and delusional disorders [a]	16	2.02	25	2.16	25	2.39	0	0.00	41	2.10	0.04 (0.8349)
Substance abuse [c]	5	0.63	***	***	***	***	***	***	***	***	0.12 (0.1277)*
Paternal polypharmacy index [d] (categorical)											
0	545	68.90	653	56.44	568	54.41	85	75.22	1198	61.50	-
1-4	234	29.58	480	41.49	452	43.30	28	24.78	714	36.65	-
5-10	12	1.52	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	-	-	-	-	-	-	-	-	-	-	30.81 (<.0001)
Paternal polypharmacy 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)		708592.50 (<.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	***		***		***		***		***		-

	Paternal exposure group										Comparison
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/ levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/ levetiracetam) N=1948**		**Valproate vs Lamotrigine /levetiracetam** -
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] – fathers with at least one prescription	96	12.14	360	31.11	***	***	***	***	456	23.41	94.38 (<.0001)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription	386	48.80	648	56.01	600	57.47	48	42.48	1034	53.08	9.80 (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	28.95	269	23.25	245	23.47	24	21.24	498	25.56	-
31-35	299	37.80	408	35.26	352	33.72	56	49.56	707	36.29	-
36-40	144	18.20	253	21.87	237	22.70	16	14.16	397	20.38	-
>40	65	8.22	129	11.15	123	11.78	6	5.31	194	9.96	-
Test statistics	-	-	-	-	-	-	-	-	-	-	15.73 (0.0077)
Father's age [e] (continuous)	32.69 (5.33)		33.39 (5.89)		33.52 (5.98)		32.24 (4.88)		33.11 (5.68)		738738.00 (0.0084)*
Mean (SD)	32 (29.00, 36.00)		33 (29.00, 37.00)		33 (29.00, 37.00)		32 (30.00, 35.00)		33 (29.00, 36.50)		-
Median (25th - 75th percentile) Min, max	***		***		***		***		***		-
Year of offspring conception [f,g]	207	26.17	58	5.01	***	***	***	***	265	13.60	-
2006-2010	287	36.28	242	20.92	***	***	***	***	529	27.16	-
2011-2015	173	21.87	403	34.83	375	35.92	28	24.78	576	29.57	-

	Paternal exposure group										Comparison
ASD Number of offspring	**Valproate N=791**		**Lamotrigine/ levetiracetam N=1157**		**Lamotrigine N=1044**		**Levetiracetam N=113**		**Total (valproate + lamotrigine/ levetiracetam) N=1948**		**Valproate vs Lamotrigine /levetiracetam -**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
2016-2019	124	15.68	454	39.24	381	36.49	73	64.60	578	29.67	-
Test statistics	-	-	-	-	-	-	-	-	-	-	310.03 (<.0001)

ASD: autism spectrum disorders; LMP2: last menstrual period date plus 2 weeks; Max: maximum; Min: minimum; SD: standard deviation.
*** Masked values indicated that data was calculated but not disclosed due to small number of participants.
* 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.
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) 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 will be grouped in each country according to the length of the study period.

16.1.1.5 Association between potential risk factors/confounders and ASD

Table 23 Association between potential offspring risk factors/confounders and ASD; ASD as outcome for sensitivity analysis 2

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Offspring risk factors/confounders								
Gender [a]								
Male	1017	52.21	25	2.46	992	97.54	Reference	-
Female	931	47.79	7	0.75	924	99.25	0.30 (0.13, 0.70)	-
Missing	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	7.81, 0.0052
Congenital CMV [b]								
No	1948	100.00	32	1.64	1916	98.36	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital rubella [b]								
No	1948	100.00	32	1.64	1916	98.36	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Foetal alcohol syndrome [b]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00, I)	0.00, 0.9931
Fragile X syndrome [b]								
No	1948	100.00	32	1.64	1916	98.36	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Lejeune/cri du chat syndrome [b]								
No	1948	100.00	32	1.64	1916	98.36	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Tuberous sclerosis [b]								
No	1948	100.00	32	1.64	1916	98.36	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-

ASD: autism spectrum disorders; CI: confidence interval; CMV: cytomegalovirus; 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 (ASD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, ie 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 24 Association between potential maternal risk factors/confounders and ASD; ASD as outcome for sensitivity analysis 2

ASD	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	***	***	***	***	2.41 (0.30, 19.52)	-
21-25	292	14.99	5	1.71	287	98.29	1.18 (0.40, 3.48)	-
26-30	686	35.22	10	1.46	676	98.54	Reference	-
31-35	650	33.37	8	1.23	642	98.77	0.84 (0.33, 2.15)	-
36-40	247	12.68	***	***	***	***	1.40 (0.47, 4.13)	-
>40	44	2.26	***	***	***	***	4.95 (1.31, 18.67)	-
Wald test	-	-	-	-	-	-	-	7.50,0.1863
Affective disorder [b]								
No	1874	96.20	27	1.44	1847	98.56	Reference	-
Yes	74	3.80	5	6.76	69	93.24	4.96 (1.85, 13.26)	10.17,0.0014
Diabetes [b]								
No	1914	98.25	***	***	***	***	Reference	-
Yes	34	1.75	***	***	***	***	1.84 (0.24, 13.89)	0.35,0.5539
Gestational diabetes [c]								
No	1874	96.20	***	***	***	***	Reference	-
Yes	74	3.80	***	***	***	***	1.71 (0.40, 7.28)	0.52, 0.4697
Neurotic disorder [b]								
No	1821	93.48	***	***	***	***	Reference	-
Yes	127	6.52	***	***	***	***	1.49 (0.45, 4.98)	0.43, 0.5122
Schizophrenia, schizotypal and delusional disorders [b]								
No	1936	99.38	***	***	***	***	Reference	-
Yes	12	0.62	***	***	***	***	12.71 (2.67, 60.49)	10.20, 0.0014
Obesity [d]								
No	1920	98.56	***	***	***	***	Reference	-
Yes	28	1.44	***	***	***	***	2.26 (0.30, 17.14)	0.62, 0.4313
CMV [c]								
No	1948	100.00	32	1.64	1916	98.36	-	-

ASD	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	-	-
Rubella [c]								
No	1948	100.00	32	1.64	1916	98.36	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse prior to LMP2 [d]								
No	1942	99.69	32	1.65	1910	98.35	Reference	-
Yes	6	0.31	0	0.00	6	100.00	0.00 (0.00, I)	0.00, 0.9888
Alcohol abuse during pregnancy [c]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	0.00 (0.00, I)	0.00, 0.9903
Substance abuse prior to LMP2 [d]								
No	***	***	***	***	***	***	Reference	-
Yes	***	***	***	***	***	***	30.87 (2.73, 349.47)	7.68, 0.0056
Substance abuse during pregnancy [c]								
No	1942	99.69	32	1.65	1910	98.35	Reference	-
Yes	6	0.31	0	0.00	6	100.00	0.00 (0.00, I)	0.00, 0.9888
Smoking prior to LMP2 [d]								
No	68	3.49	***	***	***	***	Reference	-
Yes	20	1.03	0	0.00	20	100.00	0.00 (0.00, 1.7148E157)	-
Missing	1860	95.48	***	***	***	***	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	0.00, 0.9609
Smoking during pregnancy [c]								
No	1558	79.98	20	1.28	1538	98.72	Reference	-
Yes	311	15.97	***	***	***	***	2.55 (1.18, 5.51)	-
Missing	79	4.06	***	***	***	***	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	5.71, 0.0168
Maternal polypharmacy index prior to LMP2 [c](categorical)								
0	1264	64.89	18	1.42	1246	98.58	Reference	-
1-4	663	34.03	14	2.11	649	97.89	1.49 (0.74, 3.02)	-

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
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	-	-	-	-	-	-	-	1.24, 0.5370
Maternal polypharmacy index during pregnancy [c](categorical)								
0	***	***	***	***	***	***	Reference	-
1-4	941	48.31	18	1.91	923	98.09	1.70 (0.80, 3.62)	-
5-10	***	***	***	***	***	***	5.13 (1.09, 24.04)	-
>10	***	***	***	***	***	***	-	-
Wald test	-	-	-	-	-	-	-	-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription								
No	1808	92.81	24	1.33	1784	98.67	Reference	-
Yes	140	7.19	8	5.71	132	94.29	4.51 (1.99, 10.22)	12.97, 0.0003
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription								
No	1863	95.64	24	1.29	1839	98.71	Reference	-
Yes	85	4.36	8	9.41	77	90.59	7.96 (3.46, 18.29)	23.88, <.0001
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription								
No	574	29.47	6	1.05	568	98.95	Reference	-
Yes	1374	70.53	26	1.89	1348	98.11	1.83 (0.75, 4.46)	1.75, 0.1864

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription								
No	1093	56.11	14	1.28	1079	98.72	Reference	-
Yes	855	43.89	18	2.11	837	97.89	1.66 (0.82, 3.35)	1.98, 0.1597

ASD: autism spectrum disorders; CI: confidence interval; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; OR: odds ratios.
*** 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 is calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (ASD) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, ie row percentage). The association between each characteristic 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 (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 25 Association between potential paternal risk factors/confounders and ASD; ASD as outcome for sensitivity analysis 2

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Paternal risk factors/confounders								
Affective disorder [a,b]								
No	1768	90.76	***	***	***	***	Reference	-
Yes	180	9.24	***	***	***	***	1.41 (0.49, 4.07)	0.41, 0.5229
Bipolar affective disorder [a]								
No	1843	94.61	***	***	***	***	Reference	-
Yes	105	5.39	***	***	***	***	1.17 (0.28, 4.98)	0.05, 0.8282
Mania [a]								
No	1933	99.23	32	1.66	1901	98.34	Reference	-
Yes	15	0.77	0	0.00	15	100.00	0.00 (0.00, I)	0.00, 0.9882
Neurotic disorder [a]								
No	1770	90.86	***	***	***	***	Reference	-
Yes	178	9.14	***	***	***	***	1.03 (0.31, 3.41)	0.00, 0.9621
Schizophrenia, schizotypal and delusional disorders [a]								
No	1907	97.90	***	***	***	***	Reference	-
Yes	41	2.10	***	***	***	***	1.51 (0.20, 11.36)	0.16, 0.6873
Substance abuse [c]								
No	1941	99.64	***	***	***	***	Reference	-
Yes	7	0.36	***	***	***	***	10.27 (1.20, 87.85)	4.52, 0.0334
Paternal polypharmacy index [d] (categorical)								
0	1198	61.50	17	1.42	1181	98.58	Reference	-
1-4	714	36.65	15	2.10	699	97.90	1.49 (0.74, 3.00)	-
5-10	36	1.85	0	0.00	36	100.00	0.00 (0.00, I)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	1.25, 0.5357
Concomitant medications associated with valproate-indicated psychiatric conditions [c] -fathers with at least one prescription								
No	1492	76.59	19	1.27	1473	98.73	Reference	-

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Yes	456	23.41	13	2.85	443	97.15	2.28 (1.11, 4.64)	5.10, 0.0239
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription								
No	914	46.92	15	1.64	899	98.36	Reference	-
Yes	1034	53.08	17	1.64	1017	98.36	1.00 (0.50, 2.02)	0.00, 0.9959
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	***	***	***	***	2.84 (0.82, 9.82)	-
26-30	498	25.56	7	1.41	491	98.59	1.43 (0.50, 4.09)	-
31-35	707	36.29	7	0.99	700	99.01	Reference	-
36-40	397	20.38	8	2.02	389	97.98	2.06 (0.74, 5.71)	-
>40	194	9.96	***	***	***	***	3.19 (1.06, 9.61)	-
Wald test	-	-	-	-	-	-	-	5.61, 0.3456
Year of offspring conception [f,g]								
1996-2001	265	13.60	5	1.89	260	98.11	Reference	-
2002-2007	529	27.16	16	3.02	513	96.98	1.62 (0.59, 4.48)	-
2008-2012	576	29.57	6	1.04	570	98.96	0.55 (0.17, 1.81)	-
2013-2018	578	29.67	5	0.87	573	99.13	0.45 (0.13, 1.58)	-
Wald test	-	-	-	-	-	-	-	8.88, 0.0309

ASD: autism spectrum disorders; CI: Confidence interval; LMP2: last menstrual period date plus 2 weeks; OR: odds ratios.
*** 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 is calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (ASD) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, ie row percentage). The association between each characteristic 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); b) excluding bipolar and mania; 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 will be grouped in each country according to the length of the study period.

16.1.1.6 Variable estimates from propensity score

Table 26 Variable estimates from logistic regression propensity score model; ASD as outcome for sensitivity analysis 2

ASD		Estimate	
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
Offspring risk factors/confounders			
Gender [b]			
Male	Reference	-	-
Female	1.03	0.83 - 1.29	0.7852
Maternal risk factors/confounders			
Affective disorder [c]	0.61	0.26 - 1.45	0.2613
Gestational diabetes [d]	0.19	0.04 - 1.04	0.055
Neurotic disorder [c]	1.34	0.62 2.89	0.4603
Obesity [e]	1.25	0.75, 2.08	0.3966
Substance abuse prior to LMP2 [e]	0.67	0.19, 2.33	0.5242
Smoking during pregnancy [d]	3.76	0.08, 168.16	0.4948
No			
Yes	Reference	-	-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [e] - mothers with at least one prescription	1.01	0.74, 1.38	0.934
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [d] - mothers with at least one prescription	0.82	0.43, 1.56	0.5451
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [c] -mothers with at least one prescription	0.33	0.12, 0.89	0.0285
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [d] - mothers with at least one prescription	0.93	0.73, 1.19	0.5862
Paternal risk factors/confounders	0.82	0.65, 1.03	0.0875
Affective disorder [d,f]			
Bipolar affective disorder [c]	0.41	0.21, 0.80	0.0089
Mania c	0.08	0.01, 0.44	0.0042
Neurotic disorder [c]	8.45	0.54, 133.13	0.1291
Schizophrenia, schizotypal and delusional disorders [c]	2.79	0.86, 9.06	0.0872
Concomitant medications associated with valproate-indicated psychiatric conditions [e] – fathers with at least one prescription	0.32	0.22, 0.45	<.0001
Year of offspring conception [g,h]			
1996-2001	Reference	-	-
2002-2007	0.36	0.25, 0.53	<.0001
2008-2012	0.14	0.09, 0.20	<.0001
2013-2018	0.07	0.05, 0.11	<.0001

ASD: autism spectrum disorders; CI: confidence interval; LMP2: last menstrual period date plus 2 weeks; OR: odds ratios; PS: propensity score.
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 will be considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions will be 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; h) 3-months lookback from LMP2; i) at mother's LMP2; j) calendar years will be grouped in each country according to the length of the study period.

Table 27 Balance of risk factors/confounders after PS weighting (PS scores obtained using logistic regression); ASD as outcome for sensitivity analysis 2

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0.01	Yes	0.96	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	0.97	Yes
Affective disorder [e]	0.11	**No**	0.46	Yes
Diabetes [c]	0.11	**No**	0.24	Yes
Gestational diabetes [f]	0.08	Yes	0.59	Yes
Neurotic disorder [c]	0.08	Yes	0.69	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.09	Yes	-	- ***
Obesity [g]	0.06	Yes	0.46	Yes
CMV [g]	-	- **	-	- ***
Rubella [g]	-	- **	-	- ***
Alcohol abuse prior to LMP2 [g]	0.07	Yes	-	- ***
Alcohol abuse during pregnancy [f]	-	- **	-	- ***
Substance abuse prior to LMP2 [g]	0.05	Yes	-	- ***
Substance abuse during pregnancy [f]	0	Yes	1	Yes
Smoking prior to LMP2 [g]	0.49	**No**	0.52	Yes
Smoking during pregnancy [f]	0.04	Yes	0.89	Yes
Maternal polypharmacy index prior to LMP2 [I] (categorical)	0.01*	Yes	0.84	Yes
Maternal polypharmacy index during pregnancy [f] (categorical)	0.00*	Yes	0.91	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g]– mothers with at least one prescription	0.1	Yes	0.65	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f]– mothers with at least one prescription	0.13	**No**	0.44	Yes
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [g] -mothers with at least one prescription	0.03	Yes	0.94	Yes
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [f] - mothers with at least one prescription	0.03	Yes	0.95	Yes
Paternal risk factors/confounders				
Affective disorder [e,h]	0.01	Yes	0.99	Yes
Bipolar affective disorder [e]	0.16	**No**	0.39	Yes
Mania [e]	0.04	Yes	0.36	Yes
Neurotic disorder [c]	0.13	**No**	1.37	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.07	Yes	0.46	Yes
Substance abuse [g]	0.08	Yes	-	- ***

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Paternal polypharmacy index [i] (categorical)	0.00*	Yes	0.94	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] – fathers with at least one prescription	0.05	Yes	0.89	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] – fathers with at least one prescription	0.05	Yes	0.96	Yes
Father's age [c] (categorical)	0.01*	Yes	0.81	Yes
Year of offspring conception [j]	0.00*	Yes	0.95	Yes

ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; PS: propensity score.
* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardised 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).
a) absolute standardised 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.

Table 28 Variable importance metric from random forest propensity score model

ASD Variable (or interaction)[a]	Variable importance
Offspring risk factors/confounders	
Gender [b]	0.01
Foetal alcohol syndrome [c]	0
Maternal risk factors/confounders	
Affective disorder [d]	0.04
Diabetes [d]	0.02
Gestational diabetes [c]	0.04
Neurotic disorder [d]	0.05
Schizophrenia, schizotypal and delusional disorders [d]	0.04
Obesity [f]	0.03
Alcohol abuse prior to LMP2 [f]	0
Alcohol abuse during pregnancy [e]	0
Substance abuse prior to LMP2 [f]	0
Substance abuse during pregnancy [e]	0
Smoking during pregnancy [e]	0
Maternal polypharmacy index during pregnancy [e] (categorical)	0.02
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.1
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.03
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] -mothers with at least one prescription	0.03
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]	0.09
Bipolar affective disorder [d]	0.09
Mania [d]	0.02
Schizophrenia, schizotypal and delusional disorders [d]	0.11
Substance abuse [f]	0.09
Concomitant medications associated with valproate-indicated psychiatric conditions [f] – fathers with at least one prescription	0.03
Year of offspring conception [i]	0.27

ASD: autism spectrum disorder; LMP2: last menstrual period date plus 2 weeks; PS: propensity score.
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 will be considered to enter the PS model if associated with the study outcome based on univariate analyses. All two-way interactions will be 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 29 Variable estimates from logistic regression informed by random forest propensity score model

ASD	Estimate		
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
Offspring risk factors/confounders			
Gender [b]			
Male	Reference	-	-
Female	1.06	0.85 - 1.32	0.613
Maternal risk factors/confounders			
Affective disorder [d]	0.36	0.13 - 0.99	0.0478
Diabetes [d]	0.19	0.04 - 0.91	0.038
Gestational diabetes [c]	1.88	0.85 - 4.17	0.1192
Neurotic disorder [d]	1.37	0.80 - 2.33	0.248
Obesity [f]	0.7	0.19 - 2.59	0.5942
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.78	0.39 - 1.55	0.4778
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.36	0.12 - 1.06	0.063
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] -mothers with at least one prescription	0.91	0.71 - 1.17	0.4785
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.82	0.65 - 1.03	0.0929
Paternal risk factors/confounders			
Affective disorder [d,g]	0.09	0.03 - 0.28	<.0001
Schizophrenia, schizotypal and delusional disorders [d]	3.29	1.01 - 10.66	0.0473
Concomitant medications associated with valproate-indicated psychiatric conditions [f] – fathers with at least one prescription	0.27	0.19 - 0.39	<.0001
Year of offspring conception [i,j]			
1996-2001	Reference	-	-
2002-2007	0.32	0.22 - 0.46	<.0001
2008-2012	0.11	0.07 - 0.15	<.0001
2013-2018	0.06	0.04 - 0.08	<.0001

ASD: autism spectrum disorder; CI: confidence interval; LMP2: last menstrual period date plus 2 weeks; OR: odds ratio; PS: propensity score.

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 will be considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions will be 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; h) 3-months lookback from LMP2; i) at mother's LMP2; j) calendar years will be grouped in each country according to the length of the study period.

Table 30 Balance of risk factors and confounders after PS weighting (PS scores obtained using random forest model)

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0	Yes	0.85	Yes
Congenital CMV [d]	-	-**	-	-***
Congenital rubella [d]	-	-**	-	-***
Foetal alcohol syndrome [d]	0.04	Yes	-	-***
Fragile X syndrome [d]	-	-**	-	-***
Lejeune/cri du chat syndrome [d]	-	-**	-	-***
Tuberous sclerosis [d]	-	-**	-	-***
Maternal risk factors/confounders				
Mother's age [c] (categorical)	0.01*	Yes	0.76	Yes
Affective disorder [e]	0.13	**No**	0.36	Yes
Diabetes [c]	0.08	Yes	0.39	Yes
Gestational diabetes [f]	0.07	Yes	0.55	Yes
Neurotic disorder [c]	0.09	Yes	0.58	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.06	Yes	0.28	Yes
Obesity [g]	0.03	Yes	0.67	Yes
CMV [g]	-	-**	-	-***
Rubella [g]	-	-**	-	-***
Alcohol abuse prior to LMP2 [g]	0.04	Yes	0.3	Yes
Alcohol abuse during pregnancy [f]	0.04	Yes	-	-***
Substance abuse prior to LMP2 [g]	0.06	Yes	-	-***
Substance abuse during pregnancy [f]	0.01	Yes	0.74	Yes
Smoking prior to LMP2 [g]	0.4	**No**	0.4	Yes
Smoking during pregnancy [f]	0.05	Yes	0.77	Yes
Maternal polypharmacy index prior to LMP2 [i] (categorical)	0.03*	Yes	0.7	Yes
Maternal polypharmacy index during pregnancy [f] (categorical)	0.01*	Yes	0.79	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g] - mothers with at least one prescription	0.11	**No**	0.54	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f] - mothers with at least one prescription	0.13	**No**	0.42	Yes
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [g] - mothers with at least one prescription	0.01	Yes	0.84	Yes
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [f] - mothers with at least one prescription	0.05	Yes	0.84	Yes
Paternal risk factors/confounders				
Affective disorder [e,h]	0.26	**No**	0.31	Yes
Bipolar affective disorder [e]	0.16	**No**	0.37	Yes
Mania [e]	0.03	Yes	0.58	Yes
Neurotic disorder [c]	0.12	**No**	0.58	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.03	Yes	0.69	Yes
Substance abuse [g]	0.06	Yes	2.8	**No**

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Paternal polypharmacy index [i] (categorical)	0.03*	Yes	0.76	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] – fathers with at least one prescription	0.27	**No**	0.54	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] - fathers with at least one prescription	0.04	Yes	0.85	Yes
Father's age [c] (categorical)	0.00*	Yes	0.72	Yes
Year of offspring conception [j]	0.04*	Yes	0.92	Yes

ASD: autism spectrum disorder; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; PS: propensity score.
* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardised 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).
a) absolute standardised 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.

Table 31. Balance of risk factors after PS weighting (PS scores obtained with logistic regression informed by random forest)

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0.04	Yes	0.93	Yes
Congenital CMV [d]	-	- [**]	-	- [***]
Congenital rubella [d]	-	- [**]	-	- [***]
Foetal alcohol syndrome [d]	0.03	Yes	-	- [***]
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	0.81	Yes
Affective disorder [e]	0.14	**No**	0.35	Yes
Diabetes [c]	0.11	**No**	0.25	Yes
Gestational diabetes [f]	0.06	Yes	0.61	Yes
Neurotic disorder [c]	0.09	Yes	0.63	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.08	Yes	-	- [***]
Obesity [g]	0.06	Yes	0.43	Yes
CMV [g]	-	- [**]	-	- [***]
Rubella [g]	-	- [**]	-	- [***]
Alcohol abuse prior to LMP2 [g]	0.03	Yes	0.43	Yes
Alcohol abuse during pregnancy [f]	0.03	Yes	-	- [***]
Substance abuse prior to LMP2 [g]	0.05	Yes	-	- [***]
Substance abuse during pregnancy [f]	0.01	Yes	0.75	Yes
Smoking prior to LMP2 [g]	0.33	**No**	0.54	Yes
Smoking during pregnancy [f]	0.05	Yes	0.88	Yes
Maternal polypharmacy index prior to LMP2 [i] (categorical)	0.03*	Yes	0.77	Yes
Maternal polypharmacy index during pregnancy [f] (categorical)	0.00*	Yes	0.9	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g] - mothers with at least one prescription	0.13	**No**	0.5	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f] - mothers with at least one prescription	0.15	**No**	0.34	Yes
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [g] - mothers with at least one prescription	0.01	Yes	0.92	Yes
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [f] - mothers with at least one prescription	0.02	Yes	0.93	Yes
Paternal risk factors/confounders				
Affective disorder [e,h]	0.15	**No**	0.54	Yes
Bipolar affective disorder [e]	0.32	**No**	-	- [***]
Mania [e]	0.08	Yes	-	- [***]
Neurotic disorder [c]	0.04	Yes	1.05	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.06	Yes	0.5	Yes
Substance abuse [g]	0.1	Yes	-	- [***]

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Paternal polypharmacy index [i] (categorical)	0.00*	Yes	0.98	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] – fathers with at least one prescription	0.06	Yes	0.86	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] - fathers with at least one prescription	0.04	Yes	0.93	Yes
Father's age [c] (categorical)	0.00*	Yes	0.74	Yes
Year of offspring conception [j]	0.01*	Yes	0.92	Yes

ASD: autism spectrum disorder; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; PS: propensity score.
* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardised 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).
a) absolute standardised 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.

16.1.2 Sweden

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

Table 32 Offspring demographic characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD Number of offspring	**Valproate N=930**		**Lamotrigine/levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/levetiracetam) N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Gestational age (weeks)										
<28 (extremely preterm)	2	0.22	0	0.00	0	0.00	0	0.00	2	0.08
28-31 (very preterm)	6	0.65	10	0.70	8	0.66	2	0.92	16	0.68
32-36 (moderate to late preterm)	37	3.98	54	3.79	43	3.56	11	5.07	91	3.87
37-41 (at term)	827	88.92	1263	88.69	1075	89.06	188	86.64	2090	88.79
≥42 (post-term)	58	6.24	97	6.81	81	6.71	16	7.37	155	6.58
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	1	0.11	0	0.00	0	0.00	0	0.00	1	0.04
1000-1499 (very low)	6	0.65	5	0.35	2	0.17	3	1.38	11	0.47
1500-2499 (low)	31	3.33	36	2.53	30	2.49	6	2.76	67	2.85
≥2500	892	95.91	1381	96.98	1173	97.18	208	95.85	2273	96.56
Missing	0	0.00	2	0.14	2	0.17	0	0.00	2	0.08
Gender [a]										
Male	464	49.89	741	52.04	640	53.02	101	46.54	1205	51.19
Female	466	50.11	683	47.96	567	46.98	116	53.46	1149	48.81
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of birth										
2007	86	9.25	38	2.67	36	2.98	2	0.92	124	5.27

	Paternal exposure group									
ASD Number of offspring	**Valproate N=930**		**Lamotrigine/levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/levetiracetam) N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
2008	79	8.49	55	3.86	49	4.06	6	2.76	134	5.69
2009	82	8.82	64	4.49	60	4.97	4	1.84	146	6.20
2010	72	7.74	77	5.41	74	6.13	3	1.38	149	6.33
2011	70	7.53	98	6.88	87	7.21	11	5.07	168	7.14
2012	78	8.39	102	7.16	94	7.79	8	3.69	180	7.65
2013	71	7.63	101	7.09	89	7.37	12	5.53	172	7.31
2014	91	9.78	120	8.43	102	8.45	18	8.29	211	8.96
2015	74	7.96	142	9.97	114	9.44	28	12.90	216	9.18
2016	67	7.20	137	9.62	111	9.20	26	11.98	204	8.67
2017	67	7.20	161	11.31	132	10.94	29	13.36	228	9.69
2018	47	5.05	150	10.53	117	9.69	33	15.21	197	8.37
2019	46	4.95	179	12.57	142	11.76	37	17.05	225	9.56
Total number of years of follow-up	6311.57		7188.54		6342.53		846.01		13500.11	
Mean follow-up year	6.79		5.05		5.25		3.9		5.73	

ASD: autism spectrum 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 will be 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 33 Offspring clinical characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD **Number of offspring**	**Valproate N=930**		**Lamotrigine/levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/levetiracetam) N=2354**	
	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	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
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	1	0.11	0	0.00	0	0.00	0	0.00	1	0.04
Medication use										
Exposure to AEDs [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Outcomes										
ASD (ever, not only as 1st NDD diagnosis)	19	2.04	12	0.84	11	0.91	1	0.46	31	1.32
ASD (as 1st NDD diagnosis)	15	1.61	9	0.63	8	0.66	1	0.46	24	1.02
NDD including ASD	49	5.27	40	2.81	33	2.73	7	3.23	89	3.78
Age at the first diagnosis (years)										
ASD (ever, not only as 1st NDD diagnosis) [b,c]										
0-1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2-3	3	0.32	5	0.35	4	0.33	1	0.46	8	0.34
4-5	6	0.65	4	0.28	4	0.33	0	0.00	10	0.42
6-7	2	0.22	2	0.14	2	0.17	0	0.00	4	0.17
8-9	5	0.54	1	0.07	1	0.08	0	0.00	6	0.25
10-11	3	0.32	0	0.00	0	0.00	0	0.00	3	0.13
Total (offspring with the outcome)	19	2.05	12	0.84	11	0.91	1	0.46	31	1.31

	Paternal exposure group									
ASD Number of offspring	**Valproate N=930**		**Lamotrigine/levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/levetiracetam) N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
NDD including ASD [b,c]										
0-1	5	0.54	5	0.35	4	0.33	1	0.46	10	0.42
2-3	7	0.75	6	0.42	5	0.41	1	0.46	13	0.55
4-5	10	1.08	8	0.56	6	0.50	2	0.92	18	0.76
6-7	11	1.18	9	0.63	9	0.75	0	0.00	20	0.85
8-9	9	0.97	10	0.70	7	0.58	3	1.38	19	0.81
10-11	7	0.75	2	0.14	2	0.17	0	0.00	9	0.38
Total (offspring with the outcome)	49	5.27	40	2.8	33	2.74	7	3.22	89	3.77

AED: antiepileptic drug; ASD: autism spectrum disorders; 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) between index (childbirth) and exit date; b) categories might be adapted according to the data.

Table 34 Maternal demographic characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD Number of offspring	**Valproate N=930**		**Lamotrigine/ levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/levetiracetam) N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Mother's age [a]										
≤20 years	18	1.94	23	1.62	20	1.66	3	1.38	41	1.74
21-25	140	15.05	169	11.87	146	12.10	23	10.60	309	13.13
26-30	293	31.51	419	29.42	355	29.41	64	29.49	712	30.25
31-35	288	30.97	470	33.01	395	32.73	75	34.56	758	32.20
36-40	160	17.20	297	20.86	252	20.88	45	20.74	457	19.41
>40	31	3.33	46	3.23	39	3.23	7	3.23	77	3.27
Mean (SD)	30.76 (5.27)		31.45 (5.25)		31.44 (5.26)		31.54 (5.26)		31.18 (5.27)	
Median (25th - 75th 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

ASD: autism spectrum disorders; Max: maximum; Min: minimum; SD: standard deviation.
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 will be 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 35 Maternal clinical characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of offspring	**N=930**		**N=1424**		**N=1207**		**N=217**		**N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Comorbidities										
Affective disorder [a]	78	8.39	134	9.41	117	9.69	17	7.83	212	9.01
Diabetes [a]	8	0.86	18	1.26	17	1.41	1	0.46	26	1.10
Epilepsy [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Neurotic disorder [a]	85	9.14	174	12.22	148	12.26	26	11.98	259	11.00
Schizophrenia, schizotypal and delusional disorders [a]	4	0.43	3	0.21	2	0.17	1	0.46	7	0.30
Obesity [b]	11	1.18	16	1.12	15	1.24	1	0.46	27	1.15
CMV [c]	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04
Gestational diabetes [c]	23	2.47	47	3.30	40	3.31	7	3.23	70	2.97
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	0.97	0	0.00	0	0.00	0	0.00	9	0.38
Alcohol abuse during pregnancy [c]	1	0.11	1	0.07	0	0.00	1	0.46	2	0.08
Substance abuse prior to LMP2 [b]	4	0.43	4	0.28	2	0.17	2	0.92	8	0.34
Substance abuse during pregnancy [c]	2	0.22	2	0.14	1	0.08	1	0.46	4	0.17
Smoking prior to LMP2 [b]										
Yes	151	16.24	177	12.43	145	12.01	32	14.75	328	13.93
No	739	79.46	1171	82.23	997	82.60	174	80.18	1910	81.14
Missing	40	4.30	76	5.34	65	5.39	11	5.07	116	4.93
Smoking during pregnancy [c]										
Yes	71	7.63	74	5.20	62	5.14	12	5.53	145	6.16
No	832	89.46	1310	91.99	1111	92.05	199	91.71	2142	90.99
Missing	27	2.90	40	2.81	34	2.82	6	2.76	67	2.85
Medication use										
Exposure to AEDs prior to LMP2 [d]										

	Paternal exposure group									
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of offspring	**N=930**		**N=1424**		**N=1207**		**N=217**		**N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Valproate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00	0	0.00	0	0.00	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 [c]	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	0	0.00	0	0.00	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
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	0	0.00	0	0.00	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00	0	0.00	0	0.00	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	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	0	0.00	0	0.00	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
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	930	100.00	1424	100.00	1207	100.00	217	100.00	2354	100.00
K-means cluster during pregnancy [c]										
unexposed	930	100.00	1424	100.00	1207	100.00	217	100.00	2354	100.00

	Paternal exposure group									
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of offspring	**N=930**		**N=1424**		**N=1207**		**N=217**		**N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Maternal polypharmacy index prior to LMP2 [d]										
0	623	66.99	965	67.77	816	67.61	149	68.66	1588	67.46
1-4	288	30.97	428	30.06	362	29.99	66	30.41	716	30.42
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
Mean (SD)	0.65 (1.21)		0.64 (1.22)		0.66 (1.26)		0.53 (1.00)		0.64 (1.22)	
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, 8.00		0.00, 11.00		0.00, 11.00		0.00, 6.00		0.00, 11.00	
Maternal polypharmacy index during pregnancy [c]										
0	492	52.90	694	48.74	583	48.30	111	51.15	1186	50.38
1-4	419	45.05	686	48.17	583	48.30	103	47.47	1105	46.94
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
Mean (SD)	0.90 (1.28)		1.02 (1.44)		1.06 (1.48)		0.83 (1.14)		0.97 (1.38)	
Median (25^{th} - 75^{th} percentile)	0 (0.00, 1.00)		1 (0.00, 2.00)		1 (0.00, 2.00)		0 (0.00, 1.00)		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	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	98	10.54	193	13.55	173	14.33	20	9.22	291	12.36
Concomitant medications associated with valproate-indicated psychiatric	53	5.70	109	7.65	99	8.20	10	4.61	162	6.88

	Paternal exposure group									
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of offspring	**N=930**		**N=1424**		**N=1207**		**N=217**		**N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
conditions during pregnancy [c] - mothers with at least 1 prescription										
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] -mothers with at least one prescription	571	61.40	863	60.60	737	61.06	126	58.06	1434	60.92
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	392	42.15	658	46.21	560	46.40	98	45.16	1050	44.60

AED: antiepileptic drug; ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period plus 2 weeks; Max: Maximum; Min: Minimum; 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 Sweden during the study period.

Table 36 Paternal demographic characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD Number of offspring	**Valproate N=930**		**Lamotrigine/levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/levetiracetam) N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Father's age [a]										
≤20 years	5	0.54	8	0.56	8	0.66	0	0.00	13	0.55
21-25	65	6.99	75	5.27	58	4.81	17	7.83	140	5.95
26-30	207	22.26	284	19.94	244	20.22	40	18.43	491	20.86
31-35	314	33.76	503	35.32	434	35.96	69	31.80	817	34.71
36-40	224	24.09	353	24.79	300	24.86	53	24.42	577	24.51
>40	115	12.37	201	14.12	163	13.50	38	17.51	316	13.42
Mean (SD)	33.71 (6.04)		34.36 (6.19)		34.26 (5.93)		34.96 (7.45)		34.10 (6.14)	
Median	33		34		34		34		34	
(25^{th} - 75^{th} percentile)	(29.00, 38.00)		(30.00, 38.00)		(30.00, 38.00)		(30.00, 39.00)		(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	
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of offspring conception [b]										
2006	65	6.99	29	2.04	28	2.32	1	0.46	94	3.99
2007	78	8.39	55	3.86	48	3.98	7	3.23	133	5.65
2008	84	9.03	52	3.65	48	3.98	4	1.84	136	5.78
2009	73	7.85	81	5.69	78	6.46	3	1.38	154	6.54
2010	70	7.53	93	6.53	83	6.88	10	4.61	163	6.92
2011	70	7.53	97	6.81	90	7.46	7	3.23	167	7.09
2012	79	8.49	98	6.88	90	7.46	8	3.69	177	7.52
2013	82	8.82	127	8.92	107	8.86	20	9.22	209	8.88
2014	89	9.57	114	8.01	92	7.62	22	10.14	203	8.62
2015	58	6.24	157	11.03	128	10.60	29	13.36	215	9.13
2016	73	7.85	153	10.74	125	10.36	28	12.90	226	9.60
2017	45	4.84	158	11.10	124	10.27	34	15.67	203	8.62
2018	55	5.91	161	11.31	123	10.19	38	17.51	216	9.18
2019	9	0.97	49	3.44	43	3.56	6	2.76	58	2.46

ASD: autism spectrum disorders: LMP2: last menstrual period plus 2 weeks; Max: Maximum; Min: Minimum; 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 will be 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 37 Paternal clinical characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD Number of offspring	**Valproate N=930**		**Lamotrigine/ levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/ levetiracetam) N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Comorbidities										
Bipolar affective disorder excl. bipolar disorder and mania [a]	104	11.18	426	29.92	417	34.55	9	4.15	530	22.51
Bipolar affective disorder [a]	122	13.12	418	29.35	418	34.63	0	0.00	540	22.94
Mania [a]	13	1.40	20	1.40	20	1.66	0	0.00	33	1.40
Neurotic disorder [a]	127	13.66	388	27.25	371	30.74	17	7.83	515	21.88
Schizophrenia, schizotypal and delusional disorders [a]	38	4.09	51	3.58	48	3.98	3	1.38	89	3.78
Lifestyle characteristics										
Substance abuse [b]	12	1.29	10	0.70	7	0.58	3	1.38	22	0.93
Medication use										
AED indication										
Epilepsy	655	70.43	663	46.56	476	39.44	187	86.18	1318	55.99
Bipolar affective disorder and mania	122	13.12	410	28.79	410	33.97	0	0.00	532	22.60
Other/unknown	153	16.45	351	24.65	321	26.59	30	13.82	504	21.41
K-means cluster prior to LMP2 [c]										
cluster A	387	41.61	612	42.98	505	41.84	107	49.31	999	42.44
cluster B	287	30.86	474	33.29	408	33.80	66	30.41	761	32.33
cluster C	256	27.53	338	23.74	294	24.36	44	20.28	594	25.23
Paternal polypharmacy index [e]										
0	612	65.81	684	48.03	534	44.24	150	69.12	1296	55.06
1-4	288	30.97	679	47.68	617	51.12	62	28.57	967	41.08
5-10	27	2.90	58	4.07	53	4.39	5	2.30	85	3.61
>10	3	0.32	3	0.21	3	0.25	0	0.00	6	0.25
Mean (SD)	0.77 (1.51)		1.13 (1.58)		1.23 (1.63)		0.56 (1.11)		0.99 (1.56)	
Median	0		1		1		0		0	
(25^{th} - 75^{th} percentile)	(0.00, 1.00)		(0.00, 2.00)		(0.00, 2.00)		(0.00, 1.00)		(0.00, 1.00)	

	Paternal exposure group									
ASD Number of offspring	**Valproate N=930**		**Lamotrigine/ levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/ levetiracetam) N=2354**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
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	225	24.19	622	43.68	592	49.05	30	13.82	847	35.98
Concomitant medications associated with neuropsychiatric adverse events [b] - fathers with at least one prescription	449	48.28	908	63.76	813	67.36	95	43.78	1357	57.65

AED: antiepileptic drug; ASD: autism spectrum disorders; LMP2: last menstrual period plus 2 weeks; Min: minimum, Max: maximum; 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 will be described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
Cluster A: constant high exposure, cluster B: constant low exposure.
a) all available data prior to index date (childbirth); b) 12-months lookback from LMP2; c) 3-months lookback from LMP2.

16.1.2.2 Cumulative incidence proportion

Table 38 Cumulative incidence proportion (risk) of ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	930	1424	1207	217	2354
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	882	1241	1062	179	2123
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	833	1089	943	146	1922
2-3 years	n	1	2	1	1	3
	n/N*100	0.12 (-0.12, 0.36)	0.18 (-0.07, 0.44)	0.11 (-0.10, 0.31)	0.68 (-0.65, 2.02)	0.16 (-0.02, 0.33)
	N	763	928	812	116	1691
3-4 years	n	2	3	3	0	5
	n/N*100	0.26 (-0.10, 0.62)	0.32 (-0.04, 0.69)	0.37 (-0.05, 0.79)	0.00 (0.00, 0.00)	0.30 (0.04, 0.55)
	N	690	790	700	90	1480
4-5 years	n	1	1	1	0	2
	n/N*100	0.14 (-0.14, 0.43)	0.13 (-0.12, 0.37)	0.14 (-0.14, 0.42)	0.00 (0.00, 0.00)	0.14 (-0.05, 0.32)
	N	613	646	584	62	1259
5-6 years	n	5	3	3	0	8
	n/N*100	0.82 (0.10, 1.53)	0.46 (-0.06, 0.99)	0.51 (-0.07, 1.09)	0.00 (0.00, 0.00)	0.64 (0.20, 1.07)
	N	519	526	481	45	1045
6-7 years	n	2	2	2	0	4
	n/N*100	0.39 (-0.15, 0.92)	0.38 (-0.15, 0.91)	0.42 (-0.16, 0.99)	0.00 (0.00, 0.00)	0.38 (0.01, 0.76)
	N	447	427	393	34	874
7-8 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	370	326	300	26	696
8-9 years	n	3	1	1	0	4

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	930	1424	1207	217	2354
	n/N*100	0.81 (-0.10, 1.72)	0.31 (-0.29, 0.91)	0.33 (-0.32, 0.99)	0.00 (0.00, 0.00)	0.57 (0.01, 1.14)
	N	305	230	215	15	535
9-10 years	n	2	0	0	0	2
	n/N*100	0.66 (-0.25, 1.56)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.37 (-0.14, 0.89)
	N	233	154	142	12	387
10-11 years	n	1	0	0	0	1
	n/N*100	0.43 (-0.41, 1.27)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.26 (-0.25, 0.76)
	N	155	91	83	8	246
11-12 years	n	2	0	0	0	2
	n/N*100	1.29 (-0.49, 3.07)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.81 (-0.31, 1.94)
	N	930	1424	1207	217	2354
Overall (0-12 years)	n	19	12	11	1	31
	n/N*100	2.04 (1.13, 2.95)	0.84 (0.37, 1.32)	0.91 (0.38, 1.45)	0.46 (-0.44, 1.36)	1.32 (0.86, 1.78)

ASD: autism spectrum disorder.
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) will be presented.

Table 39 Cumulative incidence proportion (risk) of ASD by paternal exposure group for male offspring

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	464	741	640	101	1205
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	441	648	565	83	1089
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	415	574	504	70	989
2-3 years	n	1	2	1	1	3
	n/N*100	0.24 (-0.23, 0.71)	0.35 (-0.13, 0.83)	0.20 (-0.19, 0.59)	1.43 (-1.35, 4.21)	0.30 (-0.04, 0.65)
	N	386	484	430	54	870
3-4 years	n	0	2	2	0	2
	n/N*100	0.00 (0.00, 0.00)	0.41 (-0.16, 0.98)	0.47 (-0.18, 1.11)	0.00 (0.00, 0.00)	0.23 (-0.09, 0.55)
	N	347	416	371	45	763
4-5 years	n	1	1	1	0	2
	n/N*100	0.29 (-0.28, 0.85)	0.24 (-0.23, 0.71)	0.27 (-0.26, 0.80)	0.00 (0.00, 0.00)	0.26 (-0.10, 0.62)
	N	311	328	298	30	639
5-6 years	n	5	3	3	0	8
	n/N*100	1.61 (0.21, 3.01)	0.91 (-0.12, 1.94)	1.01 (-0.13, 2.14)	0.00 (0.00, 0.00)	1.25 (0.39, 2.11)
	N	260	271	246	25	531
6-7 years	n	1	1	1	0	2
	n/N*100	0.38 (-0.37, 1.14)	0.37 (-0.35, 1.09)	0.41 (-0.39, 1.20)	0.00 (0.00, 0.00)	0.38 (-0.14,0.90)
	N	219	212	195	17	431
7-8 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	177	161	147	14	338
8-9 years	n	2	0	0	0	2
	n/N*100	1.13 (-0.43, 2.69)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.59 (-0.23, 1.41)
	N	147	111	102	9	258
9-10 years	n	2	0	0	0	2

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	n/N*100	1.36 (-0.51, 3.23)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.78 (-0.29, 1.85)
	N	110	78	69	9	188
10-11 years	n	1	0	0	0	1
	n/N*100	0.91 (-0.86, 2.68)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.53 (-0.51, 1.57)
	N	78	44	38	6	122
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	464	741	640	101	1205
Overall (0-12 years)	n	13	9	8	1	22
	n/N*100	2.80 (1.30, 4.30)	1.21 (0.43, 2.00)	1.25 (0.39, 2.11)	0.99 (-0.94, 2.92)	1.83 (1.07, 2.58)

ASD: autism spectrum disorder.
Legend: Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which will be 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) will be presented.

Table 40 Cumulative incidence proportion (risk) of ASD by paternal exposure group for female offspring

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	466	683	567	116	1149
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	441	593	497	96	1034
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	418	515	439	76	933
2-3 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	377	444	382	62	821
3-4 years	n	2	1	1	0	3
	n/N*100	0.53 (-0.20, 1.26)	0.23 (-0.22, 0.67)	0.26 (-0.25, 0.77)	0.00 (0.00, 0.00)	0.37(-0.05, 0.78)
	N	343	374	329	45	717
4-5 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	318	286	32	620
5-6 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	259	255	235	20	514
6-7 years	n	1	1	1	0	2
	n/N*100	0.39(-0.37,1.14)	0.39(-0.37, 1.16)	0.43(-0.41, 1.26)	0.00 (0.00, 0.00)	0.39(-0.15, 0.93)
	N	228	215	198	17	443
7-8 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	193	165	153	12	358
8-9 years	n	1	1	1	0	2
	n/N*100	0.52(-0.49, 1.53)	0.61 (-0.58, 1.79)	0.65(-0.62, 1.93)	0.00 (0.00, 0.00)	0.56(-0.21, 1.33)
	N	158	119	113	6	277
9-10 years	n	0	0	0	0	0

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	466	683	567	116	1149
	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	123	76	73	3	199
10-11 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	77	47	45	2	124
11-12 years	n	2	0	0	0	2
	n/N*100	2.60 (-0.96, 6.15)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	1.61 (-0.60, 3.83)
	N	466	683	567	116	1149
Overall (0-12 years)	n	6	3	3	0	9
	n/N*100	1.29 (0.26, 2.31)	0.44 (-0.06, 0.94)	0.53 (-0.07, 1.13)	0.00 (0.00, 0.00)	0.78 (0.27, 1.29)

ASD: autism spectrum disorder.
Legend: Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which will be 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) will be presented.

16.1.2.3 Cumulative incidence rate and time to ASD diagnosis

Table 41 Cumulative incidence rate of ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	907.72	1332.22	1133.12	199.1	2239.94
0-1 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 4.06)	0 (-, 2.77)	0 (-, 3.26)	0 (-, 18.53)	0 (-, 1.65)
	PY	1759.91	2499.91	2137.62	362.29	4259.82
0-2 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 2.10)	0 (-, 1.48)	0 (-, 1.73)	0 (-, 10.18)	0 (-, 0.87)
	PY	2558.39	3512.12	3018.54	493.58	6070.51
0-3 years	n	1	2	1	1	3
	n/PY*1000	0.39 (0.01, 2.18)	0.57 (0.07, 2.06)	0.33 (0.01, 1.85)	2.03 (0.05, 11.29)	0.49 (0.10, 1.44)
	PY	3279.33	4373.14	3775.69	597.45	7652.46
0-4 years	n	3	5	4	1	8
	n/PY*1000	0.91 (0.19, 2.67)	1.14 (0.37, 2.67)	1.06 (0.29, 2.71)	1.67 (0.04, 9.33)	1.05 (0.45, 2.06)
	PY	3934.42	5088.15	4416.67	671.48	9022.57
0-5 years	n	4	6	5	1	10
	n/PY*1000	1.02 (0.28, 2.60)	1.18 (0.43, 2.57)	1.13 (0.37, 2.64)	1.49 (0.04, 8.30)	1.11 (0.53, 2.04)
	PY	4500.08	5676.41	4949.63	726.78	10176.49
0-6 years	n	9	9	8	1	18
	n/PY*1000	2 (0.91, 3.80)	1.59 (0.72, 3.01)	1.62 (0.70, 3.18)	1.38 (0.03, 7.67)	1.77 (1.05, 2.80)
	PY	4981.31	6151.46	5387.07	764.39	11132.77
0-7 years	n	11	11	10	1	22
	n/PY*1000	2.21 (1.10, 3.95)	1.79 (0.89, 3.20)	1.86 (0.89, 3.41)	1.31 (0.03, 7.29)	1.98 (1.24, 2.99)
	PY	5387.33	6530.46	5735.74	794.72	11917.79
0-8 years	n	11	11	10	1	22
	n/PY*1000	2.04 (1.02, 3.65)	1.68 (0.84, 3.01)	1.74 (0.84, 3.21)	1.26 (0.03, 7.01)	1.85 (1.16, 2.79)
	PY	5725.78	6808.61	5991.42	817.19	12534.4
0-9 years	n	14	12	11	1	26

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	n/PY*1000	2.45 (1.34, 4.10)	1.76 (0.91, 3.08)	1.84 (0.92, 3.29)	1.22 (0.03, 6.82)	2.07 (1.35, 3.04)
	PY	5994.59	7002.04	6171.63	830.41	12996.64
0-10 years	n	16	12	11	1	28
	n/PY*1000	2.67 (1.53, 4.33)	1.71 (0.89, 2.99)	1.78 (0.89, 3.19)	1.2 (0.03, 6.71)	2.15 (1.43, 3.11)
	PY	6191.88	7123.29	6282.62	840.67	13315.17
0-11 years	n	17	12	11	1	29
	n/PY*1000	2.75 (1.60, 4.40)	1.68 (0.87, 2.94)	1.75 (0.87, 3.13)	1.19 (0.03, 6.63)	2.18 (1.46, 3.13)
	PY	6311.57	7188.54	6342.53	846.01	13500.11
0-12 years	n	19	12	11	1	31
	n/PY*1000	3.01 (1.81, 4.70)	1.67 (0.86, 2.92)	1.73 (0.87, 3.10)	1.18 (0.03, 6.59)	2.3 (1.56, 3.26)

ASD: autism spectrum disorder; 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) will be presented.

Table 42. Cumulative incidence rate of ASD by paternal exposure group for males

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	455.81	695.23	600.64	94.59	1151.04
0-1 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 8.09)	0 (-, 5.31)	0 (-, 6.14)	0 (-, 39.00)	0 (-, 3.20)
	PY	880.3	1311.1	1139.78	171.32	2191.41
0-2 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 4.19)	0 (-, 2.81)	0 (-, 3.24)	0 (-, 21.53)	0 (-, 1.68)
	PY	1280.27	1841.54	1608.6	232.94	3121.81
0-3 years	n	1	2	1	1	3
	n/PY*1000	0.78 (0.02, 4.35)	1.09 (0.13, 3.92)	0.62 (0.02, 3.46)	4.29 (0.11, 23.92)	0.96 (0.20, 2.81)
	PY	1643.95	2292.25	2010.21	282.04	3936.2
0-4 years	n	1	4	3	1	5
	n/PY*1000	0.61 (0.02, 3.39)	1.75 (0.48, 4.47)	1.49 (0.31, 4.36)	3.55 (0.09, 19.75)	1.27 (0.41, 2.96)
	PY	1974.76	2662.55	2343.04	319.51	4637.31
0-5 years	n	2	5	4	1	7
	n/PY*1000	1.01 (0.12, 3.66)	1.88 (0.61, 4.38)	1.71 (0.47, 4.37)	3.13 (0.08, 17.44)	1.51 (0.61, 3.11)
	PY	2259.92	2960.99	2613.52	347.48	5220.91
0-6 years	n	7	8	7	1	15
	n/PY*1000	3.1 (1.25, 6.38)	2.7 (1.17, 5.32)	2.68 (1.08, 5.52)	2.88 (0.07, 16.03)	2.87 (1.61, 4.74)
	PY	2498.53	3199.16	2832.75	366.41	5697.69
0-7 years	n	8	9	8	1	17
	n/PY*1000	3.2 (1.38, 6.31)	2.81 (1.29, 5.34)	2.82 (1.22, 5.56)	2.73 (0.07, 15.21)	2.98 (1.74, 4.78)
	PY	2696.7	3390.21	3008.02	382.19	6086.92
0-8 years	n	8	9	8	1	17
	n/PY*1000	2.97 (1.28, 5.85)	2.65 (1.21, 5.04)	2.66 (1.15, 5.24)	2.62 (0.07, 14.58)	2.79 (1.63, 4.47)
	PY	2859.12	3526.16	3131.71	394.45	6385.28
0-9 years	n	10	9	8	1	19
	n/PY*1000	3.5 (1.68, 6.43)	2.55 (1.17, 4.85)	2.55 (1.10, 5.03)	2.54 (0.06, 14.13)	2.98 (1.79, 4.65)
	PY	2988.11	3621.97	3218.52	403.45	6610.08
0-10 years	n	12	9	8	1	21

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	455.81	695.23	600.64	94.59	1151.04
	n/PY*1000	4.02 (2.08, 7.01)	2.48 (1.14, 4.72)	2.49 (1.07, 4.90)	2.48 (0.06, 13.81)	3.18 (1.97, 4.86)
	PY	3083.88	3682.99	3272.06	410.92	6766.87
0-11 years	n	13	9	8	1	22
	n/PY*1000	4.22 (2.24, 7.21)	2.44 (1.12, 4.64)	2.44 (1.06, 4.82)	2.43 (0.06, 13.56)	3.25 (2.04, 4.92)
	PY	3145.08	3712.87	3298.21	414.66	6857.95
0-12 years	n	13	9	8	1	22
	n/PY*1000	4.13 (2.20, 7.07)	2.42 (1.11, 4.60)	2.43 (1.05, 4.78)	2.41 (0.06, 13.44)	3.21 (2.01, 4.86)

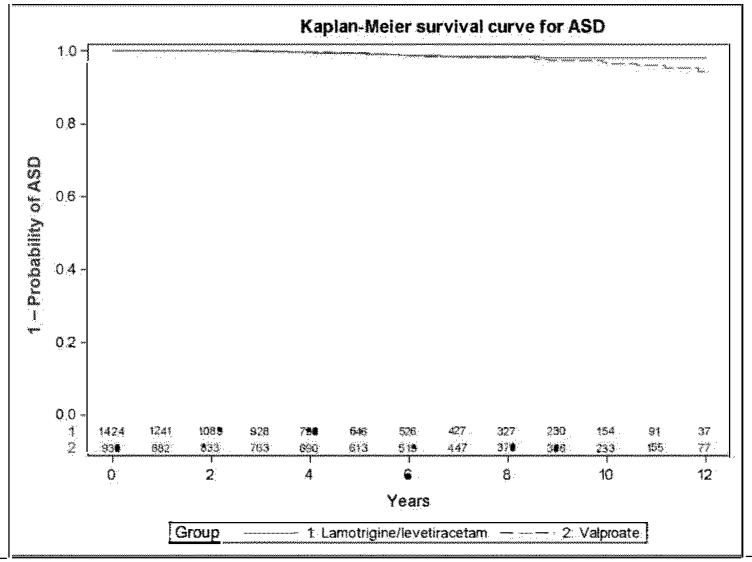
ASD: autism spectrum disorder; PY: person years.
Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which will be determined based on the results of the univariate analyses. As an example, this table presents incidence rates stratified 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) will be presented.

Table 43 Cumulative incidence rate of ASD by paternal exposure group for females

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	451.92	636.99	532.47	104.52	1088.9
0-1 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 8.16)	0 (-, 5.79)	0 (-, 6.93)	0 (-, 35.29)	0 (-, 3.39)
	PY	879.61	1188.81	997.84	190.97	2068.41
0-2 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 4.19)	0 (-, 3.10)	0 (-, 3.70)	0 (-, 19.32)	0 (-, 1.78)
	PY	1278.12	1670.58	1409.94	260.64	2948.7
0-3 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 2.89)	0 (-, 2.21)	0 (-, 2.62)	0 (-, 14.15)	0 (-, 1.25)
	PY	1635.38	2080.89	1765.48	315.41	3716.26
0-4 years	n	2	1	1	0	3
	n/PY*1000	1.22 (0.15, 4.42)	0.48 (0.01, 2.68)	0.57 (0.01, 3.16)	0 (-, 11.70)	0.81 (0.17, 2.36)
	PY	1959.66	2425.6	2073.63	351.98	4385.26
0-5 years	n	2	1	1	0	3
	n/PY*1000	1.02 (0.12, 3.69)	0.41 (0.01, 2.30)	0.48 (0.01, 2.69)	0 (-, 10.48)	0.68 (0.14, 2.00)
	PY	2240.16	2715.42	2336.12	379.3	4955.58
0-6 years	n	2	1	1	0	3
	n/PY*1000	0.89 (0.11, 3.23)	0.37 (0.01, 2.05)	0.43 (0.01, 2.38)	0 (-, 9.73)	0.61 (0.12, 1.77)
	PY	2482.78	2952.3	2554.32	397.98	5435.07
0-7 years	n	3	2	2	0	5
	n/PY*1000	1.21 (0.25, 3.53)	0.68 (0.08, 2.45)	0.78 (0.09, 2.83)	0 (-, 9.27)	0.92 (0.30, 2.15)
	PY	2690.63	3140.25	2727.72	412.53	5830.88
0-8 years	n	3	2	2	0	5
	n/PY*1000	1.11 (0.23, 3.26)	0.64 (0.08, 2.30)	0.73 (0.09, 2.65)	0 (-, 8.94)	0.86 (0.28, 2.00)
	PY	2866.66	3282.45	2859.71	422.74	6149.12
0-9 years	n	4	3	3	0	7
	n/PY*1000	1.4 (0.38, 3.57)	0.91 (0.19, 2.67)	1.05 (0.22, 3.07)	0 (-, 8.73)	1.14 (0.46, 2.35)
	PY	3006.48	3380.07	2953.11	426.96	6386.56
0-10 years	n	4	3	3	0	7

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	n/PY*1000	1.33 (0.36, 3.41)	0.89 (0.18, 2.59)	1.02 (0.21, 2.97)	0 (-, 8.64)	1.1 (0.44, 2.26)
	PY	3108	3440.3	3010.55	429.75	6548.3
0-11 years	n	4	3	3	0	7
	n/PY*1000	1.29 (0.35, 3.30)	0.87 (0.18, 2.55)	1 (0.21, 2.91)	0 (-, 8.58)	1.07 (0.43, 2.20)
	PY	3166.48	3475.67	3044.32	431.35	6642.16
0-12 years	n	6	3	3	0	9
	n/PY*1000	1.89 (0.70, 4.12)	0.86 (0.18, 2.52)	0.99 (0.20, 2.88)	0 (-, 8.55)	1.35 (0.62, 2.57)

ASD: autism spectrum disorder; PY: person years.
Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which will be 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) will be presented.



ASD	Valproate	Lamotrigine /levetiracetam	Lamotrigine	Levetiracetam	Total (valproate + lamotrigine /levetiracetam)
Number of events	19	12	11	1	31
Number of censor	911	1412	1196	216	2323
Survival time					
5th percentile	144.17 (120.57, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
10th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
25th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
median	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
75th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)

ASD: autism spectrum disorder.
Legend: Due to low number of events the median time-to-event could not be calculated.

Figure 4 Kaplan-Meier survival curve for Autism Spectrum Disorder (ASD) and distribution of time to ASD in Sweden

Table 44 Time to ASD by paternal exposure group for male offspring

	Paternal exposure group				
ASD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	13	9	8	1	22
Number of censor	451	732	632	100	1183
Survival time					
5th percentile	121.40 (84.70, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
10th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
25th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
median	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
75th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)

ASD: autism spectrum disorder.
Legend: Time-to-event analysis may be stratified according to relevant strong risk factors (such as age or gender) which will be determined based on the results of the univariate analyses. As an example, this table and the table below present stratification by gender.

Table 45 Time to ASD by paternal exposure group for female offspring

	Paternal exposure group				
ASD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	6	3	3	0	9
Number of censor	460	680	564	116	1140
Survival time					
5th percentile	144.17 (103.80, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
10th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
25th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
median	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
75th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)

ASD: autism spectrum disorder.
Legend: Time-to-event analysis may be stratified according to relevant strong risk factors (such as age or gender) which will be determined based on the results of the univariate analyses. As an example, this table and the table above present stratification by gender.

16.1.2.4 Association between potential risk factors/confounders for ASD and paternal exposure group

Table 46 Association between potential offspring risk factors/confounders for ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group										Comparison
ASD Number of offspring	Valproate N=930		Lamotrigine/ levetiracetam N=1424		Lamotrigine N=1207		Levetiracetam N=217		Total (valproate + lamotrigine/ levetiracetam) N=2354		Valproate vs Lamotrigine /levetiracetam -
	N	%	N	%	N	%	N	%	N	%	
Offspring risk factors/confounders											
Gender [a]											
Male	464	49.89	741	52.04	640	53.02	101	46.54	1205	51.19	-
Female	466	50.11	683	47.96	567	46.98	116	53.46	1149	48.81	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	1.04 (0.3090)
Congenital CMV [b]	0	0.00	1	0.07	1	0.08	0	0.00	1	0.04	1.00 (1.0000)*
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]	1	0.11	0	0.00	0	0.00	0	0.00	1	0.04	0.39 (0.3951)*

ASD: autism spectrum disorders; CMV: cytomegalovirus
* 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.
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 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.

Table 47 Association between potential maternal risk factors/confounders for ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group										Comparison
ASD Number of offspring	**Valproate N=930**		**Lamotrigine/ levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/ levetiracetam) N=2354**		**Valproate vs Lamotrigine /levetiracetam**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	-
Maternal risk factors/confounders											
Mother's age [a] (categorical)											
≤20 years	18	1.94	23	1.62	20	1.66	3	1.38	41	1.74	-
21-25	140	15.05	169	11.87	146	12.10	23	10.60	309	13.13	-
26-30	293	31.51	419	29.42	355	29.41	64	29.49	712	30.25	-
31-35	288	30.97	470	33.01	395	32.73	75	34.56	758	32.20	-
36-40	160	17.20	297	20.86	252	20.88	45	20.74	457	19.41	-
>40	31	3.33	46	3.23	39	3.23	7	3.23	77	3.27	-
Test statistics	-	-	-	-	-	-	-	-	-	-	10.10 (0.0725)
Mother's age [a] (continuous)											
Mean (SD)	30.76 (5.27)	-	31.45 (5.25)	-	31.44 (5.26)	-	31.54 (5.26)	-	31.18 (5.27)	-	1043978.50 (0.0015)*
Median (25th - 75th 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	9.41	117	9.69	17	7.83	212	9.01	0.72 (0.3966)
Diabetes [b]	8	0.86	18	1.26	17	1.41	1	0.46	26	1.10	0.84 (0.3594)
Gestational diabetes [c]	23	2.47	47	3.30	40	3.31	7	3.23	70	2.97	1.34 (0.2479)
Neurotic disorder [b]	85	9.14	174	12.22	148	12.26	26	11.98	259	11.00	5.45 (0.0196)
Schizophrenia, schizotypal and delusional disorders [b]	4	0.43	3	0.21	2	0.17	1	0.46	7	0.30	0.44 (0.4448)*
Obesity [d]	11	1.18	16	1.12	15	1.24	1	0.46	27	1.15	0.02 (0.8951)
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	0.65 (0.6500)*

	Paternal exposure group										Comparison
ASD Number of offspring	**Valproate N=930**		**Lamotrigine/ levetiracetam N=1424**		**Lamotrigine N=1207**		**Levetiracetam N=217**		**Total (valproate + lamotrigine/ levetiracetam) N=2354**		**Valproate vs Lamotrigine /levetiracetam**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	-
Smoking prior to LMP2 [d]											
No	739	79.46	1171	82.23	997	82.60	174	80.18	1910	81.14	-
Yes	151	16.24	177	12.43	145	12.01	32	14.75	328	13.93	-
Missing	40	4.30	76	5.34	65	5.39	11	5.07	116	4.93	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	6.31 (0.0120)
Smoking during pregnancy [c]											
No	832	89.46	1310	91.99	1111	92.05	199	91.71	2142	90.99	-
Yes	71	7.63	74	5.20	62	5.14	12	5.53	145	6.16	-
Missing	27	2.90	40	2.81	34	2.82	6	2.76	67	2.85	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	5.82 (0.0158)
Maternal polypharmacy index prior to LMP2 [e] (categorical)											
0	623	66.99	965	67.77	816	67.61	149	68.66	1588	67.46	-
1-4	288	30.97	428	30.06	362	29.99	66	30.41	716	30.42	-
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	-
Test statistics	-	-	-	-	-	-	-	-	-	-	0.87 (0.8331)
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)	-	1099433.50 (0.7444)*
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, 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	48.74	583	48.30	111	51.15	1186	50.38	-
1-4	419	45.05	686	48.17	583	48.30	103	47.47	1105	46.94	-
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	-

ASD Number of offspring	Paternal exposure group Valproate N=930 N	 %	 Lamotrigine/ levetiracetam N=1424 N	 %	 Lamotrigine N=1207 N	 %	 Levetiracetam N=217 N	 %	 Total (valproate + lamotrigine/ levetiracetam) N=2354 N	 %	Comparison Valproate vs Lamotrigine /levetiracetam -
Test statistics	-	-	-	-	-	-	-	-	-	-	6.20 (0.1025)
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)	-	1064877.00 (0.0427)*
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	-	-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	98	10.54	193	13.55	173	14.33	20	9.22	291	12.36	4.72 (0.0298)
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	4.61	162	6.88	3.36 (0.0669)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] -mothers with at least one prescription	571	61.40	863	60.60	737	61.06	126	58.06	1434	60.92	0.15 (0.6996)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	392	42.15	658	46.21	560	46.40	98	45.16	1050	44.60	3.75 (0.0529)

ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; Max: maximum; Min: minimum; 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.
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) 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 48 Association between potential paternal risk factors/confounders for ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group										Comparison
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of offspring	**N=930**		**N=1424**		**N=1207**		**N=217**		**N=2354**		-
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Paternal risk factors/confounders											
Affective disorder excluding bipolar affective disorder and mania [a]	104	11.18	426	29.92	417	34.55	9	4.15	530	22.51	113.16 (<.0001)
Bipolar affective disorder [a]	122	13.12	418	29.35	418	34.63	0	0.00	540	22.94	83.89 (<.0001)
Mania [a]	13	1.40	20	1.40	20	1.66	0	0.00	33	1.40	0.00 (0.9893)
Neurotic disorder [a]	127	13.66	388	27.25	371	30.74	17	7.83	515	21.88	60.80 (<.0001)
Schizophrenia, schizotypal and delusional disorders [a]	38	4.09	51	3.58	48	3.98	3	1.38	89	3.78	0.39 (0.5304)
Substance abuse [c]	12	1.29	10	0.70	7	0.58	3	1.38	22	0.93	2.10 (0.1472)
Paternal polypharmacy index [d] (categorical)											
0	612	65.81	684	48.03	534	44.24	150	69.12	1296	55.06	-
1-4	288	30.97	679	47.68	617	51.12	62	28.57	967	41.08	-
5-10	27	2.90	58	4.07	53	4.39	5	2.30	85	3.61	-
>10	3	0.32	3	0.21	3	0.25	0	0.00	6	0.25	-
Test statistics	-	-	-	-	-	-	-	-	-	-	72.95 (<.0001)
Paternal polypharmacy index [d] (continuous)											
Mean (SD)	0.77 (1.51)		1.13 (1.58)		1.23 (1.63)		0.56 (1.11)		0.99 (1.56)		977640.50 (<.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)		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 [c] – fathers with at least one prescription	225	24.19	622	43.68	592	49.05	30	13.82	847	35.98	92.74 (<.0001)
Concomitant medications associated with neuropsychiatric	449	48.28	908	63.76	813	67.36	95	43.78	1357	57.65	55.25 (<.0001)

ASD	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of offspring	N=930		N=1424		N=1207		N=217		N=2354		-
	N	%	N	%	N	%	N	%	N	%	
adverse events [c] - fathers with at least one prescription											
Father's age [e] (categorical)											-
≤20 years	5	0.54	8	0.56	8	0.66	0	0.00	13	0.55	-
21-25	65	6.99	75	5.27	58	4.81	17	7.83	140	5.95	-
26-30	207	22.26	284	19.94	244	20.22	40	18.43	491	20.86	-
31-35	314	33.76	503	35.32	434	35.96	69	31.80	817	34.71	-
36-40	224	24.09	353	24.79	300	24.86	53	24.42	577	24.51	-
>40	115	12.37	201	14.12	163	13.50	38	17.51	316	13.42	-
Test statistics	-	-	-	-	-	-	-	-	-	-	6.05 (0.3016)
Father's age [e] (continuous)											
Mean (SD)	33.71 (6.04)		34.36 (6.19)		34.26 (5.93)		34.96 (7.45)		34.10 (6.14)		1054855.00 (0.0125)*
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 [f,g]											
2006-2010	370	39.78	310	21.77	285	23.61	25	11.52	680	28.89	-
2011-2015	378	40.65	593	41.64	507	42.00	86	39.63	971	41.25	-
2016-2019	182	19.57	521	36.59	415	34.38	106	48.85	703	29.86	-
Test statistics	-	-	-	-	-	-	-	-	-	-	117.90 (<.0001)

ASD: autism spectrum disorders; LMP2: last menstrual period plus 2 weeks; Max: maximum; Min: minimum; 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.
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) 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 will be grouped in each country according to the length of the study period.

16.1.2.5 Association between potential risk factors/confounders and ASD

Table 49 Association between potential offspring risk factors/confounders and ASD; ASD as outcome for sensitivity analysis 2

ASD	Overall		Event		Non-event		Association	
Offspring risk factors/confounders	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Gender [a]								
Male	1205	51.19	22	1.83	1183	98.17	Reference	-
Female	1149	48.81	9	0.78	1140	99.22	0.42 (0.19, 0.93)	-
Missing	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	4.64, 0.0313
Congenital CMV [b]								
No	2353	99.96	31	1.32	2322	98.68	Reference	-
Yes	1	0.04	0	0.00	1	100.00	0.00 (0.00, I)	0.00, 0.9909
Congenital rubella [b]								
No	2354	100.00	31	1.32	2323	98.68	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Foetal alcohol syndrome [b]								
No	2354	100.00	31	1.32	2323	98.68	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Fragile X syndrome [b]								
No	2354	100.00	31	1.32	2323	98.68	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Lejeune/cri du chat syndrome [b]								
No	2354	100.00	31	1.32	2323	98.68	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Tuberous sclerosis [b]								
No	2353	99.96	31	1.32	2322	98.68	Reference	-
Yes	1	0.04	0	0.00	1	100.00	0.00 (0.00, I)	0.00, 0.9909

ASD: autism spectrum disorders; CI: confidence interval; 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 (ASD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, ie row percentage). The association between each characteristic 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 50 Association between potential maternal risk factors/confounders and ASD; ASD as outcome for sensitivity analysis 2

ASD	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	3	7.32	38	92.68	5.54 (1.46, 20.98)	-
21-25	309	13.13	4	1.29	305	98.71	0.92 (0.29, 2.96)	-
26-30	712	30.25	10	1.40	702	98.60	Reference	-
31-35	758	32.20	5	0.66	753	99.34	0.47 (0.16, 1.37)	-
36-40	457	19.41	8	1.75	449	98.25	1.25 (0.49, 3.19)	-
>40	77	3.27	1	1.30	76	98.70	0.92 (0.12, 7.31)	-
Wald test	-	-	-	-	-	-	-	11.30, 0.0458
Affective disorder [b]								
No	2142	90.99	24	1.12	2118	98.88	Reference	-
Yes	212	9.01	7	3.30	205	96.70	3.01 (1.28, 7.08)	6.41, 0.0114
Diabetes [b]								
No	2328	98.90	31	1.33	2297	98.67	Reference	-
Yes	26	1.10	0	0.00	26	100.00	0.00 (0.00, I)	0.00, 0.9861
Gestational diabetes [c]								
No	2284	97.03	31	1.36	2253	98.64	Reference	-
Yes	70	2.97	0	0.00	70	100.00	0.00 (0.00, I)	0.00, 0.9772
Neurotic disorder [b]								
No	2095	89.00	26	1.24	2069	98.76	Reference	-
Yes	259	11.00	5	1.93	254	98.07	1.57 (0.60, 4.12)	0.83, 0.3624
Schizophrenia, schizotypal and delusional disorders [b]								
No	2347	99.70	31	1.32	2316	98.68	Reference	-
Yes	7	0.30	0	0.00	7	100.00	0.00 (0.00, I)	0.00, 0.9891
Obesity [d]								
No	2327	98.85	31	1.33	2296	98.67	Reference	-
Yes	27	1.15	0	0.00	27	100.00	0.00 (0.00, I)	0.00, 0.9859
CMV [c]								

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
No	2353	99.96	31	1.32	2322	98.68	Reference	-
Yes	1	0.04	0	0.00	1	100.00	0.00 (0.00, I)	0.00, 0.9909
Rubella [c]								
No	2354	100.00	31	1.32	2323	98.68	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse prior to LMP2 [d]								
No	2345	99.62	31	1.32	2314	98.68	Reference	-
Yes	9	0.38	0	0.00	9	100.00	0.00 (0.00, I)	0.00, 0.9918
Alcohol abuse during pregnancy [c]								
No	2352	99.92	31	1.32	2321	98.68	Reference	-
Yes	2	0.08	0	0.00	2	100.00	0.00 (0.00, I)	0.00, 0.9913
Substance abuse prior to LMP2 [d]								
No	2346	99.66	31	1.32	2315	98.68	Reference	-
Yes	8	0.34	0	0.00	8	100.00	0.00 (0.00, I)	0.00, 0.9923
Substance abuse during pregnancy [c]								
No	2350	99.83	31	1.32	2319	98.68	Reference	-
Yes	4	0.17	0	0.00	4	100.00	0.00 (0.00, I)	0.00, 0.9918
Smoking prior to LMP2 [d]								
No	1910	81.14	23	1.20	1887	98.80	Reference	-
Yes	328	13.93	7	2.13	321	97.87	1.79 (0.76, 4.20)	-
Missing	116	4.93	1	0.86	115	99.14	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	1.78, 0.1820
Smoking during pregnancy [c]								
No	2142	90.99	25	1.17	2117	98.83	Reference	-
Yes	145	6.16	5	3.45	140	96.55	3.02 (1.14, 8.02)	-
Missing	67	2.85	1	1.49	66	98.51	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	4.95, 0.0261
Maternal polypharmacy index prior to LMP2 [c](categorical)								
0	1588	67.46	20	1.26	1568	98.74	Reference	-

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
1-4	716	30.42	10	1.40	706	98.60	1.11 (0.52, 2.38)	-
5-10	49	2.08	1	2.04	48	97.96	1.63 (0.21, 12.42)	-
>10	1	0.04	0	0.00	1	100.00	0.00 (0.00, I)	-
Wald test	-	-	-	-	-	-	-	0.27, 0.9657
Maternal polypharmacy index during pregnancy [c](categorical)								
0	1186	50.38	15	1.26	1171	98.74	Reference	-
1-4	1105	46.94	16	1.45	1089	98.55	1.15 (0.56, 2.33)	-
5-10	61	2.59	0	0.00	61	100.00	0.00 (0.00, I)	-
>10	2	0.08	0	0.00	2	100.00	0.00 (0.00, I)	-
Wald test	-	-	-	-	-	-	-	0.14, 0.9860
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription								
No	2063	87.64	25	1.21	2038	98.79	Reference	-
Yes	291	12.36	6	2.06	285	97.94	1.72 (0.70, 4.22)	1.38, 0.2393
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription								
No	2192	93.12	27	1.23	2165	98.77	Reference	-
Yes	162	6.88	4	2.47	158	97.53	2.03 (0.70, 5.87)	1.71, 0.1912
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription								
No	920	39.08	14	1.52	906	98.48	Reference	-
Yes	1434	60.92	17	1.19	1417	98.81	0.78 (0.38, 1.58)	0.49, 0.4860
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription								

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
No	1304	55.40	15	1.15	1289	98.85	Reference	-
Yes	1050	44.60	16	1.52	1034	98.48	1.33 (0.65, 2.70)	0.62, 0.4309

ASD: autism spectrum disorders; CI: confidence interval; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; OR: odds ratios.
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 (ASD) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, ie row percentage). The association between each characteristic 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 (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 51 Association between potential paternal risk factors/confounders and ASD; ASD as outcome for sensitivity analysis 2

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Paternal risk factors/confounders								
Affective disorder [a]								
No	1824	77.49	23	1.26	1801	98.74	Reference	-
Yes	530	22.51	8	1.51	522	98.49	1.20 (0.53, 2.70)	0.19, 0.6591
Bipolar affective disorder [a]								
No	1814	77.06	22	1.21	1792	98.79	Reference	-
Yes	540	22.94	9	1.67	531	98.33	1.38 (0.63, 3.02)	0.65, 0.4186
Mania [a]								
No	2321	98.60	31	1.34	2290	98.66	Reference	-
Yes	33	1.40	0	0.00	33	100.00	0.00 (0.00, I)	0.00, 0.9844
Neurotic disorder [a]								
No	1839	78.12	21	1.14	1818	98.86	Reference	-
Yes	515	21.88	10	1.94	505	98.06	1.71 (0.80, 3.66)	1.93, 0.1642
Schizophrenia, schizotypal and delusional disorders [a]								
No	2265	96.22	27	1.19	2238	98.81	Reference	-
Yes	89	3.78	4	4.49	85	95.51	3.90 (1.34, 11.40)	6.19, 0.0128
Substance abuse [c]								
No	2332	99.07	30	1.29	2302	98.71	Reference	-
Yes	22	0.93	1	4.55	21	95.45	3.65 (0.48, 28.05)	1.55, 0.2127
Paternal polypharmacy index [d] (categorical)								
0	1296	55.06	12	0.93	1284	99.07	Reference	-
1-4	967	41.08	15	1.55	952	98.45	1.69 (0.79, 3.62)	-
5-10	85	3.61	4	4.71	81	95.29	5.28 (1.67, 16.75)	-
>10	6	0.25	0	0.00	6	100.00	0.00 (0.00, I)	-
Wald test	-	-	-	-	-	-	-	8.10, 0.0439
Concomitant medications associated with valproate-indicated psychiatric conditions [c] -fathers with at least one prescription								
No	1507	64.02	14	0.93	1493	99.07	Reference	-
Yes	847	35.98	17	2.01	830	97.99	2.18 (1.07, 4.45)	4.62, 0.0316
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription								

ASD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Paternal risk factors/confounders								
No	997	42.35	9	0.90	988	99.10	Reference	-
Yes	1357	57.65	22	1.62	1335	98.38	1.81 (0.83, 3.95)	2.22, 0.1363
Father's age [e] (categorical)								
≤20 years	13	0.55	1	7.69	12	92.31	5.15 (0.62, 42.61)	-
21-25	140	5.95	3	2.14	137	97.86	1.35 (0.38, 4.81)	-
26-30	491	20.86	4	0.81	487	99.19	0.51 (0.16, 1.57)	-
31-35	817	34.71	13	1.59	804	98.41	Reference	-
36-40	577	24.51	6	1.04	571	98.96	0.65 (0.25, 1.72)	-
>40	316	13.42	4	1.27	312	98.73	0.79 (0.26, 2.45)	-
Wald test	-	-	-	-	-	-	-	5.42, 0.3663
Year of offspring conception [f,g]								
2006-2010	680	28.89	21	3.09	659	96.91	Reference	-
2011-2015	971	41.25	10	1.03	961	98.97	0.33 (0.15, 0.70)	-
2016-2019	703	29.86	0	0.00	703	100.00	0.00 (0.00, I)	-
Wald test	-	-	-	-	-	-	-	8.34, 0.0154

ASD: autism spectrum disorders; CI: confidence interval; LMP2: last menstrual period plus 2 weeks; OR: odds ratios.
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 (ASD) in each subgroup defined by the characteristic (percentage is calculated over the number of offspring with the characteristic, ie row percentage). The association between each characteristic 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); b) excluding bipolar and mania; 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 will be grouped in each country according to the length of the study period.

16.1.2.6 Variable estimates from propensity score

Table 52 Variable estimates from logistic regression propensity score model; ASD as outcome for sensitivity analysis 2

ASD		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	0.5462
Maternal risk factors/confounders			
Mother's age [b] (categorical)			
≤20 years	0.65	0.32, 1.34	0.2457
21-25	0.94	0.69, 1.28	0.6861
26-30	Reference	-	-
31-35	0.89	0.70, 1.13	0.3303
36-40	0.82	0.62, 1.08	0.1641
>40	1.27	0.73 - 2.22	0.4043
Affective disorder [d]	1.27	0.84 - 1.92	0.2596
Gestational diabetes [e]	0.29	0.14 - 0.61	0.0011
Neurotic disorder [d]	0.87	0.60 - 1.27	0.4664
Obesity [f]	0.41	0.13 - 1.30	0.1281
Substance abuse prior to LMP2 [f]	0.99	0.01 - 76.15	0.9980
Smoking prior to LMP2 [f]			
No	Reference	-	-
Yes	0.93	0.66 - 1.30	0.6623
Smoking during pregnancy [e]			
No	Reference	-	-
Yes	1.62	0.99 - 2.66	0.0547
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.70	0.46 - 1.06	0.0919
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	1.02	0.59 - 1.77	0.9335
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] -mothers with at least one prescription	1.12	0.91 - 1.37	0.2830
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.89	0.73 - 1.09	0.2678
Paternal risk factors/confounders			
Affective disorder [d,g]	0.42	0.30 - 0.58	<.0001
Bipolar affective disorder [d]	0.57	0.43 - 0.77	0.0003
Mania [d]	0.83	0.29 - 2.37	0.7247
Neurotic disorder [d]	0.87	0.64 - 1.18	0.3714
Schizophrenia, schizotypal and delusional disorders [d]	2.82	1.64 - 4.85	0.0002
Substance abuse [f]	8.38	1.39 - 50.40	0.0202
Paternal polypharmacy index [b] (categorical)			
0	Reference	-	-
1-4	0.74	0.57 - 0.97	0.0286
5-10	0.72	0.38 - 1.35	0.3051

ASD		Estimate	
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
>10	0.60	0.05 - 7.15	0.6845
Concomitant medications associated with valproate-indicated psychiatric conditions [f] – fathers with at least one prescription	0.78	0.59 - 1.04	0.0961
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with at least one prescription	0.87	0.68 - 1.11	0.2570
Year of offspring conception [i,j]			
2006-2010	Reference	-	-
2011-2015	0.56	0.45 - 0.70	<.0001
2016-2019	0.29	0.22 - 0.37	<.0001

ASD: autism spectrum disorders; CI: confidence interval; LMP2: last menstrual period date plus 2 weeks; OR: odds ratios; PS: propensity score.

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 will be considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions will be 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; h) 3-months lookback from LMP2; i) at mother's LMP2; j) calendar years will be grouped in each country according to the length of the study period.

Table 53 Balance of risk factors/confounders after PS weighting (PS scores obtained using logistic regression); ASD as outcome for sensitivity analysis 2

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0.05	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	1.00	Yes
Affective disorder [e]	0.05	Yes	0.84	Yes
Diabetes [e]	0.14	No	-	-***
Gestational diabetes [f]	0.02	Yes	0.88	Yes
Neurotic disorder [e]	0.02	Yes	0.95	Yes
Schizophrenia, schizotypal and delusional disorders [e]	0.04	Yes	-	-***
Obesity [g]	0.04	Yes	0.64	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]	0.02	Yes	1.87	Yes
Substance abuse during pregnancy [f]	0.03	Yes	-	-***
Smoking prior to LMP2 [g]	0.02	Yes	0.96	Yes
Smoking during pregnancy [f]	0.01	Yes	0.97	Yes

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Maternal polypharmacy index prior to LMP2 [i] (categorical)	0.00*	Yes	1.01	Yes
Maternal polypharmacy index during pregnancy [f] (categorical)	0.00*	Yes	0.93	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g] - mothers with at least one prescription	0.06	Yes	0.84	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f] - mothers with at least one prescription	0.05	Yes	0.82	Yes
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [g] -mothers with at least one prescription	0.04	Yes	1.01	Yes
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [f] - mothers with at least one prescription	0.01	Yes	0.99	Yes
Paternal risk factors/confounders				
Affective disorder [c,h]	0.03	Yes	0.95	Yes
Bipolar affective disorder [c]	0.01	Yes	0.98	Yes
Mania [c]	0.04	Yes	0.59	Yes
Neurotic disorder [e]	0.00	Yes	0.99	Yes
Schizophrenia, schizotypal and delusional disorders [e]	0.00	Yes	0.99	Yes
Substance abuse [g]	0.04	Yes	2.15	**No**
Paternal polypharmacy index [i] (categorical)	0.00*	Yes	0.96	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] – fathers with at least one prescription	0.03	Yes	0.98	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] - fathers with at least one prescription	0.00	Yes	0.99	Yes
Father's age [c] (categorical)	0.00*	Yes	1.05	Yes
Year of offspring conception [j]	0.00*	Yes	1.00	Yes

ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; PS: propensity score.
* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardised 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).
a) absolute standardised 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.

Table 54. Variable importance metric from random forest propensity score model; ASD as outcome for sensitivity analysis 2

ASD Variable (or interaction)[a]	Variable importance
Offspring risk factors/confounders	
Gender [b]	-0.01
Congenital CMV [c]	0.01
Tuberous sclerosis [c]	0.00
Maternal risk factors/confounders	
Mother's age [b] (categorical)	0.04
Affective disorder [d]	0.02
Diabetes [d]	0.01
Gestational diabetes [e]	0.02
Neurotic disorder [d]	-0.01
Schizophrenia, schizotypal and delusional disorders [d]	0.02
Obesity [f]	0.03
CMV [f]	0.00
Alcohol abuse prior to LMP2 [f]	0.07
Alcohol abuse during pregnancy [c]	0.00
Substance abuse prior to LMP2 [f]	0.01
Substance abuse during pregnancy [c]	0.01
Smoking prior to LMP2 [f]	0.00
Smoking during pregnancy [e]	0.02
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 [c] - 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]	0.02
Bipolar affective disorder [d]	0.03
Mania [d]	0.01
Neurotic disorder [d]	-0.02
Schizophrenia, schizotypal and delusional disorders [d]	0.06
Substance abuse [f]	0.03
Paternal polypharmacy index [h] (categorical)	0.03
Concomitant medications associated with valproate-indicated psychiatric conditions [f] – fathers with at least one prescription	0.02
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with at least one prescription	0.03
Year of offspring conception [i]	0.06

ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; PS: propensity score.
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 will be considered to enter the PS model if associated with the study outcome based on univariate analyses. All two-way interactions will be 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 55 Variable estimates from logistic regression informed by random forest propensity score model; ASD as outcome for sensitivity analysis 2

ASD		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	0.5237
Maternal risk factors/confounders			
Mother's age [b] (categorical)			
≤20 years	0.73	0.35 - 1.50	0.3913
21-25	0.94	0.69 - 1.27	0.6706
26-30	Reference	-	-
31-35	0.88	0.69 - 1.11	0.2782
36-40	0.79	0.60 - 1.04	0.0986
>40	1.26	0.72 - 2.20	0.4110
Affective disorder [d]	1.40	0.92 - 2.12	0.1155
Gestational diabetes [c]	0.27	0.12 - 0.59	0.0010
Neurotic disorder [d]	0.75	0.51 - 1.09	0.1328
Obesity [f]	0.53	0.14 - 2.10	0.3687
Smoking during pregnancy [e]			
No	Reference	-	-
Yes	1.50	1.00 - 2.25	0.0512
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.74	0.49 - 1.11	0.1479
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.93	0.54 - 1.61	0.7912
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] -mothers with at least one prescription	0.93	0.76 - 1.13	0.4696
Paternal risk factors/confounders			
Affective disorder [d,g]	0.39	0.28 - 0.55	<.0001
Bipolar affective disorder [d]	0.57	0.43 - 0.77	0.0002
Mania [d]	0.57	0.17 - 1.90	0.3583
Neurotic disorder [d]	0.90	0.66 - 1.22	0.5021
Schizophrenia, schizotypal and delusional disorders [d]	1.98	1.14 - 3.43	0.0149
Substance abuse [f]	4.90	0.65 - 37.15	0.1239
Concomitant medications associated with valproate-indicated psychiatric conditions [f] – fathers with at least one prescription	0.70	0.54 - 0.93	0.0118
Concomitant medications associated with neuropsychiatric adverse events [f] - fathers with at least one prescription	0.76	0.61 - 0.94	0.0125
Year of offspring conception [i,j]			
2006-2010	Reference	-	-
2011-2015	0.55	0.44 - 0.68	<.0001
2016-2019	0.28	0.22 - 0.36	<.0001

ASD: autism spectrum disorders; CI: confidence interval; LMP2: last menstrual period date plus 2 weeks; OR: odds ratio; PS: propensity score
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 will be considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions will be 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; h) 3-months lookback from LMP2; i) at mother's LMP2; j) calendar years will be grouped in each country according to the length of the study period.

Table 56. Balance of risk factors and confounders after PS weighting (PS scores obtained using random forest model); ASD as outcome for sensitivity analysis 2

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0.04	Yes	0.74	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)	0.01 *	Yes	0.75	Yes
Affective disorder [e]	0.05	Yes	0.64	Yes
Diabetes [c]	0.05	Yes	0.45	Yes
Gestational diabetes [f]	0.06	Yes	0.53	Yes
Neurotic disorder [c]	0.09	Yes	0.58	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.02	Yes	1.08	Yes
Obesity [g]	0.01	Yes	0.70	Yes
CMV [g]	0.04	Yes	-	- ***
Rubella [g]	-	- **	-	- ***
Alcohol abuse prior to LMP2 [g]	0.12	**No**	-	- ***
Alcohol abuse during pregnancy [f]	0.01	Yes	1.16	Yes
Substance abuse prior to LMP2 [g]	0.01	Yes	0.91	Yes
Substance abuse during pregnancy [f]	0.02	Yes	1.52	Yes
Smoking prior to LMP2 [g]	0.06	Yes	0.86	Yes
Smoking during pregnancy [f]	0.07	Yes	0.98	Yes
Maternal polypharmacy index prior to LMP2 [i] (categorical)	0.00*	Yes	0.76	Yes
Maternal polypharmacy index during pregnancy [f] (categorical)	0.01 *	Yes	0.69	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g] - mothers with at least one prescription	0.09	Yes	0.58	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f] - mothers with at least one prescription	0.07	Yes	0.57	Yes
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [g] - mothers with at least one prescription	0.03	Yes	0.73	Yes
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [f] - mothers with at least one prescription	0.05	Yes	0.73	Yes
Paternal risk factors/confounders				
Affective disorder [e,h]	0.35	**No**	0.39	Yes
Bipolar affective disorder [e]	0.31	**No**	0.44	Yes
Mania [e]	0.01	Yes	0.70	Yes
Neurotic disorder [c]	0.26	**No**	0.47	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.03	Yes	0.87	Yes
Substance abuse [g]	0.05	Yes	1.35	Yes

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Paternal polypharmacy index [i] (categorical)	0.07*	Yes	0.68	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] – fathers with at least one prescription	0.29	**No**	0.57	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] - fathers with at least one prescription	0.19	**No**	0.75	Yes
Father's age [c] (categorical)	0.00*	Yes	0.77	Yes
Year of offspring conception [j]	0.08*	Yes	0.74	Yes

ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; PS: propensity score.
* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardised 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).
a) absolute standardised 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.

Table 57 Balance of risk factors after PS weighting (PS scores obtained with logistic regression informed by random forest); ASD as outcome for sensitivity analysis 2

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0.03	Yes	0.98	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 [c]	0.14	**No**	-	- ***
Gestational diabetes [f]	0.04	Yes	0.76	Yes
Neurotic disorder [c]	0.06	Yes	0.83	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.04	Yes	-	- ***
Obesity [g]	0.05	Yes	0.49	Yes
CMV [g]	0.04	Yes	-	- ***
Rubella [g]	-	- **	-	- ***
Alcohol abuse prior to LMP2 [g]	0.10	Yes	-	- ***
Alcohol abuse during pregnancy [f]	0.04	Yes	-	- ***
Substance abuse prior to LMP2 [g]	0.03	Yes	-	- ***
Substance abuse during pregnancy [f]	-	- **	-	- ***
Smoking prior to LMP2 [g]	0.01	Yes	0.94	Yes
Smoking during pregnancy [f]	0.01	Yes	0.94	Yes
Maternal polypharmacy index prior to LMP2 [i] (categorical)	0.00*	Yes	0.98	Yes
Maternal polypharmacy index during pregnancy [f] (categorical)	0.00*	Yes	0.91	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g] - mothers with at least one prescription	0.06	Yes	0.84	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f] - mothers with at least one prescription	0.05	Yes	0.79	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	0.01	Yes	0.97	Yes
Paternal risk factors/confounders				
Affective disorder [e,h]	0.05	Yes	0.91	Yes
Bipolar affective disorder [e]	0.02	Yes	0.95	Yes
Mania [e]	0.06	Yes	0.48	Yes
Neurotic disorder [c]	0.00	Yes	0.98	Yes
Schizophrenia, schizotypal and delusional disorders [c]	0.00	Yes	0.99	Yes
Substance abuse [g]	0.01	Yes	1.29	Yes

ASD	Absolute standardised difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Paternal polypharmacy index [i] (categorical)	0.01*	Yes	0.87	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] – fathers with at least one prescription	0.03	Yes	0.96	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] - fathers with at least one prescription	0.01	Yes	0.98	Yes
Father's age [c] (categorical)	0.00*	Yes	1.02	Yes
Year of offspring conception [j]	0.00*	Yes	0.97	Yes

ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; PS: propensity score.
* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardised 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).
a) absolute standardised 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.

16.1.3 Norway

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

Table 58 Offspring demographic characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group									
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of offspring	**N=397**		**N=1019**		**N=865**		**N=154**		**N=1416**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Gestational age (weeks)										
<28 (extremely preterm)	2	0.50	3	0.29	3	0.35	0	0.00	5	0.35
28-31 (very preterm)	3	0.76	5	0.49	4	0.46	1	0.65	8	0.56
32-36 (moderate to late preterm)	21	5.29	42	4.12	35	4.05	7	4.55	63	4.45
37-41 (at term)	349	87.91	925	90.78	785	90.75	140	90.91	1274	89.97
>=42 (post-term)	22	5.54	44	4.32	38	4.39	6	3.90	66	4.66
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	3	0.76	5	0.49	4	0.46	1	0.65	8	0.56
1000-1499 (very low)	1	0.25	3	0.29	3	0.35	0	0.00	4	0.28
1500-2499 (low)	13	3.27	26	2.55	21	2.43	5	3.25	39	2.75
>=2500	380	95.72	985	96.66	837	96.76	148	96.10	1365	96.40
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gender [a]										
Male	198	49.87	539	52.89	445	51.45	94	61.04	737	52.05

ASD	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=397		N=1019		N=865		N=154		N=1416	
	N	%	N	%	N	%	N	%	N	%
Female	199	50.13	480	47.11	420	48.55	60	38.96	679	47.95
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of birth										
2010	30	7.56	86	8.44	78	9.02	8	5.19	116	8.19
2011	46	11.59	107	10.50	98	11.33	9	5.84	153	10.81
2012	44	11.08	79	7.75	71	8.21	8	5.19	123	8.69
2013	43	10.83	100	9.81	85	9.83	15	9.74	143	10.10
2014	43	10.83	116	11.38	97	11.21	19	12.34	159	11.23
2015	42	10.58	103	10.11	85	9.83	18	11.69	145	10.24
2016	43	10.83	118	11.58	93	10.75	25	16.23	161	11.37
2017	41	10.33	109	10.70	94	10.87	15	9.74	150	10.59
2018	37	9.32	97	9.52	81	9.36	16	10.39	134	9.46
2019	28	7.05	104	10.21	83	9.60	21	13.64	132	9.32
Total number of years of follow-up	1997.81		4919.33		4269.39		649.94		6917.14	
Mean follow-up year	5.03		4.83		4.94		4.22		4.88	

ASD: autism spectrum 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 will be 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 59 Offspring clinical characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

ASD	Paternal exposure group									
Number of offspring	Valproate N=397		Lamotrigine/ levetiracetam N=1019		Lamotrigine N=865		Levetiracetam N=154		Total (valproate + lamotrigine/ levetiracetam) N=1416	
	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	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
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	0	0.00	0	0.00	0	0.00	0	0.00
Medication use										
Exposure to AEDs [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Outcomes										
ASD (ever, not only as 1st NDD diagnosis)	4	1.01	4	0.39	4	0.46	0	0.00	8	0.56
ASD (as 1st NDD diagnosis)	2	0.50	3	0.29	3	0.35	0	0.00	5	0.35
NDD including ASD	14	3.53	22	2.16	20	2.31	2	1.30	36	2.54
Age at the first diagnosis (years)										
ASD (ever, not only as 1st NDD diagnosis) [b,c]										
0-1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2-3	3	0.76	1	0.10	1	0.12	0	0.00	4	0.28
4-5	1	0.25	1	0.10	1	0.12	0	0.00	2	0.14

	Paternal exposure group									
ASD **Number of offspring**	**Valproate** **N=397**		**Lamotrigine/ levetiracetam** **N=1019**		**Lamotrigine** **N=865**		**Levetiracetam** **N=154**		**Total (valproate + lamotrigine/ levetiracetam)** **N=1416**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
6-7	0	0.00	1	0.10	1	0.12	0	0.00	1	0.07
8-9	0	0.00	1	0.10	1	0.12	0	0.00	1	0.07
Total (offspring with the outcome)	4	1.01	4	0.4	4	0.48	0	0	8	0.56
NDD including ASD [b,c]										
0-1	1	0.25	0	0.00	0	0.00	0	0.00	1	0.07
2-3	4	1.01	10	0.98	9	1.04	1	0.65	14	0.99
4-5	3	0.76	4	0.39	3	0.35	1	0.65	7	0.49
6-7	5	1.26	5	0.49	5	0.58	0	0.00	10	0.71
8-9	1	0.25	3	0.29	3	0.35	0	0.00	4	0.28
Total (offspring with the outcome)	14	3.53	22	2.15	20	2.32	2	1.3	36	2.54

AED: antiepileptic drug; ASD: autism spectrum disorders; 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) between index (childbirth) and exit date; b) categories might be adapted according to the data.

Table 60 Maternal demographic characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

ASD	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=397		N=1019		N=865		N=154		N=1416	
	N	%	N	%	N	%	N	%	N	%
Mother's age [a]										
≤20 years	6	1.51	16	1.57	14	1.62	2	1.30	22	1.55
21-25	60	15.11	133	13.05	115	13.29	18	11.69	193	13.63
26-30	136	34.26	338	33.17	276	31.91	62	40.26	474	33.47
31-35	137	34.51	340	33.37	295	34.10	45	29.22	477	33.69
36-40	50	12.59	152	14.92	136	15.72	16	10.39	202	14.27
>40	8	2.02	40	3.93	29	3.35	11	7.14	48	3.39
Mean (SD)	30.38 (4.84)		30.96 (5.11)		30.99 (5.08)		30.80 (5.30)		30.80 (5.04)	
Median (25^{th} - 75^{th} percentile)	30 (27.00, 34.00)		31 (27.00, 35.00)		31 (27.00, 35.00)		30 (27.00, 33.00)		31 (27.00, 34.00)	
Min, max	19.00, 43.00		17.00, 46.00		18.00, 46.00		17.00, 43.00		17.00, 46.00	
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

ASD: autism spectrum disorders; Max: maximum; Min: minimum; SD: standard deviation.
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 will be 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 61 Maternal clinical characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

ASD	Paternal exposure group									
Number of offspring	Valproate N=397		Lamotrigine/ levetiracetam N=1019		Lamotrigine N=865		Levetiracetam N=154		Total (valproate + lamotrigine/ levetiracetam) N=1416	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Affective disorder [a]	23	5.79	103	10.11	98	11.33	5	3.25	126	8.90
Diabetes [a]	6	1.51	21	2.06	21	2.43	0	0.00	27	1.91
Epilepsy [a]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Neurotic disorder [a]	50	12.59	137	13.44	124	14.34	13	8.44	187	13.21
Schizophrenia, schizotypal and delusional disorders [a]	1	0.25	0	0.00	0	0.00	0	0.00	1	0.07
Obesity [b]	6	1.51	10	0.98	10	1.16	0	0.00	16	1.13
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gestational diabetes [c]	20	5.04	67	6.58	61	7.05	6	3.90	87	6.14
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	0.25	2	0.20	2	0.23	0	0.00	3	0.21
Alcohol abuse during pregnancy [c]	1	0.25	1	0.10	1	0.12	0	0.00	2	0.14
Substance abuse prior to LMP2 [b]	2	0.50	4	0.39	4	0.46	0	0.00	6	0.42
Substance abuse during pregnancy [c]	2	0.50	2	0.20	2	0.23	0	0.00	4	0.28
Smoking prior to LMP2 [b]										
Yes	58	14.61	121	11.87	110	12.72	11	7.14	179	12.64
No	273	68.77	773	75.86	647	74.80	126	81.82	1046	73.87
Missing	66	16.62	125	12.27	108	12.49	17	11.04	191	13.49
Smoking during pregnancy [c]										

ASD	Paternal exposure group									
Number of offspring	Valproate N=397		Lamotrigine/ levetiracetam N=1019		Lamotrigine N=865		Levetiracetam N=154		Total (valproate + lamotrigine/ levetiracetam) N=1416	
	N	%	N	%	N	%	N	%	N	%
Yes	27	6.80	43	4.22	42	4.86	1	0.65	70	4.94
No	316	79.60	872	85.57	735	84.97	137	88.96	1188	83.90
Missing	54	13.60	104	10.21	88	10.17	16	10.39	158	11.16
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	0	0.00	0	0.00	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00	0	0.00	0	0.00	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 [c]	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	0	0.00	0	0.00	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
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	0	0.00	0	0.00	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

ASD	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=397		N=1019		N=865		N=154		N=1416	
	N	%	N	%	N	%	N	%	N	%
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [c]	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	0	0.00	0	0.00	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
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	397	100.00	1019	100.00	865	100.00	154	100.00	1416	100.00
K-means cluster during pregnancy [c]										
Unexposed	397	100.00	1019	100.00	865	100.00	154	100.00	1416	100.00
Maternal polypharmacy index prior to LMP2 [d]										
0	261	65.74	649	63.69	549	63.47	100	64.94	910	64.27
1-4	125	31.49	349	34.25	298	34.45	51	33.12	474	33.47
5-10	10	2.52	21	2.06	18	2.08	3	1.95	31	2.19
>10	1	0.25	0	0.00	0	0.00	0	0.00	1	0.07
Mean (SD)	0.71 (1.36)		0.65 (1.14)		0.66 (1.15)		0.63 (1.11)		0.67 (1.21)	
Median	0		0		0		0		0	
(25^{th} - 75^{th} percentile)	(0.00, 1.00)		(0.00, 1.00)		(0.00, 1.00)		(0.00, 1.00)		(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]										

ASD Number of offspring	Paternal exposure group Valproate N=397		Lamotrigine/ levetiracetam N=1019		Lamotrigine N=865		Levetiracetam N=154		Total (valproate + lamotrigine/ levetiracetam) N=1416	
	N	%	N	%	N	%	N	%	N	%
0	210	52.90	513	50.34	431	49.83	82	53.25	723	51.06
1-4	178	44.84	477	46.81	408	47.17	69	44.81	655	46.26
5-10	9	2.27	29	2.85	26	3.01	3	1.95	38	2.68
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mean (SD)	0.87 (1.23)		0.95 (1.32)		0.97 (1.35)		0.83 (1.16)		0.93 (1.30)	
Median (25th - 75th percentile)	0 (0.00, 1.00)		0 (0.00, 1.00)		1 (0.00, 1.00)		0 (0.00, 1.00)		0 (0.00, 1.00)	
Min, max	0.00, 6.00		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 [b] - mothers with at least one prescription	31	7.81	111	10.89	99	11.45	12	7.79	142	10.03
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	12	3.02	62	6.08	58	6.71	4	2.60	74	5.23
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] - mothers with at least one prescription	269	67.76	694	68.11	594	68.67	100	64.94	963	68.01
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	162	40.81	440	43.18	380	43.93	60	38.96	602	42.51

ASD: autism spectrum disorders; AED: antiepileptic drug; CMV: cytomegalovirus; LMP2: last menstrual period plus 2 weeks; Max: Maximum; Min: Minimum; 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.

Table 62 Paternal demographic characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

ASD	Paternal exposure group									
Number of offspring	Valproate N=397		Lamotrigine/ levetiracetam N=1019		Lamotrigine N=865		Levetiracetam N=154		Total (valproate + lamotrigine/ levetiracetam) N=1416	
	N	%	N	%	N	%	N	%	N	%
Father's age [a]										
≤20 years	2	0.50	3	0.29	2	0.23	1	0.65	5	0.35
21-25	29	7.30	69	6.77	57	6.59	12	7.79	98	6.92
26-30	106	26.70	224	21.98	185	21.39	39	25.32	330	23.31
31-35	141	35.52	331	32.48	276	31.91	55	35.71	472	33.33
36-40	85	21.41	240	23.55	211	24.39	29	18.83	325	22.95
>40	34	8.56	152	14.92	134	15.49	18	11.69	186	13.14
Mean (SD)	32.94 (5.63)		34.07 (6.25)		34.23 (6.30)		33.20 (5.90)		33.76 (6.10)	
Median (25^{th} - 75^{th} percentile)	32 (29.00, 37.00)		34 (30.00, 38.00)		34 (30.00, 38.00)		33 (29.00, 37.00)		33 (30.00, 38.00)	
Min, max	20.00, 53.00		18.00, 64.00		18.00, 64.00		20.00, 51.00		18.00, 64.00	
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of offspring conception [b]										
2009	21	5.29	60	5.89	54	6.24	6	3.90	81	5.72
2010	43	10.83	110	10.79	102	11.79	8	5.19	153	10.81
2011	41	10.33	81	7.95	71	8.21	10	6.49	122	8.62
2012	48	12.09	102	10.01	90	10.40	12	7.79	150	10.59
2013	40	10.08	102	10.01	82	9.48	20	12.99	142	10.03
2014	46	11.59	111	10.89	94	10.87	17	11.04	157	11.09
2015	48	12.09	113	11.09	91	10.52	22	14.29	161	11.37

ASD	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=397		N=1019		N=865		N=154		N=1416	
	N	%	N	%	N	%	N	%	N	%
2016	37	9.32	110	10.79	95	10.98	15	9.74	147	10.38
2017	33	8.31	100	9.81	80	9.25	20	12.99	133	9.39
2018	32	8.06	106	10.40	87	10.06	19	12.34	138	9.75
2019	8	2.02	24	2.36	19	2.20	5	3.25	32	2.26

ASD: autism spectrum 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 will be 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 63 Paternal clinical characteristics by paternal exposure group; ASD as outcome for sensitivity analysis 2

ASD	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of offspring	N=397		N=1019		N=865		N=154		N=1416	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Bipolar affective disorder excl. bipolar disorder and mania [a]	31	7.81	227	22.28	226	26.13	1	0.65	258	18.22
Bipolar affective disorder [a]	56	14.11	283	27.77	283	32.72	0	0.00	339	23.94
Mania [a]	6	1.51	7	0.69	7	0.81	0	0.00	13	0.92
Neurotic disorder [a]	30	7.56	157	15.41	155	17.92	2	1.30	187	13.21
Schizophrenia, schizotypal and delusional disorders [a]	11	2.77	18	1.77	18	2.08	0	0.00	29	2.05
Lifestyle characteristics										
Substance abuse [b]	10	2.52	22	2.16	22	2.54	0	0.00	32	2.26
Medication use										
AED indication										
Epilepsy	230	57.93	418	41.02	278	32.14	140	90.91	648	45.76
Bipolar affective disorder and mania	54	13.60	281	27.58	281	32.49	0	0.00	335	23.66
Other/unknown	113	28.46	320	31.40	306	35.38	14	9.09	433	30.58
K-means cluster prior to LMP2 [c]										
Group A	278	70.03	783	76.84	656	75.84	127	82.47	1061	74.93
Group B	119	29.97	236	23.16	209	24.16	27	17.53	355	25.07
Paternal polypharmacy index [c]										

ASD Number of offspring	Paternal exposure group									
	Valproate N=397		Lamotrigine/ levetiracetam N=1019		Lamotrigine N=865		Levetiracetam N=154		Total (valproate + lamotrigine/ levetiracetam) N=1416	
	N	%	N	%	N	%	N	%	N	%
0	255	64.23	519	50.93	415	47.98	104	67.53	774	54.66
1-4	136	34.26	467	45.83	420	48.55	47	30.52	603	42.58
5-10	6	1.51	31	3.04	28	3.24	3	1.95	37	2.61
>10	0	0.00	2	0.20	2	0.23	0	0.00	2	0.14
Mean (SD)	0.65 (1.14)		1.01 (1.49)		1.09 (1.53)		0.58 (1.17)		0.91 (1.41)	
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, 7.00		0.00, 13.00		0.00, 13.00		0.00, 8.00		0.00, 13.00	
Concomitant medications associated with valproate-indicated psychiatric conditions [b] – fathers with at least one prescription	85	21.41	363	35.62	355	41.04	8	5.19	448	31.64
Concomitant medications associated with neuropsychiatric adverse events [b] - fathers with atleast one prescription	225	56.68	657	64.47	587	67.86	70	45.45	882	62.29

AED: antiepileptic drug; ASD: autism spectrum disorders, LMP2: last menstrual period plus 2 weeks; Max: maximum; Min: minimum; 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 will be described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.
Cluster A: constant high exposure, cluster B: constant low exposure.
a) all available data prior to index date (childbirth); b) 12-months lookback from LMP2; c) 3-months lookback from LMP2.

16.1.3.2 Cumulative incidence proportion

Table 64 Cumulative incidence proportion (risk) of ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	397	1019	865	154	1416
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	367	913	780	133	1280
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	329	815	698	117	1144
2-3 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	286	703	603	100	989
3-4 years	n	3	1	1	0	4
	n/N*100	1.05 (-0.13, 2.23)	0.14 (-0.14, 0.42)	0.17 (-0.16, 0.49)	0.00 (0.00, 0.00)	0.40 (0.01, 0.80)
	N	241	584	509	75	825
4-5 years	n	1	1	1	0	2
	n/N*100	0.41 (-0.40, 1.23)	0.17 (-0.16, 0.51)	0.20 (-0.19, 0.58)	0.00 (0.00, 0.00)	0.24 (-0.09, 0.58)
	N	197	481	423	58	678
5-6 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)

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	N	156	365	326	39	521
6-7 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	115	266	242	24	381
7-8 years	n	0	1	1	0	1
	n/N*100	0.00 (0.00, 0.00)	0.38 (-0.36, 1.11)	0.41 (-0.40, 1.22)	0.00 (0.00, 0.00)	0.26 (-0.25, 0.78)
	N	74	189	173	16	263
8-9 years	n	0	1	1	0	1
	n/N*100	0.00 (0.00, 0.00)	0.53 (-0.51, 1.56)	0.58 (-0.55, 1.71)	0.00 (0.00, 0.00)	0.38 (-0.36, 1.12)
	N	28	84	76	8	112
9-10 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	397	1019	865	154	1416
Overall (0-10 years)	n	4	4	4	0	8
	n/N*100	1.01 (0.03, 1.99)	0.39 (0.01, 0.78)	0.46 (0.01, 0.91)	0.00 (0.00, 0.00)	0.56 (0.17, 0.96)

ASD: autism spectrum disorder.
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) will be presented.

Table 65 Cumulative incidence proportion (risk) of ASD by paternal exposure group for male offspring

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	198	539	445	94	737
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	183	480	401	79	663
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	160	425	356	69	585
2-3 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	140	370	312	58	510
3-4 years	n	1	1	1	0	2
	n/N*100	0.71 (-0.68, 2.11)	0.27 (-0.26, 0.80)	0.32 (-0.31, 0.95)	0.00 (0.00, 0.00)	0.39 (-0.15, 0.93)
	N	119	313	267	46	432
4-5 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	105	256	221	35	361
5-6 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	84	187	162	25	271
6-7 years	n	0	0	0	0	0

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	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	63	127	114	13	190
7-8 years	n	0	1	1	0	1
	n/N*100	0.00 (0.00, 0.00)	0.79 (-0.75, 2.32)	0.88 (-0.83, 2.59)	0.00 (0.00, 0.00)	0.53 (-0.50, 1.56)
	N	41	92	81	11	133
8-9 years	n	0	1	1	0	1
	n/N*100	0.00 (0.00, 0.00)	1.09 (-1.03, 3.21)	1.23 (-1.17, 3.64)	0.00 (0.00, 0.00)	0.75 (-0.72, 2.22)
	N	14	46	39	7	60
9-10 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	198	539	445	94	737
Overall (0-10 years)	n	1	3	3	0	4
	n/N*100	0.51 (-0.48, 1.49)	0.56 (-0.07, 1.18)	0.67 (-0.09, 1.43)	0.00 (0.00, 0.00)	0.54 (0.01, 1.07)

ASD: autism spectrum disorder.
Legend: Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which will be 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) will be presented.

Table 66 Cumulative incidence proportion (risk) of ASD by paternal exposure group for female offspring

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	199	480	420	60	679
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	184	433	379	54	617
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	169	390	342	48	559
2-3 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	146	333	291	42	479
3-4 years	n	2	0	0	0	2
	n/N*100	1.37 (-0.52, 3.26)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.42 (-0.16, 1.00)
	N	122	271	242	29	393
4-5 years	n	1	1	1	0	2
	n/N*100	0.82 (-0.78, 2.42)	0.37 (-0.35, 1.09)	0.41 (-0.40, 1.22)	0.00 (0.00, 0.00)	0.51 (-0.19, 1.21)
	N	92	225	202	23	317
5-6 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	72	178	164	14	250
6-7 years	n	0	0	0	0	0

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	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	52	139	128	11	191
7-8 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	33	97	92	5	130
8-9 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	14	38	37	1	52
9-10 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	199	480	420	60	679
Overall (0-10 years)	n	3	1	1	0	4
	n/N*100	1.51 (-0.19, 3.20)	0.21 (-0.20, 0.62)	0.24 (-0.23, 0.70)	0.00 (0.00, 0.00)	0.59 (0.01, 1.16)

ASD: autism spectrum disorder.
Legend: Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which will be 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) will be presented.

16.1.3.3 Cumulative incidence rate and time to ASD diagnosis

Table 67 Cumulative incidence rate of ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	380.75	965.26	821.79	143.47	1346.01
0-1 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 9.69)	0 (-, 3.82)	0 (-, 4.49)	0 (-, 25.71)	0 (-, 2.74)
	PY	726.19	1829.32	1560.76	268.55	2555.5
0-2 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 5.08)	0 (-, 2.02)	0 (-, 2.36)	0 (-, 13.74)	0 (-, 1.44)
	PY	1036.23	2590.85	2215.53	375.32	3627.08
0-3 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 3.56)	0 (-, 1.42)	0 (-, 1.67)	0 (-, 9.83)	0 (-, 1.02)
	PY	1304.01	3236.17	2771.68	464.48	4540.18
0-4 years	n	3	1	1	0	4
	n/PY*1000	2.3 (0.47, 6.72)	0.31 (0.01, 1.72)	0.36 (0.01, 2.01)	0 (-, 7.94)	0.88 (0.24, 2.26)
	PY	1525.49	3770.55	3239.56	530.99	5296.05
0-5 years	n	4	2	2	0	6
	n/PY*1000	2.62 (0.71, 6.71)	0.53 (0.06, 1.92)	0.62 (0.07, 2.23)	0 (-, 6.95)	1.13 (0.42, 2.47)
	PY	1702.39	4189.93	3608.81	581.12	5892.32
0-6 years	n	4	2	2	0	6
	n/PY*1000	2.35 (0.64, 6.02)	0.48 (0.06, 1.72)	0.55 (0.07, 2.00)	0 (-, 6.35)	1.02 (0.37, 2.22)

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	PY	1839.63	4509.02	3895.51	613.51	6348.65
0-7 years	n	4	2	2	0	6
	n/PY*1000	2.17 (0.59, 5.57)	0.44 (0.05, 1.60)	0.51 (0.06, 1.85)	0 (-, 6.01)	0.95 (0.35, 2.06)
	PY	1930.73	4737.24	4103.39	633.86	6667.98
0-8 years	n	4	3	3	0	7
	n/PY*1000	2.07 (0.56, 5.30)	0.63 (0.13, 1.85)	0.73 (0.15, 2.14)	0 (-, 5.82)	1.05 (0.42, 2.16)
	PY	1983.33	4876.67	4230.94	645.73	6860.01
0-9 years	n	4	4	4	0	8
	n/PY*1000	2.02 (0.55, 5.16)	0.82 (0.22, 2.10)	0.95 (0.26, 2.42)	0 (-, 5.71)	1.17 (0.50, 2.30)
	PY	1997.81	4919.33	4269.39	649.94	6917.14
0-10 years	n	4	4	4	0	8
	n/PY*1000	2 (0.55, 5.13)	0.81 (0.22, 2.08)	0.94 (0.26, 2.40)	0 (-, 5.68)	1.16 (0.50, 2.28)

ASD: autism spectrum disorder; 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) will be presented.

Table 68 Cumulative incidence rate of ASD by paternal exposure group for males

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	188.82	511.27	424.53	86.74	700.08
0-1 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 19.54)	0 (-, 7.22)	0 (-, 8.69)	0 (-, 42.53)	0 (-, 5.27)
	PY	358.61	962.18	801.21	160.97	1320.79
0-2 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 10.29)	0 (-, 3.83)	0 (-, 4.60)	0 (-, 22.92)	0 (-, 2.79)
	PY	509.26	1358.33	1134.36	223.96	1867.59
0-3 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 7.24)	0 (-, 2.72)	0 (-, 3.25)	0 (-, 16.47)	0 (-, 1.98)
	PY	639.5	1697.75	1421.63	276.12	2337.25
0-4 years	n	1	1	1	0	2
	n/PY*1000	1.56 (0.04, 8.71)	0.59 (0.01, 3.28)	0.7 (0.02, 3.92)	0 (-, 13.36)	0.86 (0.10, 3.09)
	PY	752.3	1982.61	1666.17	316.44	2734.91
0-5 years	n	1	1	1	0	2
	n/PY*1000	1.33 (0.03, 7.41)	0.5 (0.01, 2.81)	0.6 (0.02, 3.34)	0 (-, 11.66)	0.73 (0.09, 2.64)
	PY	847.41	2201.14	1853.39	347.75	3048.55
0-6 years	n	1	1	1	0	2
	n/PY*1000	1.18 (0.03, 6.57)	0.45 (0.01, 2.53)	0.54 (0.01, 3.01)	0 (-, 10.61)	0.66 (0.08, 2.37)
	PY	921.22	2359.24	1991.07	368.18	3280.46
0-7 years	n	1	1	1	0	2

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	n/PY*1000	1.09 (0.03, 6.05)	0.42 (0.01, 2.36)	0.5 (0.01, 2.80)	0 (-, 10.02)	0.61 (0.07, 2.20)
	PY	970.9	2466.98	2086.52	380.45	3437.88
0-8 years	n	1	2	2	0	3
	n/PY*1000	1.03 (0.03, 5.74)	0.81 (0.10, 2.93)	0.96 (0.12, 3.46)	0 (-, 9.70)	0.87 (0.18, 2.55)
	PY	999.64	2539.79	2149.62	390.17	3539.43
0-9 years	n	1	3	3	0	4
	n/PY*1000	1 (0.03, 5.57)	1.18 (0.24, 3.45)	1.4 (0.29, 4.08)	0 (-, 9.45)	1.13 (0.31, 2.89)
	PY	1008.19	2562.34	2168.37	393.98	3570.53
0-10 years	n	1	3	3	0	4
	n/PY*1000	0.99 (0.03, 5.53)	1.17 (0.24, 3.42)	1.38 (0.29, 4.04)	0 (-, 9.36)	1.12 (0.31, 2.87)

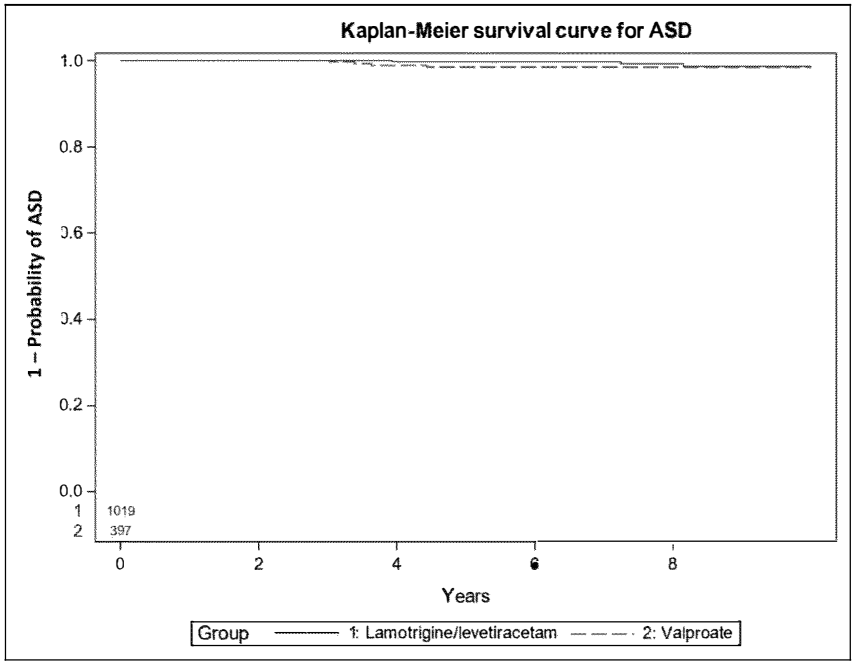
ASD: autism spectrum disorder; PY: person years.
Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which will be determined based on the results of the univariate analyses. As an example, this table presents incidence rates stratified 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) will be presented.

Table 69 Cumulative incidence rate of ASD by paternal exposure group for females

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	191.94	453.99	397.27	56.73	645.93
0-1 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 19.22)	0 (-, 8.13)	0 (-, 9.29)	0 (-, 65.03)	0 (-, 5.71)
	PY	367.58	867.13	759.55	107.58	1234.71
0-2 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 10.04)	0 (-, 4.25)	0 (-, 4.86)	0 (-, 34.29)	0 (-, 2.99)
	PY	526.97	1232.52	1081.16	151.36	1759.49
0-3 years	n	0	0	0	0	0
	n/PY*1000	0 (-, 7.00)	0 (-, 2.99)	0 (-, 3.41)	0 (-, 24.37)	0 (-, 2.10)
	PY	664.51	1538.42	1350.05	188.36	2202.93
0-4 years	n	2	0	0	0	2
	n/PY*1000	3.01 (0.36, 10.87)	0 (-, 2.40)	0 (-, 2.73)	0 (-, 19.58)	0.91 (0.11, 3.28)
	PY	773.19	1787.94	1573.39	214.55	2561.13
0-5 years	n	3	1	1	0	4
	n/PY*1000	3.88 (0.80, 11.34)	0.56 (0.01, 3.12)	0.64 (0.02, 3.54)	0 (-, 17.19)	1.56 (0.43, 4.00)
	PY	854.98	1988.79	1755.42	233.37	2843.77
0-6 years	n	3	1	1	0	4
	n/PY*1000	3.51 (0.72, 10.25)	0.5 (0.01, 2.80)	0.57 (0.01, 3.17)	0 (-, 15.81)	1.41 (0.38, 3.60)
	PY	918.41	2149.78	1904.44	245.33	3068.19
0-7 years	n	3	1	1	0	4

		Paternal exposure group				
ASD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
	n/PY*1000	3.27 (0.67, 9.55)	0.47 (0.01, 2.59)	0.53 (0.01, 2.93)	0 (-, 15.04)	1.3 (0.36, 3.34)
	PY	959.83	2270.27	2016.86	253.4	3230.09
0-8 years	n	3	1	1	0	4
	n/PY*1000	3.13 (0.64, 9.13)	0.44 (0.01, 2.45)	0.5 (0.01, 2.76)	0 (-, 14.56)	1.24 (0.34, 3.17)
	PY	983.7	2336.88	2081.32	255.56	3320.58
0-9 years	n	3	1	1	0	4
	n/PY*1000	3.05 (0.63, 8.91)	0.43 (0.01, 2.38)	0.48 (0.01, 2.68)	0 (-, 14.43)	1.2 (0.33, 3.08)
	PY	989.62	2356.99	2101.02	255.96	3346.61
0-10 years	n	3	1	1	0	4
	n/PY*1000	3.03 (0.63, 8.86)	0.42 (0.01, 2.36)	0.48 (0.01, 2.65)	0 (-, 14.41)	1.2 (0.33, 3.06)

ASD: autism spectrum disorder; PY: person years.
Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which will be 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) will be presented.



	Paternal exposure group				
ASD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	4	4	4	0	8
Number of censor	393	1015	861	154	1408
Survival time					
5th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)

	Paternal exposure group				
ASD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
10th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
25th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
median	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
75th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)

ASD: autism spectrum disorder.
Legend: Due to low number of events the median time-to-event could not be calculated.

Figure 5 Kaplan-Meier survival curve for Autism Spectrum Disorder (ASD) and distribution of time to ASD in Norway

Table 70 Time to ASD by paternal exposure group for male offspring

	Paternal exposure group				
ASD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	1	3	3	0	4
Number of censor	197	536	442	94	733
Survival time					
5th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
10th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
25th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
median	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
75th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)

ASD: autism spectrum disorder.
Legend: Time-to-event analysis may be stratified according to relevant strong risk factors (such as age or gender) which will be determined based on the results of the univariate analyses. As an example, this table and the table below present stratification by gender.

Table 71 Time to ASD by paternal exposure group for female offspring

	Paternal exposure group				
ASD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	3	1	1	0	4
Number of censor	196	479	419	60	675
Survival time					
5th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
10th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
25th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
median	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
75th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)

ASD: autism spectrum disorder.
Legend: Time-to-event analysis may be stratified according to relevant strong risk factors (such as age or gender) which will be determined based on the results of the univariate analyses. As an example, this table and the table above present stratification by gender.

16.1.3.4 Association between potential risk factors/confounders for ASD and paternal exposure group

Table 72 Association between potential offspring risk factors/confounders for ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group										Comparison
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of offspring	**N=397**		**N=1019**		**N=865**		**N=154**		**N=1416**		**-**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Offspring risk factors/confounders											
Gender [a]											
Male	198	49.87	539	52.89	445	51.45	94	61.04	737	52.05	-
Female	199	50.13	480	47.11	420	48.55	60	38.96	679	47.95	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	1.04 (0.3067)
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	-

ASD: autism spectrum disorders; CMV: cytomegalovirus.*
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.
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 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.

Table 73 Association between potential maternal risk factors/confounders for ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group										Comparison
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=397**		**N=1019**		**N=865**		**N=154**		**N=1416**		-
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Maternal risk factors/confounders											
Mother's age [a] (categorical)											
≤20 years	6	1.51	16	1.57	14	1.62	2	1.30	22	1.55	-
21-25	60	15.11	133	13.05	115	13.29	18	11.69	193	13.63	-
26-30	136	34.26	338	33.17	276	31.91	62	40.26	474	33.47	-
31-35	137	34.51	340	33.37	295	34.10	45	29.22	477	33.69	-
36-40	50	12.59	152	14.92	136	15.72	16	10.39	202	14.27	-
>40	8	2.02	40	3.93	29	3.35	11	7.14	48	3.39	-
Test statistics	-	-	-	-	-	-	-	-	-	-	5.26 (0.3845)
Mother's age [a] (continuous)											
Mean (SD)	30.38 (4.84)	-	30.96 (5.11)	-	30.99 (5.08)	-	30.80 (5.30)	-	30.80 (5.04)	-	269835.50 (0.0973)*
Median (25^{th} - 75^{th} percentile)	30 (27.00, 34.00)	-	31 (27.00, 35.00)	-	31 (27.00, 35.00)	-	30 (27.00, 33.00)	-	31 (27.00, 34.00)	-	-
Min, max	19.00, 43.00	-	17.00, 46.00	-	18.00, 46.00	-	17.00, 43.00	-	17.00, 46.00	-	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Affective disorder [b]	23	5.79	103	10.11	98	11.33	5	3.25	126	8.90	6.56 (0.0104)
Diabetes [b]	6	1.51	21	2.06	21	2.43	0	0.00	27	1.91	0.46 (0.4971)
Gestational diabetes [c]	20	5.04	67	6.58	61	7.05	6	3.90	87	6.14	1.17 (0.2792)

	Paternal exposure group										Comparison
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=397**		**N=1019**		**N=865**		**N=154**		**N=1416**		-
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Neurotic disorder [b]	50	12.59	137	13.44	124	14.34	13	8.44	187	13.21	0.18 (0.6713)
Schizophrenia, schizotypal and delusional disorders [b]	1	0.25	0	0.00	0	0.00	0	0.00	1	0.07	0.28 (0.2804)*
Obesity [d]	6	1.51	10	0.98	10	1.16	0	0.00	16	1.13	0.72 (0.3967)
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	0.25	2	0.20	2	0.23	0	0.00	3	0.21	1.00 (1.0000)*
Alcohol abuse during pregnancy [c]	1	0.25	1	0.10	1	0.12	0	0.00	2	0.14	0.48 (0.4823)*
Substance abuse prior to LMP2 [d]	2	0.50	4	0.39	4	0.46	0	0.00	6	0.42	0.67 (0.6751)*
Substance abuse during pregnancy [c]	2	0.50	2	0.20	2	0.23	0	0.00	4	0.28	0.31 (0.3138)*
Smoking prior to LMP2 [d]											
No	273	68.77	773	75.86	647	74.80	126	81.82	1046	73.87	-
Yes	58	14.61	121	11.87	110	12.72	11	7.14	179	12.64	-
Missing	66	16.62	125	12.27	108	12.49	17	11.04	191	13.49	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	3.08 (0.0793)
Smoking during pregnancy [c]											
No	316	79.60	872	85.57	735	84.97	137	88.96	1188	83.90	-
Yes	27	6.80	43	4.22	42	4.86	1	0.65	70	4.94	-
Missing	54	13.60	104	10.21	88	10.17	16	10.39	158	11.16	-

ASD Number of pregnancies	Paternal exposure group Valproate N=397		Lamotrigine/ levetiracetam N=1019		Lamotrigine N=865		Levetiracetam N=154		Total (valproate + lamotrigine/ levetiracetam) N=1416		Comparison Valproate vs Lamotrigine /levetiracetam
	N	%	N	%	N	%	N	%	N	%	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	4.78 (0.0288)
Maternal polypharmacy index prior to LMP2 c(categorical)											
0	261	65.74	649	63.69	549	63.47	100	64.94	910	64.27	-
1-4	125	31.49	349	34.25	298	34.45	51	33.12	474	33.47	-
5-10	10	2.52	21	2.06	18	2.08	3	1.95	31	2.19	-
>10	1	0.25	0	0.00	0	0.00	0	0.00	1	0.07	-
Test statistics	-	-	-	-	-	-	-	-	-	-	3.68 (0.2982)
Maternal polypharmacy index prior to LMP2 c (continuous)											
Mean (SD)	0.71 (1.36)	-	0.65 (1.14)	-	0.66 (1.15)	-	0.63 (1.11)	-	0.67 (1.21)	-	278931.00 (0.6906)*
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	210	52.90	513	50.34	431	49.83	82	53.25	723	51.06	-
1-4	178	44.84	477	46.81	408	47.17	69	44.81	655	46.26	-
5-10	9	2.27	29	2.85	26	3.01	3	1.95	38	2.68	-
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-

ASD Number of pregnancies	Paternal exposure group Valproate N=397		Lamotrigine/ levetiracetam N=1019		Lamotrigine N=865		Levetiracetam N=154		Total (valproate + lamotrigine/ levetiracetam) N=1416		Comparison Valproate vs Lamotrigine /levetiracetam -
	N	%	N	%	N	%	N	%	N	%	
Test statistics	-	-	-	-	-	-	-	-	-	-	0.96 (0.6181)
Maternal polypharmacy index during pregnancy[c] (continuous)											
Mean (SD)	0.87 (1.23)	-	0.95 (1.32)	-	0.97 (1.35)	-	0.83 (1.16)	-	0.93 (1.30)	-	274428.00 (0.2821)*
Median (25th - 75th percentile)	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	1 (0.00, 1.00)	-	0 (0.00, 1.00)	-	0 (0.00, 1.00)	-	-
Min, max	0.00, 6.00	-	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	31	7.81	111	10.89	99	11.45	12	7.79	142	10.03	3.01 (0.0826)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least one prescription	12	3.02	62	6.08	58	6.71	4	2.60	74	5.23	5.41 (0.0201)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription	269	67.76	694	68.11	594	68.67	100	64.94	963	68.01	0.02 (0.8997)

ASD Number of pregnancies	Paternal exposure group										Comparison
	Valproate N=397		Lamotrigine/ levetiracetam N=1019		Lamotrigine N=865		Levetiracetam N=154		Total (valproate + lamotrigine/ levetiracetam) N=1416		Valproate vs Lamotrigine /levetiracetam -
	N	%	N	%	N	%	N	%	N	%	
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	162	40.81	440	43.18	380	43.93	60	38.96	602	42.51	0.66 (0.4171)

ASD: autism spectrum disorders; CMV: cytomegalovirus; LMP2: last menstrual period date plus 2 weeks; Max: maximum; Min: minimum; 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.
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) 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 74 Association between potential paternal risk factors/confounders for ASD by paternal exposure group; ASD as outcome for sensitivity analysis 2

	Paternal exposure group										Comparison
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of offspring	**N=397**		**N=1019**		**N=865**		**N=154**		**N=1416**		-
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Paternal risk factors/confounders											
Affective disorder excluding bipolar affective disorder and mania [a]	31	7.81	227	22.28	226	26.13	1	0.65	258	18.22	40.14 (<.0001)
Bipolar affective disorder [a]	56	14.11	283	27.77	283	32.72	0	0.00	339	23.94	29.30 (<.0001)
Mania [a]	6	1.51	7	0.69	7	0.81	0	0.00	13	0.92	2.13 (0.1440)
Neurotic disorder [a]	30	7.56	157	15.41	155	17.92	2	1.30	187	13.21	15.36 (<.0001)
Schizophrenia, schizotypal and delusional disorders [a]	11	2.77	18	1.77	18	2.08	0	0.00	29	2.05	1.44 (0.2307)
Substance abuse [c]	10	2.52	22	2.16	22	2.54	0	0.00	32	2.26	0.17 (0.6823)
Paternal polypharmacy index [d] (categorical)											
0	255	64.23	519	50.93	415	47.98	104	67.53	774	54.66	-
1-4	136	34.26	467	45.83	420	48.55	47	30.52	603	42.58	-
5-10	6	1.51	31	3.04	28	3.24	3	1.95	37	2.61	-
>10	0	0.00	2	0.20	2	0.23	0	0.00	2	0.14	-
Test statistics	-	-	-	-	-	-	-	-	-	-	21.57 (<.0001)
Paternal polypharmacy index [d] (continuous)											
Mean (SD)	0.65 (1.14)		1.01 (1.49)		1.09 (1.53)		0.58 (1.17)		0.91 (1.41)		251233.00 (<.0001)*
Median (25^{th} - 75^{th} 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)		-

	Paternal exposure group										Comparison
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of offspring	**N=397**		**N=1019**		**N=865**		**N=154**		**N=1416**		-
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Min, max	0.00, 7.00		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] – fathers with at least one prescription	85	21.41	363	35.62	355	41.04	8	5.19	448	31.64	26.68 (<.0001)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with atleast one prescription	225	56.68	657	64.47	587	67.86	70	45.45	882	62.29	7.40 (0.0065)
Father's age [e] (categorical)											-
≤20 years	2	0.50	3	0.29	2	0.23	1	0.65	5	0.35	-
21-25	29	7.30	69	6.77	57	6.59	12	7.79	98	6.92	-
26-30	106	26.70	224	21.98	185	21.39	39	25.32	330	23.31	-
31-35	141	35.52	331	32.48	276	31.91	55	35.71	472	33.33	-
36-40	85	21.41	240	23.55	211	24.39	29	18.83	325	22.95	-
>40	34	8.56	152	14.92	134	15.49	18	11.69	186	13.14	-
Test statistics	-	-	-	-	-	-	-	-	-	-	13.34 (0.0204)
Father's age [e] (continuous)											
Mean (SD)	32.94 (5.63)		34.07 (6.25)		34.23 (6.30)		33.20 (5.90)		33.76 (6.10)		261253.00 (0.0037)*
Median (25th - 75th percentile)	32 (29.00, 37.00)		34 (30.00, 38.00)		34 (30.00, 38.00)		33 (29.00, 37.00)		33 (30.00, 38.00)		-

	Paternal exposure group										Comparison
ASD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of offspring	**N=397**		**N=1019**		**N=865**		**N=154**		**N=1416**		**-**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Min, max	20.00, 53.00		18.00, 64.00		18.00, 64.00		20.00, 51.00		18.00, 64.00		-
Year of offspring conception [f,g]											
2009-2013	193	48.61	455	44.65	399	46.13	56	36.36	648	45.76	-
2014-2019	204	51.39	564	55.35	466	53.87	98	63.64	768	54.24	-
Test statistics	-	-	-	-	-	-	-	-	-	-	1.81 (0.1788)

ASD: autism spectrum disorders; LMP2: last menstrual period date plus 2 weeks; Max: maximum; Min: minimum; 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.
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) 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 will be grouped in each country according to the length of the study period.