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, Corrigendum v1.0 to VALNAC09345 Final Study Report V1.1

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

Corrigendum to the Final Study Report Approval and Sign-off

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

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PASS information

Title	A post-authorisation safety study (PASS) to evaluate the paternal exposure to valproate and the risk of neurodevelopmental disorders including autism spectrum disorder as well as congenital abnormalities in offspring – a population-based retrospective study
Version identifier of the final study protocol	Version 6.0
Date of last version of the final study protocol	23 January 2023
EU PAS register number	EUPAS34201
Active substance	Antiepileptic drugs (AEDs) including valproate ATC WHO code: N03A
Medicinal product	Antiepileptic drugs (AEDs) including valproate
Product reference	EMEA/H/A-31/1454
Marketing authorisation holder(s)	The joint initiative involves several companies via a consortium: APOTEX EUROPE B.V.; ARISTO PHARMA GMBH; ARROW GENERIQUES; BETAPHARM ARZNEIMITTEL GMBH; CONSILIENT HEALTH LIMITED; CRESCENT PHARMA LIMITED; DESITIN ARZNEIMITTEL GMBH; GENERIS FARMACEUTICA S.A.; G.L. PHARMA GMBH; SANDOZ/HEXAL AG; LUPIN HEALTHCARE LIMITED; MYLAN BVBA/SPRL: BE; VIATRIS SANTE (LYON): FR; NEURAXPHARM ARZNEIMITTEL GMBH; ORION CORPORATION; 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. **Primary objective** 1. To investigate the risk of NDD, including ASD, in offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment at the time of conception. **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 at the time of conception, in Norway and Denmark. 3. To describe AED exposure (posology and duration) data and health characteristics of male patients prescribed AEDs (including valproate and lamotrigine/levetiracetam) in treatment of epilepsy and other indications at the time of conception of their offspring, both for NDD and CM cohort.

	4. To identify potentially important risk factors for outcomes of interest, in offspring paternally exposed to valproate (monotherapy) or lamotrigine/levetiracetam 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) and to lamotrigine/levetiracetam in combination with other AEDs, excluding valproate, at the time of conception. 6. To describe the risk factors and frequency of NDD, including ASD, as well as CM in paternally and maternally matched exposure-discordant (valproate versus lamotrigine/levetiracetam monotherapy) siblings at conception. 7. To investigate the risk of CM in live offspring paternally exposed to valproate (monotherapy), compared to lamotrigine/levetiracetam treatment at the time of conception in Sweden. 8. To describe the frequency of CM by target body system organ class in live and non-live offspring paternally exposed to valproate (monotherapy), and to lamotrigine/levetiracetam treatment at the time of conception.
Country(-ies) of study	The study is conducted in Denmark, Sweden, and Norway.
Authors	[redacted]

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; MYLAN BVBA/SPRL: BE; VIATRIS SANTE (LYON): FR; VIATRIS GX BV/SRL: BE; 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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1. List of Abbreviations

Abbreviation	Definition
ADHD	Attention Deficit Hyperactivity Disorder
AED	Antiepileptic Drug
AR	Assessment Report
aHR	Adjusted Hazard Ratio
ASD	Autism Spectrum Disorder
ATC	Anatomical Therapeutic Chemical
CI	Confidence Interval
CM	Congenital Malformations
DDD	Defined Daily Dose
DST	Denmark Statistics
EMA	European Medicines Agency
HR	Hazard Ratio
ICD-10	International Statistical Classification of Diseases and Related Health Problems 10th Revision
IVF	in vitro fertilization
IQR	Interquartile Range
IUGR	Intrauterine Growth Retardation
LMP2	Last Menstrual Period Date Plus 2 weeks
MAH	Marketing Authorisation Holders
MBR	Medical Birth Registry
NDD	Neurodevelopmental Disorders
NPR	National Patient Registry
OR	Odds Ratio
PASS	Post-Authorisation Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PS	Propensity Score
PY	Person-years
QC	Quality Control
SSRI	Selective Serotonin Reuptake Inhibitors
WHO	World Health Organisation

2. Erratum

In 2023, the marketing authorisation holders (MAHs) submitted a final study report to the European Medicines Agency's (EMA) Pharmacovigilance Risk Assessment Committee (PRAC) (please see final study report v1.0 and v1.1) as part of a post-authorisation safety study (PASS) to evaluate the association between paternal exposure to valproate and the risk of neurodevelopmental disorders (NDD), including autism spectrum disorder (ASD) as well as congenital malformations (CM) in offspring. The original submission included a description of the study methodology, statistical data analysis, findings, discussion, and interpretation. In a subsequent investigation, however, the MAHs identified the presence of unforeseen outages, which compromised the reliability and accuracy of the initial findings:

- Regarding Norwegian data: the diagnostic codes from the Norwegian Patient Registry were only available from 2008 onward, as explained in more detail in Section 2.1. Therefore, 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. Considering the anticipated changes in the Norwegian data and expected results, the meta-analysis has also been repeated.
- Regarding Danish data:
    - a gap in information affected less than 2.0% (37 out of 2,031) of the offspring born between January and September 1997 due to a shorter than required lookback period (from 1 January 1996), ranging from 3 to 11 months, instead of the required 12 months per protocol, as explained in more detail in Section 2.2. An investigation was performed by including data from 1995 and the cohort creation programs were rerun, which did not result in the exclusion of offspring born in 1997, and all parents remained part of the study cohort. The results for Denmark were not impacted (despite the protocol deviation for these 37 offspring and their parents) and are therefore considered final.
    - an additional mistake in the meta-analysis of NDD risk and rate ratios (Tables 9 and 10 of the final study report v1.1) was identified during the quality control (QC) process, involving the Danish data. The issue arose from using outdated versions of the Danish results from Table 23 and Table 24, when producing Tables 9 and 10 for the final study report v1.1. Tables 9 and 10 (numbered as Tables 2 and 3 in this corrigendum) have been updated to reflect the final and correct version of the Danish Tables 23 and 24, which were properly reported in the final study report v1.1 and therefore not updated.

The MAHs and IQVIA acknowledge the importance of maintaining the highest standards of scientific integrity, and presenting reliable and correct results, which are essential for decision-making to ensure 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 QC 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 potential limitations and biases arising from the identified outages in Norway and Denmark.

The MAHs further acknowledge that in the process of rerunning the analysis, the QC investigation involved an examination of the impact of the identified outages on the findings.

The meta-analysis for hazard ratio (HR) and cumulative incidence rates and proportions, as well the main NDD analysis for Norway, were carefully rerun. This included updating cohort characteristics, cumulative incidence rates and proportions, univariate analyses of risk factors/confounders, effect estimation, propensity scores (PS), time-to-event analysis, sensitivity analyses, and exploratory analyses. Additionally, for CM, cohort characteristics, cumulative incidence proportions, univariate analyses of risk factors/confounders, and effect estimation were successfully rerun. However, for CM, the PS logistic model did not converge due to a quasi-complete separation caused by the low event numbers. Hence, the results related to the PS model were not produced, including the PS model itself, the random forest model informed by the PS model, their respective balance assessments, and the PS-weighted effect estimates.

Considering the study population changed as a result of the correction of erroneous data and the subsequent shift in the study start period to 2010, it was expected for these changes to have an impact on the fathers' medical characteristics (comorbidities, risk, and confounding factor proportions), number of observed events, and estimated relative risks. Indeed, the change in the study population did lead to variations in the distribution of confounders and risk factors, and some confounders and risk factors associated with the outcome differed. However, a comparison between the previous and the current analyses is not feasible because the previous analyses were based on an incorrect and incomplete source data. As explained above, in the initial analysis, it was wrongly assumed that the variables in the 24-month lookback period were 0, however they were missing due to them not being available. Consequently, it cannot be determined what differences exist between the 2 sets of results accurately. The erroneous data introduced uncertainties, making any comparison invalid and unreliable. Therefore, we must rely solely on the corrected analysis starting from 2010 to obtain valid and meaningful findings. Still, it is essential to note that the study findings based on these updated results are consistent with what has been previously reported. Reproducibility in this context does not require that the confounders and risk factors remain the same, as long as the main associations between the exposure and outcome remain consistent. For instance, the meta-analysis of the PS-weighted HR (primary outcome) reports a pooled HR of 1.50 (95% confidence interval [CI]: 1.09, 2.07), which aligns with the previous findings that observed a pooled PS-adjusted HR of 1.47 (95% CI: 1.10, 1.96).

All these new results have been included in this corrigendum, along with an updated discussion that reflects the latest findings. For Norway, sensitivity analysis 2 and exploratory analysis 8 were included in the addendum v2.0. The results for Sweden and Denmark remain unaffected and are therefore considered final, as reported in the final study report v1.1.

Therefore, the purpose of this corrigendum is to address the identified outages and take appropriate corrective actions. This includes superseding the previously produced results submitted to PRAC for Norway, updating the results of the meta-analysis, as well as adjusting the discussion of the results as presented in the final report 1.1 to reflect the rectified results. In addition, Tables 9 and 10 (final study report v1.1), and Tables 36 and 57 for Denmark have been rectified.

A summary of the identified issues is presented in the following sections.

2.1 Norway Summary

In Norway, the Prescription Registry contains a reimbursement code variable that is informative of medications' indication. The reimbursement codes are a mixture of International Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10) codes, International Classification of Primary Care, 2nd edition (ICPC2) codes, and numeric codes where 7 represents epilepsy and 18 represents psychiatric disorders. There are also other broad reimbursement codes for affective disorders. Not all prescriptions include details about reimbursement, and the quality and validity of these reimbursement codes are uncertain, considering that no validation studies have been identified on this topic. For example, it is possible doctors may use codes related to epilepsy or bipolar disorder instead of the precise indication to ensure that the prescription is eligible for reimbursement for the patient, if the true indication is not entitled to a reimbursement. For that reason, the reimbursement codes were not used to identify indications in Norway. Instead, the same approach as the one used in Denmark and Sweden, ie, based on ICD-10 only, was also used in Norway; these ICD-10 codes were sourced from the Norwegian Patient Registry.

The Norwegian Patient Registry captures diagnoses for every encounter with specialized healthcare at a hospital, outpatient clinic, or from contracted specialists, including psychiatric healthcare encounters for both children and adults. However, the Norwegian Patient Registry can only be linked to other registries starting from 2008. It is important to note that the Norwegian Patient Registry does not capture information on private hospital stays financed by insurance or paid for directly by the patient, nor diagnoses originating in primary care. Recent investigations into the data used in this study revealed that primary care providers prescribed 60% of antiepileptic drugs (AEDs) in Norway. However, if fathers receiving these AEDs did not seek medical care beyond primary care, there was a possibility that their diagnoses might be missing. As a result, there could be significant missing data for the variable "indication" or a substantial percentage of indications categorized as “Other/unknown”. While investigating the root cause of the high percentage of "Other/unknown" indications in Norway (50.6% in the valproate group and 44.5% in the lamotrigine/levetiracetam group), it became evident that diagnostic codes from the Norwegian Patient Registry were only available from 2008 onwards. This was identified as a significant outage as the study period originally began in 2006 in this country (please see section 9.2.1 of the study protocol v6.0), but due to the unavailability of Norwegian Patient Registry data prior to 2008, a revised study period starting in 2010 was used instead (please see section 9.2.1 of the study protocol v7.0). This decision was made to ensure a 24-month lookback period for the study variables, particularly for fathers (please see section 9.2.3.1 of the study protocol v7.0). Specifically, to ensure an adequate and sufficient lookback period for the study variables, only pregnancies that ended in 2010 were considered. The fact that the Norwegian Patient Registry, which provided diagnostic codes, can be linked to other registries only from 2008 had implications on the robustness and validity of the Norwegian results presented in the final study report v1.1, as follows:

1. Inclusion/exclusion criteria: before 2008, the absence of diagnostic codes presented challenges in applying certain criteria for study inclusion and exclusion. Specifically, when it came to excluding fathers and mothers with a history of CM or NDD, diagnostic codes were necessary. However, these codes were only available for a portion of the study's timeframe, potentially resulting in the inclusion of units that should have been excluded.

2. Medical history variables and confounders/risk factors: the study used diagnostic codes to derive variables for comorbidities, confounders, and risk factors. The lack of diagnostic codes until 2008 meant that before this year these variables resulted as "absent" for all patients, resulting in misclassification of these derived variables. For mothers and children, this did not represent a significant concern as medical history was mostly collected through the Medical Birth Registry (MBR), which has been available since 2004.
3. Outcome events in 2006 and 2007: while diagnosis of NDD, including ASD, is rare in the first years of life, if any offspring born in 2006 and 2007 were diagnosed with this outcome before 2008, this diagnosis would not have been captured in the current study. This limitation did not apply to CM diagnoses, as these were recorded in the MBR from 2004 onward.

2.2 Denmark Summary

1. Issue related to data gap affecting 37 offspring

Following the identification of the outages in the Norwegian data that affected the reliability of the initial findings, a comprehensive data review was conducted for the other 2 data sources used in the Valproate Paternal Exposure study. While no issues were found in the Swedish results, an issue pertaining to the results for Denmark was identified. Similar to the investigation conducted for the Norwegian data, a thorough investigation was initiated for the Valproate Paternal Exposure Denmark dataset to determine the underlying cause of this potential issue.

In particular, an issue related to a data gap within the Danish Cohort affected 37 out of 2,031 (ie, less than 2.0%) of the offspring. In the present study, the data were requested from the Danish Birth Registry starting from 1 January 1997, for both the primary outcome cohort and the secondary outcome cohort (from 1 April 2004). Additionally, data from the National Patient Registry (NPR) was requested for the mothers and fathers of the offspring, beginning from 1 January 1996. This resulted in a possible gap in information for offspring born between January 1997 and September 1997. A full 12-month lookback period from the last menstrual period date plus 2 weeks (LMP2) was required for a family unit (offspring linked to the father and mother) to be included in the study. This requirement was in accordance with the study protocol v6.0 (see section 9.3.3). However, for the offspring born between January 1997 and September 1997, the LMP2 date was in 1996 (between March 1996 and November 1996). For these 37 out of 2,031 offspring born before October, the available lookback period from LMP2 in the extracted data (from 1 January 1996) ranged from 3 to 11 months, instead of the required 12 months per protocol, in these 37 out of 2,031 offspring born before October 1997. This issue could only be investigated and the possible consequences assessed by going back to the root data of the NPR; only Denmark Statistics (DST) is granted this direct access to the NPR root data. Hence, DST performed the necessary analyses to assess the impact of this outage on the reliability of the study findings. The DST was able to include data from the year 1995 and rerun the cohort creation programs accordingly. The rerun did not lead to any exclusion of offspring born in 1997. Despite the additional lookback time, all parents were still included in the study cohort. Furthermore, IQVIA requested an assessment from the DST to determine whether the distribution of all derived variables was affected by the extended lookback time. The DST conducted the analysis and reported that there were

no differences in the distribution of all derived variables for parents of offspring born in 1997 when comparing the data before and after the inclusion of NPR data from 1995. Based on these findings, it was concluded that the addition of NPR data from 1995 did not impact the inclusion or exclusion of offspring born in 1997, nor did it affect the distribution of confounders for their parents. Therefore, there is no need to rerun Danish tables or analyses in the present study.

Nonetheless, not having the 12-month lookback period for these 37 offspring represents a deviation from the protocol and is therefore documented in this corrigendum.

2. Issue with Tables 9 and Table 10, meta-analysis of NDD risk and rate ratios

In addition, an issue was detected in the meta-analysis of NDD risk and rate ratios (Tables 9 and 10 of the final study report v1.1) with regards to the Danish results used in these tables. This error was detected during the QC process of the updated Tables 9 and 10 based on the rerun of the Norway analysis. It was discovered that not only the Norwegian data, but also the Danish data had been changed in the meta-analysis. To address this, queries were sent to the DST, performing the analyses, and it was discovered that outdated versions of the Danish results from Table 23 and Table 24 were used when creating Tables 9 and 10 for the final study report v1.1.

As a result, Tables 9 and 10 have been revised (designated as Tables 2 and 3 in this corrigendum) to incorporate the final and correct version of the Danish Tables 23 and 24, which were also presented in the original final study report v1.1 and therefore remained unchanged. Besides, Table 9 and Table 10 (Tables 2 and 3 in the corrigendum) were updated to include the cumulative incidence proportions and rates for Denmark and Sweden for 3 additional different follow-up periods: 10-11 years, 11-12 years, and overall, 0-12 years. The purpose of this update was twofold. First, to replace the cumulative incidence proportions and rates for Denmark which were previously reported in the final study report v1.1 with outdated figures. Second, to align the reported follow-up length with the initial duration of 12 years for the 3 countries. The additional follow-up periods were reported for Denmark and Sweden, since in Norway, the cumulative incidence proportions and rates could only be calculated until 10 years of age due to a reduction in the study time period. Due to the reduction in study time period in Norway and subsequent restriction at 10 years old for the risk and rate ratios, this age limit was also applied to Sweden and Denmark to be able to meta-analyse results from all 3 countries.

3. Corrections of errors (typos) detected during the PRAC Assessment of the final study report v1.1 (refer Appendix, Section 8.2 for corrected/updated tables)

   3.1. For sensitivity analysis 5 (primary outcome NDD including ASD), in the final study report v1.1, Table 36 for Denmark, presenting the results for sensitivity analysis 5A (primary outcome NDD including ASD), contains a typographical error for the valproate versus lamotrigine group size, which should read n=1,837 instead of n=2,137.

   To further clarify: overall, the main analysis included n=1,950 participants, comprising n=793 valproate, n=113 levetiracetam, and n=1,044 lamotrigine. In sensitivity analysis 5A, the total number of participants is n=1,837, which includes both valproate and lamotrigine groups. For sensitivity analysis 5B, the total number of participants is n=906, which comprises both valproate and levetiracetam groups.

3.2. For sensitivity analysis 6 in Denmark, there was a typographical error in the final study report v1.1, Table 36; the sample size for this analysis is n=1,950 instead of n=2,355.

3.3. For sensitivity analysis 9 in Denmark, there was a typographical error in the final study report v1.1, Table 57; the sample size for this analysis is missing, now included n=646.

3.4. For sensitivity analysis 9 in Denmark, there were typographical errors in the final study report v1.1, Table 57; the reported crude odds ratio (OR) estimates for this analysis are 0.61 (0.35, 1.06) instead of 0.61 (0.34, 1.06), and the adjusted OR for this analysis is 0.60 (0.34, 1.06) instead of 0.61 (0.34, 1.06).

3.5. Additionally, previously mentioned Table 36 and Table 57, are now included and updated, in the corrigendum.

3. Results

In this corrigendum, we present the corrected results related to the primary outcome (NDD, including ASD) and the secondary outcome (CM) in Norway (Box 1). These results supersede those reported in the final study report v1.1.

The results of cumulative incidence proportions ratio, cumulative incidence rates ratio, crude and PS-weighted, Cox regression models, and crude logistic regression models for both outcomes cohorts were pooled in a meta-analysis and presented in Section 3.1. Meta-analysis of adjusted logistic regression models could not be conducted due to non-convergence of the PS-weighted model for the secondary outcome in Norway. Please see Section 3.2.2.5 for further details.

For Denmark, the cumulative incidence proportions ratio and cumulative incidence rates ratio reported in Table 9 and Table 10 (meta-analysis of cumulative incidence proportions, and risks, respectively) in the final study report version 1.1, were based on an outdated version of the Danish results from Table 23 and Table 24 (see section 10.3.1.2 and section 10.3.1.3). In this corrigendum, the updated corrected version of Table 9 and Table 10 are reported, which are now numbered as Table 1 and Table 2) (Box 1).

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

Analysis description	Norway		Denmark[2]	
	NDD	CM	NDD	CM
Meta-analysis	x	x	x	-
Main analysis - Cohort characteristics	x	x	-	-
Main analysis - Cumulative incidence rate and time-to-event	x	NA	-	-
Main analysis - Cumulative incidence proportion	x	x	-	-
Main analysis - Univariate Analyses of association of risk factors/confounders with exposure and/or outcome	x	x	-	-
Main analysis - Effect estimation	x	x	-	-
Main analysis - Propensity score	x	x	-	-
Case assessment	x	NA	-	-
Exploratory objective analyses	x	x[1]	-	-
Sensitivity analyses	x[1]	x	-	-

NDD: Neurodevelopmental disorders; CM: Congenital malformation; NA: Not applicable.
Legend: "x" indicates the analysis was performed and is presented in this final report
[1] The results for sensitivity analyses 2 (risk of ASD) and for exploratory analyses 8 (CM by target body system organ class) are provided as an addendum v2.0 alongside the current corrigendum v1.0
[2] The symbol "-" denotes that the results for Denmark remain unaffected and are reported in the final study report v1.1. However, Tables 9 and 10 (meta-analysis, NDD cumulative incidence and incidence rate ratios), Table 36 (sensitivity analyses NDD, number of patients per group) and Table 57 (sensitivity analyses CM, number of patients and ORs) were incorrect in the final report v1.1 and are updated in this corrigendum.

3.1 Meta-analysis

This section supersedes section 10.1 from the final study report v1.1.

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

The meta-analysis of cumulative incidence proportions ratios, cumulative incidence rates ratios, crude, and adjusted Cox regression models for NDD including ASD in Sweden, Norway, and Denmark are presented in Table 1 to Table 4.

The meta-analysis of cumulative incidence proportions ratios, and crude logistic regression models for CM in Norway and Denmark are presented in Table 5 and Table 6. Meta-analysis of adjusted logistic regression models could not be conducted due to non-convergence of the PS-weighted model for the secondary outcome in Norway. Please see Section 3.2.2.5 for further details.

3.1.1 Neurodevelopmental disorders including autism spectrum disorder cohort

This section supersedes section 10.1.1 from the final study report v1.1.

Table 1 presents the pooled risk ratios of the cumulative incidence proportions in the primary outcome cohort. Table 2 presents the pooled rate ratios of the cumulative incidence proportions in the primary outcome cohort.

Table 1 and Table 2 additionally include the cumulative incidence proportions and rates for Denmark and Sweden for the following additional follow-up periods: 10-11 years, 11-12 years, and overall, 0-12 years (Table 1), and 0-11 years and 0-12 years (Table 2). The purpose of this is twofold. First, it aims to replace the cumulative incidence proportions for Denmark that were previously reported in the final study report v1.1 due to an identified outage (as explained in Section 2 and Section 2.2). Second, it aims to align the reported follow-up period length with the initial duration of 12 years. The additional follow-up periods were reported for Denmark and Sweden only, since in Norway, the cumulative incidence proportions could only be calculated until 10 years of age. Due to the shorter study time period in Norway and subsequent restriction at 10 years old for the risk and rate ratios, this age restriction was also applied to Sweden and Denmark to be able to meta-analyse results from all 3 countries, as reported in this corrigendum.

Table 1 presents the pooled risk ratios of the cumulative incidence proportions of the primary outcome cohort. Chi-square with 95% CI and I^2 statistic were used to assess the heterogeneity between country-specific estimates. No heterogeneity was observed between country-specific estimates for the overall period of study follow-up (I^2=0.0, 95% CI: 0.0, 0.9; p=0.7574). A higher risk of NDD including ASD was observed in offspring from fathers exposed to valproate when compared to lamotrigine/levetiracetam group in the meta-analysis considering the overall period of study follow-up (0-10 years RR=1.58, 95% CI: 1.21, 2.05; p=0.0006).

Table 1 Meta-analysis of the cumulative incidence proportions; primary outcome

	Risk ratio (valproate vs lamotrigine/levetiracetam composite monotherapy)							
NDD	**Sweden**	**Norway**	**Denmark**	**I^2 (95% CI), p-value**	**Meta-analysis (random effect)**	**P-value (random effect)**	**Meta-analysis (fixed effect)**	**P-value (fixed effect)**
Follow-up period								
0-1 years	0.38 (0.04-3.42)	NA	***	NA	NA	NA	NA	NA
1-2 years	2.82 (0.52-15.39)	NA	NA	NA	NA	NA	NA	NA
2-3 years	0.44 (0.09-2.18)	1.24 (0.23-6.75)	***	0.00 (0.00-0.90), 0.6472	0.81 (0.32-2.03)	0.653	0.81 (0.32-2.03)	0.653
3-4 years	1.84 (0.52-6.51)	0.83 (0.17-4.09)	***	0.00 (0.00-0.90), 0.7362	1.42 (0.64-3.13)	0.3841	1.42 (0.64-3.13)	0.3841
4-5 years	0.58 (0.15-2.32)	0.97 (0.19-4.98)	***	0.00 (0.00-0.90), 0.4983	1.02 (0.44-2.38)	0.963	1.02 (0.44-2.38)	0.963
5-6 years	1.72 (0.56-5.22)	4.93 (0.45-54.03)	***	0.67 (0.00-0.90), 0.0489	1.05 (0.17-6.51)	0.9618	1.23 (0.49-3.04)	0.6601
6-7 years	0.59 (0.17-2.00)	0.95 (0.19-4.86)	***	0.55 (0.00-0.87), 0.1105	1.33 (0.34-5.30)	0.6822	1.08 (0.45-2.62)	0.8617
7-8 years	2.28 (0.59-8.75)	9.63 (1.09-85.27)	***	0.62 (0.00-0.89), 0.0710	1.92 (0.45-8.16)	0.3777	1.53 (0.66-3.58)	0.3229
8-9 years	0.65 (0.21-2.01)	0.93 (0.10-8.78)	***	0.00 (0.00-0.90), 0.4839	1.03 (0.48-2.23)	0.9309	1.03 (0.48-2.23)	0.9309
9-10 years	0.77 (0.22-2.62)	NA	***	NA	NA	NA	NA	NA
Overall (0-10 years)	1.41 (0.95-2.09)	1.74 (0.95-3.19)	1.71 (1.12-2.60)	0.00 (0.00-0.90), 0.7574	1.58 (1.21-2.05)	0.0006	1.58 (1.21-2.05)	0.0006
10-11 years [a]	2.68 (0.30-23.79)	-	***	-	-	-	-	-
11-12 years [a]	0.88 (0.15-5.16)	-	***	-	-	-	-	-
Overall (0-12 years) [a]	1.53 (1.05-2.23)	-	1.80 (1.22-2.65)	-	-	-	-	-

CI: Confidence interval; NA: Not available; NDD: Neurodevelopmental disorders.
Legend: Risk ratio, ie, ratio of the cumulative incidence proportions of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) is presented for each country separately and combined (meta-analysis). The 95% CI is presented as well. The risk ratios for Denmark are missing due to the fact that the cumulative incidence proportions are masked.
[a] Additional follow-up periods reported for Denmark and Sweden. In Norway, the cumulative incidence proportions could only be calculated until 10 years of age. Subsequent restriction at 10 years old for the risk ratios was also applied to Sweden and Denmark in order to meta-analyse results from all 3 countries.
*** Masked values indicating that data was calculated but not disclosed.

Table 2 presents the pooled ratios of the cumulative incidence rates of the primary outcome cohort. No heterogeneity was observed between country-specific estimates for the overall period of study follow-up (I^2=0.0, 95% CI: 0.0, 0.9; p=0.4985). A non-significant higher cumulative incidence rate of NDD including ASD in offspring from fathers exposed to valproate was observed in comparison to the lamotrigine/levetiracetam group in the meta-analysis, considering the overall period of study follow-up (0-10 years RR=1.26, 95% CI: 0.97, 1.64; p=0.0891).

Table 2 Meta-analysis of the cumulative incidence rates; primary outcome

	Rate ratio (valproate vs lamotrigine/levetiracetam composite monotherapy)							
NDD	**Sweden**	**Norway**	**Denmark**	**I^2 (95% CI), p-value**	**Meta-analysis (random effect)**	**P-value (random effect)**	**Meta-analysis (fixed effect)**	**P-value (fixed effect)**
Follow-up period								
0-1 years	0.37 (0.04-3.29)	NA	***	NA	NA	NA	NA	NA
0-2 years	1.19 (0.36-3.89)	NA	***	NA	NA	NA	NA	NA
0-3 years	0.81 (0.32-2.05)	2.51 (0.63-10.03)	1.19 (0.46-3.09)	0.00 (0.00-0.90), 0.4109	1.17 (0.64-2.12)	0.6174	1.17 (0.64-2.12)	0.6174
0-4 years	1.09 (0.53-2.27)	1.50 (0.54-4.11)	***	0.00 (0.00-0.90), 0.8759	1.25 (0.78-2.00)	0.352	1.25 (0.78-2.00)	0.352
0-5 years	0.95 (0.50-1.81)	1.32 (0.56-3.12)	***	0.00 (0.00-0.90), 0.6638	1.19 (0.79-1.79)	0.4014	1.19 (0.79-1.79)	0.4014
0-6 years	1.13 (0.65-1.96)	1.55 (0.70-3.41)	***	0.00 (0.00-0.90), 0.6627	1.15 (0.80-1.64)	0.4599	1.15 (0.80-1.64)	0.4599
0-7 years	1.03 (0.62-1.70)	1.41 (0.69-2.87)	***	0.00 (0.00-0.90), 0.7282	1.19 (0.86-1.66)	0.2877	1.19 (0.86-1.66)	0.2877
0-8 years	1.16 (0.73-1.84)	1.80 (0.95-3.43)	1.16 (0.70-1.90)	0.00 (0.00-0.90), 0.4954	1.28 (0.94-1.72)	0.1118	1.28 (0.94-1.72)	0.1118
0-9 years	1.10 (0.71-1.68)	1.69 (0.91-3.13)	***	0.00 (0.00-0.90), 0.5265	1.27 (0.96-1.68)	0.0929	1.27 (0.96-1.68)	0.0929
0-10 years	1.09 (0.73-1.63)	1.69 (0.91-3.13)	1.29 (0.84-1.99)	0.00 (0.00-0.90), 0.4985	1.26 (0.97-1.64)	0.0891	1.26 (0.97-1.64)	0.0891
0-11 years [a]	1.14 (0.77-1.70)	-	***	-	-	-	-	-
0-12 years [a]	1.16 (0.79-1.70)	-	1.29 (0.87-1.91)	-	-	-	-	-

CI: Confidence interval; NA: Not available; NDD: Neurodevelopmental disorders.
Legend: Rate ratio, ie, ratio of the cumulative incidence rate of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) is presented for each country separately and combined (meta-analysis). The 95% confidence interval (CI) is presented as well. The rate ratios for Denmark are missing due to the fact that the cumulative incidence rates are masked.
[a] Additional follow-up periods reported for Denmark and Sweden. In Norway, the cumulative incidence rates could only be calculated until 10 years of age. Subsequent restriction at 10 years old for the rate ratios was also applied to Sweden and Denmark in order to meta-analyse results from all 3 countries
*** Masked values indicating that data was calculated but not disclosed.

Table 3 and Table 4 present, respectively, the meta-analysis of the crude and adjusted hazard ratios (aHR) for NDD, including ASD, obtained from Cox regression models comparing offspring from fathers exposed to valproate, to offspring from fathers exposed to lamotrigine/levetiracetam. Although no influential subjects were identified in the crude models for Denmark and Sweden (ie, the dfbetas criterion did not lead to the exclusion of any subject), 15 influential subjects were excluded in Norway. All the excluded subjects had NDD including ASD events, and were excluded from the valproate group. As a result, there were no events left in the valproate group, and the crude Cox regression model yielded an invalid HR estimate (please see Table 22 and Section 3.2.1.7 for further details). In order to be able to meta-analyse the crude HRs, a meta-analysis including crude HR from all countries, without excluding influential subjects, was performed. This approach, however, represented a deviation from the study protocol.

No heterogeneity was observed between country -specific estimates either in the crude Cox regression models (I^2=0.0, 95% CI: 0.00, 89.60; p=0.4315) or in the adjusted Cox regression models (I^2=0.0, 95% CI: 0.0, 89.6; p=0.8333). No higher risk was observed in the meta-analysis of crude Cox regression models (HR: 1.13, 95% CI: 0.85, 1.49; p=0.3982). In the meta-analysis of adjusted Cox regression models, a significantly higher risk of NDD, including ASD, among offspring from fathers exposed to valproate in comparison to the lamotrigine/levetiracetam group was observed (HR: 1.50, 95% CI: 1.09, 2.07; p=0.0138).

Table 3 Meta-analysis of the hazard ratios obtained from the crude Cox regression model; primary outcome[1]

NDD	Crude Cox model Hazard Ratio						
	Sweden	Norway	Denmark	Meta-analysis (random effect)	P-value	Meta-analysis (fixed effect)	P-value
Number of events/Number of offspring: valproate group	49/930	15/398	43/793				
Number of events/Number of offspring: lamotrigine/levetiracetam group	41/1425	23/1018	41/1157				
I^2 (95% CI)				0.00 (0.00-0.90)	0.4315		
Crude HR (95% CI): valproate vs lamotrigine/levetiracetam	1.16 (0.76, 1.76)	1.60 (0.81, 3.15)	0.94 (0.60, 1.46)	1.13 (0.85-1.49)	0.3982	1.13 (0.85-1.49)	0.3982

CI: Confidence interval; HR: Hazard ratio; NDD: Neurodevelopmental disorders;
Legend: Hazard ratio of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) is presented for each country separately and combined (meta-analysis). The 95% CI is presented as well. The meta-analysis was based on results from the crude model from all countries.
[1] The results reported in this table comprise the crude HR (95% CI) without excluding influential subjects and this approach represented a deviation from the study protocol

Table 4 Meta-analysis of the hazard ratios obtained from the PS-weighted Cox regression model; primary outcome

NDD	PS-weighted Cox model Hazard Ratio						
	Sweden	Norway	Denmark	Meta-analysis (random effect)	P-value	Meta-analysis (fixed effect)	P-value
Number of events/Number of offspring: valproate group	47/841	13/325	38/678				
Number of events/Number of offspring: lamotrigine/levetiracetam group	34/1334	21/910	36/118				
I^2 (95% CI)				0.00 (0.00-0.90)	0.8333		
PS-weighted HR (95% CI): valproate vs lamotrigine/levetiracetam	1.54 (0.95-2.51)	1.76 (0.83-3.71)	1.34 (0.79-2.25)	1.50 (1.09-2.07)	0.0138	1.50 (1.09-2.07)	0.0138

CI: Confidence interval; HR: Hazard ratio; LMP2: Last menstrual period date plus 2 weeks; NDD: Neurodevelopmental disorders; PS: Propensity score.
Legend: Hazard ratio of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) were presented for each country separately and combined (meta-analysis).
[1] **The logistic regression PS model included all variables from Table 31 (see final study report v1.1), Table 73 (see final study report v1.1), Table 21 (in this corrigendum), described as follows:**
Denmark - Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Substance abuse during pregnancy", "Smoking during pregnancy", "Maternal polypharmacy index prior LMP2", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of: "concomitant medications associated with neuropsychiatric adverse events prior LMP2", "year of offspring conception"
Sweden - Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking prior to LMP2", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior LMP2", fathers with at least one prescription of: "concomitant medications associated with neuropsychiatric adverse events prior LMP2", "year of offspring conception"
Norway - Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse 12 months prior LMP2", "Year of offspring conception"

3.1.2 Congenital Malformation cohort

This section supersedes section 10.1.2 from the final study report v1.1.

Table 5 presents the pooled risk ratios of cumulative incidence proportions of the secondary outcome cohort. Table 5 additionally includes the cumulative incidence proportions for Denmark for 3 additional follow-up periods: 10-11 years, 11-12 years, and overall, 0-12 years. The purpose of this is to align the reported follow-up period length with the initial duration of 12 years. The additional follow-up periods were reported for Denmark, since in Norway, the cumulative incidence proportions could only be calculated until 10 years of age. Due to the shorter study time period in Norway and subsequent restriction at 10 years old for the risk ratios, this age restriction was also applied to Denmark to be able to meta-analyse results from both countries.

Chi-square with 95% CI and I^2 statistic were used to assess the heterogeneity between country-specific estimates. Heterogeneity was observed between country-specific estimates for the overall period of study follow-up (I^2=0.8, 95% CI: 0.1, 1.0; p=0.0278), and for 0-1 years of follow-up (I^2=0.8, 95% CI: 0.3, 1.0; p=0.0122). However, no higher risk of CM in offspring from fathers exposed to valproate was observed in comparison to the lamotrigine/levetiracetam group in the meta-analysis considering both the overall period of study follow-up (0-10 years RR 0.84, 95% CI: 0.54, 1.30; p=0.4262), or the specific periods of follow-up (Table 5).

Table 6 presents the meta-analysis of the crude OR for CM obtained from logistic regression models comparing offspring from fathers exposed to valproate to offspring from the lamotrigine/levetiracetam group. Again, heterogeneity was observed between country-specific estimates in the crude logistic regression models (I^2=0.5, 95% CI: Not available, p=0.1590). However, no difference in the risk for CM was observed among offspring from fathers exposed to valproate group compared to the lamotrigine/levetiracetam in the meta-analysis of crude OR (OR 0.81, 95% CI: 0.48, 1.36, p=0.4216). Meta-analysis of adjusted logistic regression models could not be conducted due to non-convergence of the PS-weighted model for the main secondary outcome analysis in Norway, ie, the PS-weighted OR could not be produced. For this reason, it was not possible to produce the following tables: Meta-analysis of the ORs obtained from the PS-weighted logistic model, and Meta-analysis of the ORs obtained from the PS-weighted logistic model on offspring with concordant K-means exposure cluster. Please see Section 3.2.2.5 for further details.

Table 5 Meta-analysis of the cumulative incidence proportions; secondary outcome

	Risk ratio (valproate vs lamotrigine/levetiracetam composite monotherapy)						
CM	**Norway**	**Denmark**	**I^2 (95% CI), p-value**	**Meta-analysis (random effect)**	**P-value (random effect)**	**Meta-analysis (fixed effect)**	**P-value (fixed effect)**
Follow-up period							
0-1 years	1.12 (0.81-1.57)	0.58 (0.39-0.86)	0.84 (0.34-0.96), 0.0122	0.81 (0.42-1.56)	0.5362	0.86 (0.66-1.11)	0.2377
1-2 years	0.80 (0.35-1.86)	0.83 (0.36-1.90)	0.00 (NA), 0.9512	0.82 (0.45-1.47)	0.5011	0.82 (0.45-1.47)	0.5011
2-3 years	1.23 (0.37-4.06)	1.21 (0.43-3.37)	0.00 (NA), 0.9815	1.22 (0.56-2.65)	0.6202	1.22 (0.56-2.65)	0.6202
3-4 years	0.41 (0.05-3.36)	***	0.00 (NA), 0.9024	0.36 (0.11-1.25)	0.108	0.36 (0.11-1.25)	0.108
4-5 years	1.19 (0.11-13.09)	***	0.00 (NA), 0.5713	0.65 (0.21-2.04)	0.459	0.65 (0.21-2.04)	0.459
5-6 years	1.46 (0.35-6.03)	0.50 (0.05-4.80)	0.00 (NA), 0.4337	1.08 (0.32-3.58)	0.9061	1.08 (0.32-3.58)	0.9061
6-7 years	NA	0.35 (0.04-3.10)	NA	NA	NA	NA	NA
7-8 years	0.58 (0.06-5.09)	1.28 (0.08-20.44)	0.00 (NA), 0.6552	0.78 (0.14-4.34)	0.7787	0.78 (0.14-4.34)	0.7787
8-9 years	0.64 (0.07-5.62)	NA	NA	NA	NA	NA	NA
9-10 years	NA	NA	NA	NA	NA	NA	NA
Overall (0-10 years)	1.04 (0.80-1.37)	0.66 (0.49-0.89)	0.79 (0.11-0.95), 0.0278	0.84 (0.54-1.30)	0.4262	0.85 (0.70-1.04)	0.114
10-11 years	-	NA	-	-	-	-	-
11-12 years	-	NA	-	-	-	-	-
Overall (0-12 years)	-	0.66 (0.48-0.88)	-	-	-	-	-

CI: Confidence interval; CM: Congenital malformations; NA: Not available.
Legend: Risk ratio, ie, ratio of the cumulative incidence proportions of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) is presented for each country separately and combined (meta-analysis). The 95% CI is presented as well. I^2 estimates the proportion of the variance in study estimates that was due to heterogeneity, and it ranged from 0 (no heterogeneity) to 1 (heterogeneity).
Notes: The main analysis on the secondary outcome analysis was not conducted in Sweden as only live offspring could be analyzed in Sweden. Several risk ratios for Denmark were missing due to the fact that both valproate and lamotrigine/levetiracetam groups had 0 events in the corresponding years. It was not possible to calculate the risk ratios and perform the meta-analysis in those years. The confidence interval for I^2 statistic was not available for some groups.
*** Masked values indicating that data was calculated but not disclosed.

Table 6 Meta-analysis of the odds ratios obtained from the crude logistic model; secondary outcome

	Odds ratio (valproate vs lamotrigine/levetiracetam composite monotherapy)					
CM - Crude logistic model	**Norway**	**Denmark**	**Meta-analysis (random effect)**	**P-value (random effect)**	**Meta-analysis (fixed effect)**	**P-value (fixed effect)**
Number of events/Number of offspring in the valproate group	24/169	23/259				
Number of events/Number of offspring in the lamotrigine/levetiracetam group	46/344	53/389				
I^2 (95% CI), p-value			0.50 (NA)[1], 0.1590			
Paternal exposure: valproate vs levetiracetam/lamotrigine	1.06 (0.62-1.82)	0.62 (0.37-1.04)	0.81 (0.48-1.36)	0.4216	0.80 (0.55-1.16)	0.2455

CI: Confidence interval; CM: Congenital malformations; NA: Not available; OR: Odds ratio.
Legend: OR of the outcome between the 2 exposure groups (valproate vs lamotrigine/levetiracetam composite monotherapy) is presented for Norway and Denmark separately and combined (meta-analysis). The 95% CI is presented as well.

[1] It was not possible to obtain confidence interval estimates – this is likely due to the insufficient number of studies included

3.2 Results for Norway

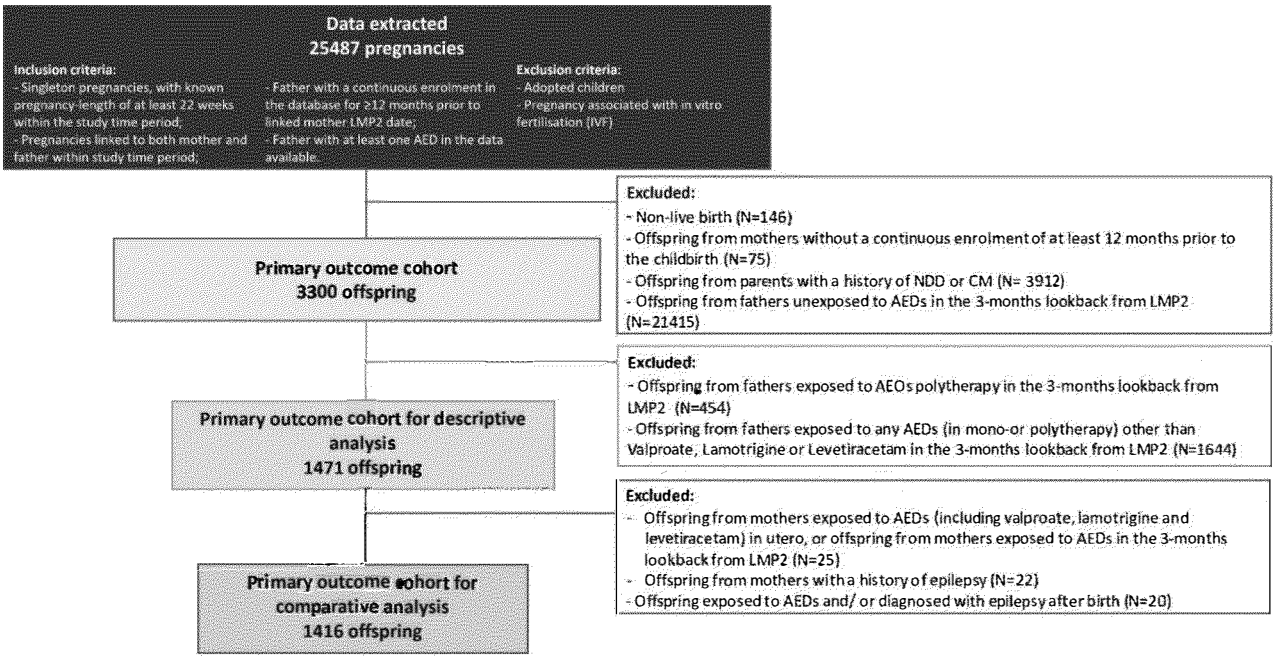
This section supersedes section 10.5 from the final study report v1.1.

After applying all the inclusion and exclusion criteria, a total of 25,487 pregnancies were identified in databases in Norway. Subsequently, additional exclusion criteria, not mutually exclusive, were applied to obtain the populations used for the descriptive and comparative analysis for each outcome, separately.

Please note that during stepwise exclusions from the cohorts post data extraction (primary outcome cohort and secondary outcome cohort), some characteristics were absent as they were either 1 of the exclusion criteria or characteristics associated with the exclusion criteria. Offspring with epilepsy, fathers exposed to other AEDs than those of interest, and mothers exposed to AEDs or with a history of epilepsy are examples of excluded characteristics. Although these populations are described in this report, they are not part of the comparative analysis.

The selection of the Primary outcome cohort is presented in Figure 1.

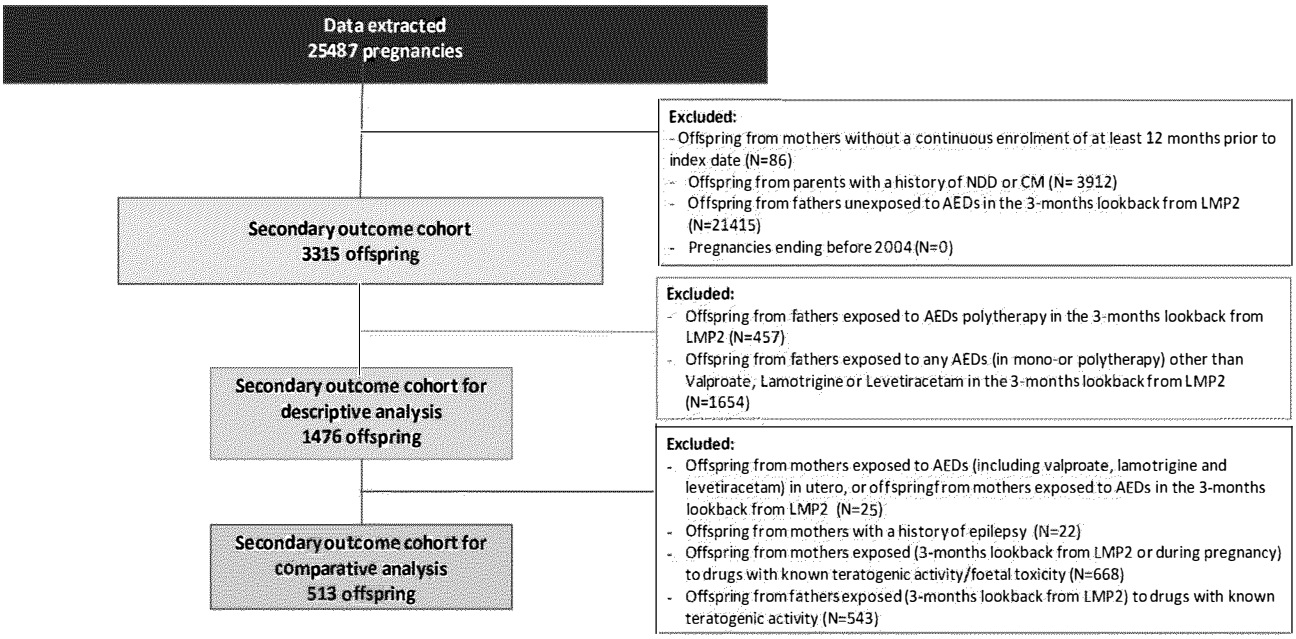
From all the 25,487 pregnancies identified, the following were excluded: non-live births (N=146), offspring from a mother without a continuous enrolment in database of at least 12 months prior to the childbirth (N=75), offspring from parents with a history of NDD including ASD or CM (N=3,912), offspring from a father unexposed to AEDs in the 3-month lookback period from LMP2 (N=21,415). Thus, the primary outcome cohort consisted of 3,300 offspring. Briefly, there were 1,471 offspring included in the primary outcome cohort for descriptive analyses, and 1,416 offspring in the primary outcome cohort for comparative analyses.



AED: Antiepileptic drug; LMP2: Last menstrual period plus 2 weeks; CM: Congenital Malformation; NDD: Neurodevelopmental disorders.
Legend: The same child could be counted in different exclusion categories, explaining why numbers do not necessarily add up.

Figure 1 Study population of the Primary outcome cohort in Norway

The selection of the secondary outcome cohort used to assess risk of CM is depicted in Figure 2. The secondary outcome cohort for descriptive analyses consisted of 1,476 offspring, and the secondary outcome cohort for comparative analyses consisted of 513 offspring.



AED: Antiepileptic drug; CM: Congenital Malformation; NDD: Neurodevelopmental disorders; LMP2: Last menstrual period plus 2 weeks.
Legend: The same child could be counted in different exclusion categories, explaining why numbers do not necessarily add up.

Figure 2 Study population of the Secondary outcome cohort in Norway

3.2.1 Neurodevelopmental disorders including autism spectrum disorder

This section supersedes section 10.5.1 from the final study report v1.1.

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

This section supersedes section 10.5.1.1 from the final study report v1.1.

This section presents the demographic and clinical characteristics of offspring, mothers, and fathers according to paternal exposure in monotherapy to valproate, lamotrigine or levetiracetam and the comparator group of composite lamotrigine/levetiracetam monotherapy. This analysis was performed in the primary outcome cohort for descriptive analyses, which was described in Figure 1.

Table 7 shows offspring demographic characteristics of the primary outcome cohort for descriptive analyses by paternal exposure group. A total of 413 offspring paternally exposed to valproate and 1,058 offspring paternally exposed to lamotrigine/levetiracetam were included. The majority of offspring were male (52.1%) (49.6% in those paternally exposed to valproate and 53.1% in those paternally exposed to lamotrigine/levetiracetam), born at term between 37-41 weeks of gestational age (overall 89.8%; 87.7% in those paternally exposed to valproate and 90.6% in those paternally exposed to lamotrigine/levetiracetam), and weighing ≥2,500 g (overall 96.3%; 95.6% in those paternally exposed to valproate and 96.6% in those paternally exposed to lamotrigine/levetiracetam). A higher proportion of offspring in the lamotrigine/levetiracetam group were born in the later years of the study time period compared to those in the valproate group, where an overall decrease in the proportions of offspring born over the study period was observed, with larger decreases observed in the later years (9.0% in 2018 and 6.8% in 2019) (Table 7). The total offspring-years of follow-up was 7,164.4 (2,055.8 for valproate and 5,108.6 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 7).

Regarding clinical characteristics of offspring by paternal exposure to valproate and lamotrigine/levetiracetam groups (Table 8), 1.9% offspring paternally exposed to valproate and 1.0% paternally exposed to lamotrigine/levetiracetam were diagnosed with epilepsy, and 1.2% of offspring paternally exposed to valproate and 0.8% of offspring paternally exposed to lamotrigine/levetiracetam were exposed to AEDs between birth and exit date.

In the descriptive cohort, 4.1% of offspring paternally exposed to valproate and 2.4% of offspring paternally exposed to lamotrigine/levetiracetam were diagnosed having an NDD including ASD during the follow-up. The median (interquartile range [IQR]) age in years at the first diagnosis of NDD including ASD was 5.1 (3.4, 7.3) for the valproate and 4.3 (3.6, 6.6) for the lamotrigine/levetiracetam group Table 8.

ASD as the first NDD diagnosis, during all the study period, was observed in 0.7% of offspring paternally exposed to valproate and in 0.3% of offspring paternally exposed to lamotrigine/levetiracetam. All ASD diagnoses, ever and not only as a first diagnosis, were observed in 1.2% of offspring paternally exposed to valproate and in 0.4% of offspring paternally exposed to lamotrigine/levetiracetam. The median (IQR) age in

years at the first diagnosis of ASD was 3.6 (3.4, 4.4) for offspring paternally exposed to valproate and 5.6 (4.0, 7.7) for offspring paternally exposed to lamotrigine/levetiracetam.

Table 7 Offspring demographic characteristics by paternal exposure group; Primary outcome cohort in Norway (N=1,471)

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/ Levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of pregnancies	**N=413**		**N=1058**		**N=896**		**N=162**		**N=1471**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Gestational age (weeks)										
<28 (extremely preterm)	2	0.48	3	0.28	3	0.33	0	0.00	5	0.34
28-31 (very preterm)	3	0.73	6	0.57	5	0.56	1	0.62	9	0.61
32-36 (moderate to late preterm)	23	5.57	43	4.06	36	4.02	7	4.32	66	4.49
37-41 (at term)	362	87.65	959	90.64	813	90.74	146	90.12	1321	89.80
≥42 (post-term)	23	5.57	47	4.44	39	4.35	8	4.94	70	4.76
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	3	0.73	6	0.57	5	0.56	1	0.62	9	0.61
1000-1499 (very low)	1	0.24	3	0.28	3	0.33	0	0.00	4	0.27
1500-2499 (low)	14	3.39	27	2.55	22	2.46	5	3.09	41	2.79
≥2500	395	95.64	1022	96.60	866	96.65	156	96.30	1417	96.33
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gender [a]										
Male	205	49.64	562	53.12	465	51.90	97	59.88	767	52.14
Female	208	50.36	496	46.88	431	48.10	65	40.12	704	47.86
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Year of birth										
2010	33	7.99	90	8.51	82	9.15	8	4.94	123	8.36
2011	48	11.62	117	11.06	107	11.94	10	6.17	165	11.22
2012	45	10.90	85	8.03	76	8.48	9	5.56	130	8.84
2013	47	11.38	105	9.92	88	9.82	17	10.49	152	10.33

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/ Levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of pregnancies	**N=413**		**N=1058**		**N=896**		**N=162**		**N=1471**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
2014	43	10.41	120	11.34	99	11.05	21	12.96	163	11.08
2015	43	10.41	105	9.92	87	9.71	18	11.11	148	10.06
2016	44	10.65	122	11.53	96	10.71	26	16.05	166	11.28
2017	45	10.90	109	10.30	94	10.49	15	9.26	154	10.47
2018	37	8.96	97	9.17	81	9.04	16	9.88	134	9.11
2019	28	6.78	108	10.21	86	9.60	22	13.58	136	9.25
Total number of years of follow-up	2055.84		5108.58		4422.37		686.21		7164.42	
Mean follow-up year	4.98		4.83		4.94		4.24		4.87	

NDD: Neurodevelopmental disorders.
Legend: Number of offspring represented the total number of offspring with linked mother and father. The same mother/father could appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 8 Offspring clinical characteristics by paternal exposure group; Primary outcome cohort in Norway (N=1,471)

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/ Levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of pregnancies	**N=413**		**N=1058**		**N=896**		**N=162**		**N=1471**	
	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	8	1.94	10	0.95	7	0.78	3	1.85	18	1.22
Fetal alcohol syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fragile X syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lejeune/cri du chat syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tuberous sclerosis	0	0.00	1	0.09	1	0.11	0	0.00	1	0.07
Medication use										
Exposure to AEDs [a]	5	1.21	8	0.76	6	0.67	2	1.23	13	0.88
Outcomes										
ASD (ever, not only as 1st NDD diagnosis)	5	1.21	4	0.38	4	0.45	0	0.00	9	0.61
ASD (as 1st NDD diagnosis)	3	0.73	3	0.28	3	0.33	0	0.00	6	0.41
NDD including ASD	17	4.12	25	2.36	21	2.34	4	2.47	42	2.86
Outcomes (ICD-10 codes, ever) [b]										
Intellectual Disability - Mild	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Intellectual Disability - Moderate	0	0.00	1	0.09	1	0.11	0	0.00	1	0.07
Intellectual Disability - Severe	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Intellectual Disability - Profound	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

NDD	Paternal exposure group									
	Valproate		Lamotrigine/ Levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of pregnancies	N=413		N=1058		N=896		N=162		N=1471	
	N	%	N	%	N	%	N	%	N	%
Other Intellectual Disability	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Unspecified Intellectual Disability	1	0.24	2	0.19	2	0.22	0	0.00	3	0.20
Specific developmental disorders of speech and language	6	1.45	10	0.95	9	1.00	1	0.62	16	1.09
Specific developmental disorders of scholastic skills	0	0.00	3	0.28	3	0.33	0	0.00	3	0.20
Mixed specific developmental delays	2	0.48	2	0.19	1	0.11	1	0.62	4	0.27
Pervasive developmental disorders	5	1.21	4	0.38	4	0.45	0	0.00	9	0.61
Other disorders of psychological development	0	0.00	1	0.09	1	0.11	0	0.00	1	0.07
Unspecified disorder of psychological development	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mental disorder, not otherwise specified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dyslexia and other symbolic dysfunctions, not elsewhere classified	1	0.24	0	0.00	0	0.00	0	0.00	1	0.07
Hyperkinetic disorders	6	1.45	7	0.66	7	0.78	0	0.00	13	0.88
Other specified behavioral and emotional disorders with onset usually occurring in childhood and adolescence	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Tic disorders	1	0.24	1	0.09	0	0.00	1	0.62	2	0.14
Specific developmental disorder of motor function	1	0.24	2	0.19	2	0.22	0	0.00	3	0.20

NDD	Paternal exposure group									
	Valproate		Lamotrigine/ Levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of pregnancies	N=413		N=1058		N=896		N=162		N=1471	
	N	%	N	%	N	%	N	%	N	%
Stereotyped movement disorders	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Essential tremor	0	0.00	1	0.09	0	0.00	1	0.62	1	0.07
Other specified forms of tremor	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Myoclonus	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other chorea	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other specified extrapyramidal and movement disorders	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Extrapyramidal and movement disorder, unspecified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Idiopathic nonfamilial dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Spasmodic torticollis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Idiopathic orofacial dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Blepharospasm	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other dystonia	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Dystonia, unspecified	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Extrapyramidal and movement disorders in diseases classified elsewhere	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Age at the first diagnosis (years)										
ASD (ever, not only as 1st NDD diagnosis) [c]										
0-1	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
2-3	3	0.73	1	0.09	1	0.11	0	0.00	4	0.27

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/ Levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of pregnancies	**N=413**		**N=1058**		**N=896**		**N=162**		**N=1471**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
4-5	2	0.48	1	0.09	1	0.11	0	0.00	3	0.20
6-7	0	0.00	1	0.09	1	0.11	0	0.00	1	0.07
8-9	0	0.00	1	0.09	1	0.11	0	0.00	1	0.07
10-11	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total (offspring with the outcome)	5	1.21	4	0.36	4	0.44	0	0.00	9	0.61
Offspring without a diagnosis	408	98.79	1054	99.62	892	99.55	162	100.00	1462	99.39
Mean (SD)	3.91 (0.83)		5.83 (2.18)		5.83 (2.18)		-		4.76 (1.77)	
Median (25th - 75th percentile)	3.63 (3.38, 4.43)		5.62 (3.97, 7.69)		5.62 (3.97, 7.69)		-		4.01 (3.63, 5.07)	
Min, max	3.02, 5.07		3.93, 8.14		3.93, 8.14		-		3.02, 8.14	
NDD including ASD [c]										
0-1	2	0.48	0	0.00	0	0.00	0	0.00	2	0.14
2-3	4	0.97	10	0.95	9	1.00	1	0.62	14	0.95
4-5	4	0.97	6	0.57	3	0.33	3	1.85	10	0.68
6-7	6	1.45	6	0.57	6	0.67	0	0.00	12	0.82
8-9	1	0.24	3	0.28	3	0.33	0	0.00	4	0.27
10-11	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Total (offspring with the outcome)	17	4.11	25	2.37	21	2.33	4	2.47	42	2.86
Offspring without a diagnosis	396	95.88	1033	97.64	875	97.66	158	97.53	1429	97.14
Mean (SD)	5.06 (2.42)		5.01 (1.82)		5.11 (1.95)		4.48 (0.73)		5.03 (2.05)	
Median (25th - 75th percentile)	5.07 (3.38, 7.30)		4.34 (3.55, 6.63)		4.28 (3.29, 6.88)		4.53 (3.94, 5.01)		4.58 (3.38, 6.88)	
Min, max	0.60, 8.15		2.95, 8.26		2.95, 8.26		3.55, 5.30		0.60, 8.26	

AED: Antiepileptic drugs; ASD: Autism Spectrum Disorders; CMV: Cytomegalovirus; ICD-10: International Statistical Classification of Diseases and Related Health Problems 10th Revision; LMP2: Last menstrual period date plus 2 weeks; NDD: Neurodevelopmental disorders; SD: Standard deviation
Legend: Number of offspring represented the total number of offspring with linked mother and father. The same mother/father could appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) between index (childbirth) and exit date
b) ICD-10 codes refer to all records of NDD including ASD during the entire follow-up. Since offspring might have more than one distinct ICD-10 code, the sum of the distinct ICD-10 codes might not coincide with the total number of offspring with the composite outcome
c) Categories may be adapted according to the data

Overall, the median (IQR) age of mothers from the primary outcome cohort for descriptive analyses at childbirth was 30.0 (27.0-34.0) years for the valproate group and 31.0 (27.0-34.0) years for the lamotrigine/levetiracetam group (Table 9). The most prevalent clinical characteristics recorded in mothers prior to childbirth were: neurotic disorder which was observed in 12.8% of mothers of offspring paternally exposed to valproate and in 13.6% 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 10.9% of mothers of offspring paternally exposed to lamotrigine/levetiracetam; and gestational diabetes which was observed in 5.3% of mothers of offspring paternally exposed to valproate and in 6.6% of mothers of offspring paternally exposed to lamotrigine/levetiracetam (Table 10).

Regarding maternal lifestyle characteristics of the 1,471 offspring included in the primary outcome cohort for descriptive analyses, 5.2% had a record of smoking during pregnancy (6.8% in valproate exposure group and 4.5% in lamotrigine/levetiracetam exposure group). Correspondingly, the proportion of mothers smoking prior to LMP2 pregnancy was 13.0% (14.8% and 12.3 in the valproate and lamotrigine/levetiracetam exposure groups, respectively), although a relatively high proportion of missingness (13.4%) was observed.

A polypharmacy index during pregnancy between 1 and 4 was observed in 44.8% of mothers of offspring paternally exposed to valproate group, and in 47.3% of mothers of offspring paternally exposed to lamotrigine/levetiracetam group. Regarding the use of concomitant medications associated with neuropsychiatric adverse events during pregnancy, 41.2% of mothers of offspring paternally exposed to valproate, and 43.8% of mothers of offspring paternally exposed to lamotrigine/levetiracetam had at least one prescription (Table 10).

Regarding paternal demographic characteristics, the overall median (IQR) age of fathers at childbirth was 33.0 (30.0-37.0) years (32.0 [29.0-37.0] years in the valproate group and 33.5 [30.0-38.0] years in the lamotrigine/levetiracetam group). The proportions of offspring paternally exposed to valproate conceived per year oscillated between 5.8% and 12.4% over the period 2009-2018, before declining to 1.9% in 2019. Likewise, in the lamotrigine/levetiracetam, the proportions of offspring conceived per year oscillated between 6.0% and 11.2% over the period 2009-2018, before declining to 2.4% in 2019. (Table 11).

Regarding clinical characteristics of the fathers from the primary outcome cohort for descriptive analyses, in the group of offspring paternally exposed to valproate, 14.0% of fathers presented bipolar affective disorder, 7.8% presented affective disorder excluding bipolar disorder and mania, and 7.5% presented neurotic disorder. Among offspring paternally exposed to lamotrigine/levetiracetam, proportions were generally higher with 27.7% of fathers presenting bipolar affective disorder, 22.6% of fathers presenting affective disorder excluding bipolar disorder and mania, and 15.6% presenting neurotic disorder (Table 12).

The indication for AED treatment was epilepsy 46.1% (57.9% in the valproate group, 41.5% in the lamotrigine/levetiracetam group), bipolar affective disorder and mania 23.5% (13.6% in the valproate group, 27.4% in the lamotrigine/levetiracetam group)[1], and unknown/other 30.4% (28.6% in the valproate group, 31.1%

[1] 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

in the lamotrigine/levetiracetam group) (Table 12). Regarding the use of concomitant medications associated with neuropsychiatric adverse events, 56.2% of fathers of offspring paternally exposed to valproate, and 64.6% of fathers of offspring paternally exposed to lamotrigine/levetiracetam had at least one prescription.

The K-means algorithm, analyzing defined daily dose (DDD) trajectories in fathers exposed to AEDs 3 months prior to conception (ie, prior to LMP2) identified 2 different clusters A and B (Figure 3), one with constant high exposure to AEDs (ie, a high quantity of DDDs of exposure in the 14 days intervals of the assessment period, cluster A) and one with constant low exposure (cluster B). In the valproate group, a larger proportion of fathers were in cluster A (70.0%) than in cluster B (30.0%). In the lamotrigine/levetiracetam group, the same was observed (76.4% in cluster A and 23.6% in cluster B) (Table 12).

than one diagnosis was found (eg, epilepsy and bipolar disorder), only one indication was selected, with priority given to epilepsy, followed by bipolar disorder. In case, none of these diagnoses are found in the medical history, the indication was considered “other/unknown”.

Table 9 Maternal demographic characteristics by paternal exposure group; Primary outcome cohort in Norway (N=1,471)

	Paternal exposure group									
NDD Number of pregnancies	Valproate N=413		Lamotrigine/ Levetiracetam N=1058		Lamotrigine N=896		Levetiracetam N=162		Total (valproate + lamotrigine/levetiracetam) N=1471	
	N	%	N	%	N	%	N	%	N	%
Mother's age [a]										
≤20 years	7	1.69	17	1.61	15	1.67	2	1.23	24	1.63
21-25	61	14.77	142	13.42	120	13.39	22	13.58	203	13.80
26-30	142	34.38	351	33.18	285	31.81	66	40.74	493	33.51
31-35	145	35.11	349	32.99	304	33.93	45	27.78	494	33.58
36-40	50	12.11	158	14.93	142	15.85	16	9.88	208	14.14
>40	8	1.94	41	3.88	30	3.35	11	6.79	49	3.33
Mean (SD)	30.34 (4.83)		30.93 (5.13)		30.99 (5.10)		30.57 (5.29)		30.76 (5.06)	
Median (25^{th} - 75^{th} percentile)	30.00 (27.00, 34.00)		31.00 (27.00, 34.00)		31.00 (28.00, 35.00)		30.00 (27.00, 33.00)		31.00 (27.00, 34.00)	
Min, max	18.00, 43.00		17.00, 46.00		18.00, 46.00		17.00, 43.00		17.00, 46.00	
Missing	-		-		-		-		-	

NDD: Neurodevelopmental disorders; SD: Standard deviation.
Legend: Number of pregnancies represented the total number of offspring with linked mother and father. The same mother/father could appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)

Table 10 Maternal clinical characteristics by paternal exposure group; Primary outcome cohort in Norway (N=1,471)

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/ Levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of pregnancies	**N=413**		**N=1058**		**N=896**		**N=162**		**N=1471**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Comorbidities										
Affective disorder [a]	24	5.81	115	10.87	109	12.17	6	3.70	139	9.45
Diabetes [a]	7	1.69	23	2.17	23	2.57	0	0.00	30	2.04
Epilepsy [a]	7	1.69	15	1.42	12	1.34	3	1.85	22	1.50
Neurotic disorder [a]	53	12.83	144	13.61	130	14.51	14	8.64	197	13.39
Schizophrenia, schizotypal and delusional disorders [a]	1	0.24	0	0.00	0	0.00	0	0.00	1	0.07
Obesity [b]	6	1.45	10	0.95	10	1.12	0	0.00	16	1.09
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gestational diabetes [c]	22	5.33	70	6.62	64	7.14	6	3.70	92	6.25
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	0.24	2	0.19	2	0.22	0	0.00	3	0.20
Alcohol abuse during pregnancy [c]	1	0.24	1	0.09	1	0.11	0	0.00	2	0.14
Substance abuse prior to LMP2 [b]	2	0.48	4	0.38	4	0.45	0	0.00	6	0.41
Substance abuse during pregnancy [c]	2	0.48	2	0.19	2	0.22	0	0.00	4	0.27
Smoking prior to LMP2 [b]										
No	286	69.25	797	75.33	666	74.33	131	80.86	1083	73.62
Yes	61	14.77	130	12.29	118	13.17	12	7.41	191	12.98
Missing	66	15.98	131	12.38	112	12.50	19	11.73	197	13.39

NDD	Paternal exposure group									
	Valproate		Lamotrigine/ Levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of pregnancies	N=413		N=1058		N=896		N=162		N=1471	
	N	%	N	%	N	%	N	%	N	%
Smoking during pregnancy [c]										
No	331	80.15	904	85.44	760	84.82	144	88.89	1235	83.96
Yes	28	6.78	48	4.54	47	5.25	1	0.62	76	5.17
Missing	54	13.08	106	10.02	89	9.93	17	10.49	160	10.88
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	15	1.42	15	1.67	0	0.00	15	1.02
Levetiracetam	0	0.00	2	0.19	2	0.22	0	0.00	2	0.14
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	1	0.24	0	0.00	0	0.00	0	0.00	1	0.07
Carboxamide derivatives	3	0.73	2	0.19	1	0.11	1	0.62	5	0.34
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	0	0.00	18	1.70	17	1.90	1	0.62	18	1.22
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	13	1.23	13	1.45	0	0.00	13	0.88
Levetiracetam	1	0.24	2	0.19	2	0.22	0	0.00	3	0.20
Barbiturates and derivatives	1	0.24	0	0.00	0	0.00	0	0.00	1	0.07

NDD	Paternal exposure group									
	Valproate		Lamotrigine/ Levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of pregnancies	N=413		N=1058		N=896		N=162		N=1471	
	N	%	N	%	N	%	N	%	N	%
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	1	0.09	1	0.11	0	0.00	1	0.07
Carboxamide derivatives	4	0.97	2	0.19	1	0.11	1	0.62	6	0.41
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	1	0.24	16	1.51	15	1.67	1	0.62	17	1.16
K means cluster prior to LMP2 [d]										
Unexposed	410	99.27	1039	98.20	879	98.10	160	98.77	1449	98.50
Group A	2	0.48	14	1.32	12	1.34	2	1.23	16	1.09
Group B	1	0.24	5	0.47	5	0.56	0	0.00	6	0.41
K means cluster during pregnancy [c]										
Unexposed	409	99.03	1040	98.30	880	98.21	160	98.77	1449	98.50
Group A	2	0.48	11	1.04	9	1.00	2	1.23	13	0.88
Group B	2	0.48	7	0.66	7	0.78	0	0.00	9	0.61
Maternal polypharmacy index prior to LMP2 [d]										
0	267	64.65	669	63.23	563	62.83	106	65.43	936	63.63
1-4	134	32.45	367	34.69	314	35.04	53	32.72	501	34.06
5-10	11	2.66	22	2.08	19	2.12	3	1.85	33	2.24
>10	1	0.24	0	0.00	0	0.00	0	0.00	1	0.07
Mean (SD)	0.74 (1.39)		0.67 (1.15)		0.67 (1.15)		0.63 (1.13)		0.69 (1.22)	

NDD	Paternal exposure group									
	Valproate		Lamotrigine/ Levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of pregnancies	N=413		N=1058		N=896		N=162		N=1471	
	N	%	N	%	N	%	N	%	N	%
Median (25th - 75th percentile)	0.00 (0.00, 1.00)		0.00 (0.00, 1.00)		0.00 (0.00, 1.00)		0.00 (0.00, 1.00)		0.00 (0.00, 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]										
0	218	52.78	528	49.91	443	49.44	85	52.47	746	50.71
1-4	185	44.79	500	47.26	426	47.54	74	45.68	685	46.57
5-10	10	2.42	30	2.84	27	3.01	3	1.85	40	2.72
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mean (SD)	0.88 (1.25)		0.97 (1.33)		0.99 (1.35)		0.87 (1.19)		0.94 (1.31)	
Median (25th - 75th percentile)	0.00 (0.00, 1.00)		1.00 (0.00, 2.00)		1.00 (0.00, 2.00)		0.00 (0.00, 1.00)		0.00 (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	38	9.20	122	11.53	108	12.05	14	8.84	160	10.88
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	16	3.87	69	6.52	62	6.92	7	4.32	85	5.78
Concomitant medications associated with neuropsychiatric adverse events prior to	283	68.52	723	68.34	619	69.08	104	64.20	1006	68.39

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/ Levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	
Number of pregnancies	**N=413**		**N=1058**		**N=896**		**N=162**		**N=1471**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
LMP2 [b] -mothers with at least one prescription Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	170	41.16	463	43.76	398	44.42	65	40.12	633	43.03

AED: Antiepileptic drugs; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; NDD: Neurodevelopmental disorders; SD: Standard deviation.
Legend: Number of offspring represented the total number of offspring with linked mother and father. The same mother/father could appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) all available data prior to index date (childbirth)
b) 12 months lookback from LMP2
c) during pregnancy (from LMP2 until index date)
d) 3 months lookback from LMP2
e) Oxazolidine derivatives were not sold in Norway during the study period
Cluster A1: Constant moderate exposure, Cluster B1: Constant low exposure
Cluster A2: Constant low exposure, Cluster B2: Constant moderate-low exposure

Table 11 Paternal demographic characteristics by paternal exposure group; Primary outcome cohort in Norway (N=1,471)

NDD	Paternal exposure group									
	Valproate		Lamotrigine/ Levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of pregnancies	N=413		N=1058		N=896		N=162		N=1471	
	N	%	N	%	N	%	N	%	N	%
Father's age [a]										
≤20 years	2	0.48	3	0.28	2	0.22	1	0.62	5	0.34
21-25	30	7.26	74	6.99	60	6.70	14	8.64	104	7.07
26-30	109	26.39	236	22.31	193	21.54	43	26.54	345	23.45
31-35	150	36.32	343	32.42	286	31.92	57	35.19	493	33.51
36-40	87	21.07	247	23.35	218	24.33	29	17.90	334	22.71
>40	35	8.47	155	14.65	137	15.29	18	11.11	190	12.92
Mean (SD)	32.93 (5.62)		33.99 (6.23)		34.18 (6.28)		32.93 (5.90)		33.69 (6.08)	
Median (25th - 75th percentile)	32.00 (29.00, 37.00)		33.50 (30.00, 38.00)		34.00 (30.00, 38.00)		33.00 (29.00, 36.00)		33.00 (30.00, 37.00)	
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 [b]										
2009	24	5.81	63	5.95	57	6.36	6	3.70	87	5.91
2010	44	10.65	118	11.15	109	12.17	9	5.56	162	11.01
2011	42	10.17	89	8.41	78	8.71	11	6.79	131	8.91
2012	51	12.35	108	10.21	94	10.49	14	8.64	159	10.81
2013	42	10.17	104	9.83	83	9.26	21	12.96	146	9.93
2014	47	11.38	114	10.78	96	10.71	18	11.11	161	10.94
2015	49	11.86	117	11.06	94	10.49	23	14.20	166	11.28
2016	40	9.69	111	10.49	96	10.71	15	9.26	151	10.27
2017	34	8.23	100	9.45	80	8.93	20	12.35	134	9.11
2018	32	7.75	109	10.30	89	9.93	20	12.35	141	9.59
2019	8	1.94	25	2.36	20	2.23	5	3.09	33	2.24

LMP2: Last menstrual period date plus 2 weeks; NDD: Neurodevelopmental disorders; SD: Standard deviation
Legend: Number of offspring represented the total number of offspring with linked mother and father. The same mother/father could appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at index (childbirth)
b) at mother's LMP2

Table 12 Paternal clinical characteristics by paternal exposure group; Primary outcome cohort in Norway (N=1,471)

NDD	Paternal exposure group									
	Valproate		Lamotrigine/ Levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of pregnancies	N=413		N=1058		N=896		N=162		N=1471	
	N	%	N	%	N	%	N	%	N	%
Comorbidities										
Bipolar affective disorder excl. bipolar disorder and mania [a]	32	7.75	239	22.59	237	26.45	2	1.23	271	18.42
Bipolar affective disorder [a]	58	14.04	293	27.69	293	32.70	0	0.00	351	23.86
Mania [a]	6	1.45	7	0.66	7	0.78	0	0.00	13	0.88
Neurotic disorder [a]	31	7.51	165	15.60	163	18.19	2	1.23	196	13.32
Schizophrenia, schizotypal and delusional disorders [a]	11	2.66	20	1.89	20	2.23	0	0.00	31	2.11
Lifestyle characteristics										
Substance abuse [b]	11	2.66	23	2.17	23	2.57	0	0.00	34	2.31
Medication use										
AED indication										
Epilepsy	239	57.87	439	41.49	291	32.48	148	91.36	678	46.09
Bipolar affective disorder and mania	56	13.56	290	27.41	290	32.37	0	0.00	346	23.52
Other/unknown	118	28.57	329	31.10	315	35.16	14	8.64	447	30.39
K means cluster [c]										
Group A	289	69.98	808	76.37	674	75.22	134	82.72	1097	74.58
Group B	124	30.02	250	23.63	222	24.78	28	17.28	374	25.42

NDD	Paternal exposure group									
	Valproate		Lamotrigine/ Levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/levetiracetam)	
Number of pregnancies	N=413		N=1058		N=896		N=162		N=1471	
	N	%	N	%	N	%	N	%	N	%
Paternal polypharmacy index [c]										
0	264	63.92	540	51.04	429	47.88	111	68.52	804	54.66
1-4	143	34.62	483	45.65	435	48.55	48	29.63	626	42.56
5-10	6	1.45	33	3.12	30	3.35	3	1.85	39	2.65
>10	0	0.00	2	0.19	2	0.22	0	0.00	2	0.14
Mean (SD)	0.66 (1.15)		1.01 (1.49)		1.09 (1.53)		0.56 (1.15)		0.91 (1.41)	
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 1.00)		0.00 (0.00, 2.00)		1.00 (0.00, 2.00)		0.00 (0.00, 1.00)		0.00 (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	89	21.55	382	36.11	372	41.52	10	6.17	471	32.02
Concomitant medications associated with neuropsychiatric adverse events [b] - fathers with at least one prescription	233	56.42	683	64.56	611	68.19	72	44.44	916	62.27

AED: Antiepileptic drugs; LMP2: Last menstrual period date plus 2 weeks; NDD: Neurodevelopmental disorders; SD: Standard deviation

Legend: Number of offspring represented the total number of offspring with linked mother and father. The same mother/father could 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.

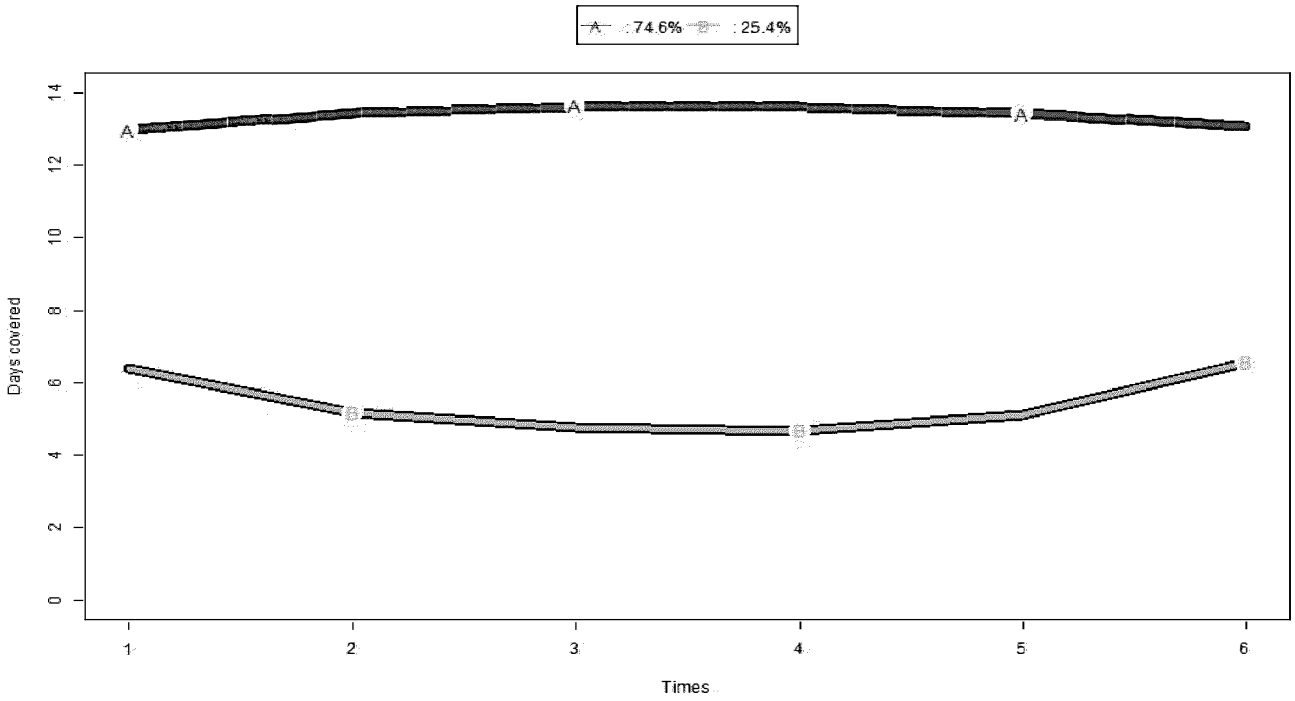
a) all available data prior to index date (childbirth)

b) 12 months lookback from LMP2

c) 3 months lookback from LMP2

Cluster A: constant high exposure; Cluster B: constant low exposure

AEDD



AED: Antiepileptic drugs

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

Figure 3 Mean defined daily dose (DDD) trajectories for fathers exposed to AEDs in the 3 months lookback prior to Last Menstrual Period Date Plus 2 weeks (LMP2) in Norway

3.2.1.2 Cumulative incidence proportion

This section supersedes section 10.5.1.2 from the final study report v1.1.

Cumulative incidence proportions (risk) of NDD including ASD by paternal exposure group are presented overall in Table 13, and stratified by gender in Table 52 and Table 53 (please see Appendix Section 8.1.3).

The cumulative incidence proportions (risk) of NDD including ASD for 0-10 years of follow-up appeared to be higher in offspring paternally exposed to valproate (4.1%, 95% CI: 2.2, 6.0) than in offspring paternally exposed to lamotrigine/levetiracetam (2.4%, 95% CI: 1.5, 3.3), although the 95% CI overlapped (Table 13).

The cumulative incidence proportion for 0-10 years of follow-up also appeared to be higher in male (3.7%, 95% CI: 2.3, 5.0) than female offspring (2.0%, 95% CI: 1.0, 3.0) (Table 52 and Table 53, Appendix Section 8.1.3).

However, these proportions should be interpreted with caution since these are crude estimates, no adjustments were made. In addition, offspring diagnosed with epilepsy and/treated with AEDs and/or exposed to AEDs in utero were not excluded in the descriptive cohort (Table 52 and Table 53, see Appendix Section 8.1.3).

Table 13 Cumulative incidence proportion (risk) of NDD by paternal exposure group; Primary outcome cohort in Norway

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	413	1058	896	162	1471
0-1 years	n	1	0	0	0	1
	n/N*100	0.24 (-0.23, 0.72)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.07 (-0.07, 0.20)
	N	381	948	808	140	1329
1-2 years	n	1	0	0	0	1
	n/N*100	0.26 (-0.25, 0.78)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.08 (-0.07, 0.22)
	N	342	850	726	124	1192
2-3 years	n	2	4	4	0	6
	n/N*100	0.58 (-0.22, 1.39)	0.47 (0.01, 0.93)	0.55 (0.01, 1.09)	0.00 (0.00, 0.00)	0.50 (0.10, 0.91)
	N	294	733	626	107	1027
3-4 years	n	2	6	5	1	8
	n/N*100	0.68 (-0.26, 1.62)	0.82 (0.17, 1.47)	0.80 (0.10, 1.50)	0.93 (-0.89, 2.76)	0.78 (0.24, 1.32)
	N	249	605	525	80	854
4-5 years	n	2	5	3	2	7
	n/N*100	0.80 (-0.31, 1.91)	0.83 (0.11, 1.55)	0.57 (-0.07, 1.22)	2.50 (-0.92, 5.92)	0.82 (0.21, 1.42)
	N	203	500	438	62	703
5-6 years	n	2	1	0	1	3
	n/N*100	0.99 (-0.37, 2.34)	0.20 (-0.19, 0.59)	0.00 (0.00, 0.00)	1.61 (-1.52, 4.75)	0.43 (-0.06, 0.91)
	N	160	381	340	41	541
6-7 years	n	2	5	5	0	7
	n/N*100	1.25 (-0.47, 2.97)	1.31 (0.17, 2.46)	1.47 (0.19, 2.75)	0.00 (0.00, 0.00)	1.29 (0.34, 2.25)
	N	115	277	252	25	392

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
7-8 years	n	4	1	1	0	5
	n/N*100	3.48 (0.13, 6.83)	0.36 (-0.35, 1.07)	0.40 (-0.38, 1.17)	0.00 (0.00, 0.00)	1.28 (0.16, 2.39)
	N	70	195	179	16	265
8-9 years	n	1	3	3	0	4
	n/N*100	1.43 (-1.35, 4.21)	1.54 (-0.19, 3.27)	1.68 (-0.20, 3.56)	0.00 (0.00, 0.00)	1.51 (0.04, 2.98)
	N	27	82	75	7	109
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	413	1058	896	162	1471
Overall (0-10 years)	n	17	25	21	4	42
	n/N*100	4.12 (2.20, 6.03)	2.36 (1.45, 3.28)	2.34 (1.35, 3.33)	2.47 (0.08, 4.86)	2.86 (2.00, 3.71)

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

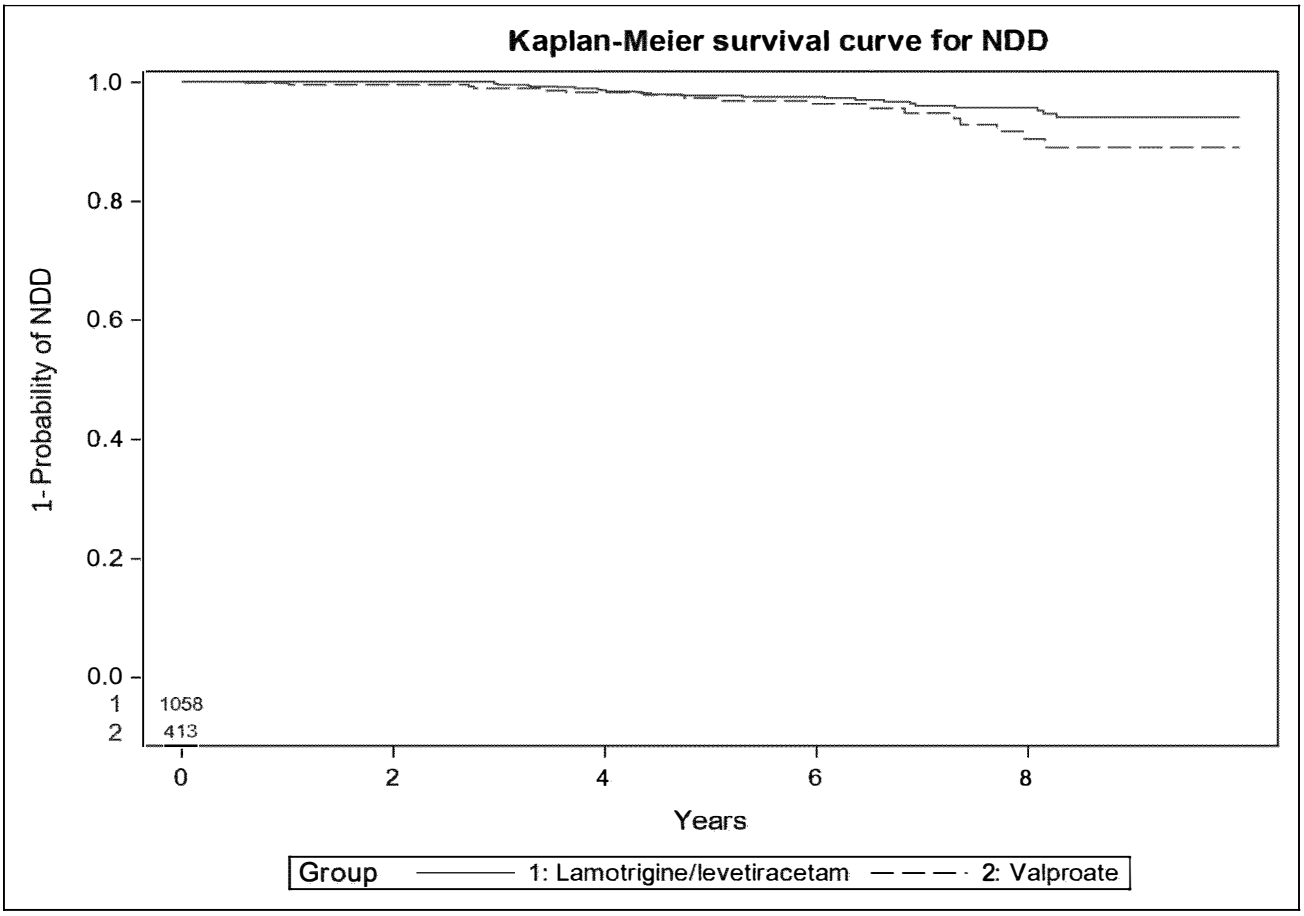
3.2.1.3 Cumulative incidence rate and time to NDD diagnosis

This section supersedes section 10.5.1.3 from the final study report v1.1.

Cumulative incidence rates of NDD including ASD by paternal exposure group are presented overall in Table 14, and stratified by gender in Table 54 and Table 55 (see Appendix Section 8.1.4). Considering the overall study follow-up, a higher incidence rate of NDD including ASD was observed among offspring paternally exposed to valproate (8.3, [95% CI: 4.8, 13.2] per 1,000 person-years [PY]) than among those paternally exposed to lamotrigine/levetiracetam (4.9, [95% CI: 3.2, 7.2] per 1,000 PY), although the 95% CIs for the 2 groups overlapped. When stratifying by gender, the same pattern was observed in both male and female offspring subgroups. When considering the overall period of follow-up, the cumulative incidence rate in male offspring was higher than in female offspring, in both paternal exposure groups.

Regarding the time to first diagnosis of NDD including ASD, the crude estimate for both exposure groups is presented as Kaplan-Meier curves. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event. The 5th percentile of the time to NDD including ASD was 83.1 (95% CI: 44.2, -) months for the valproate and 99.1 (95% CI: 80.8, -) months for the lamotrigine/levetiracetam paternal exposure groups (Figure 4).

In the valproate paternal exposure group, for male offspring, the 5th percentile of the time to NDD including ASD was 79.0 (95% CI: 53.1, -) months and for female offspring, it was 89.5 (95% CI: 33.0, -) months. In the lamotrigine/levetiracetam paternal exposure group, the corresponding 5th percentile value for male was 83.7 (95% CI: 52.8, -) months, while for female it was not possible to provide the estimate (Table 56).



	Paternal exposure group				
NDD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	17	25	21	4	42
Number of censor	396	1033	875	158	1429
Survival time					
5th percentile	83.10 (44.20, -)	99.07 (80.77, -)	99.07 (80.77, -)	64.47 (52.83, -)	89.53 (77.43, -)
10th percentile	99.23 (88.83, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
25th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
median	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)
75th percentile	- (-, -)	- (-, -)	- (-, -)	- (-, -)	- (-, -)

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

Figure 4 Kaplan-Meier survival curve for Neurodevelopmental Disorders (NDD) and distribution of time to NDD in Norway

Table 14 Cumulative incidence rate of NDD by paternal exposure group; Primary outcome cohort in Norway

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	395.92	1002.17	850.95	151.23	1398.1
0-1 years	n	1	0	0	0	1
	n/PY*1000	2.53 (0.06, 14.07)	0.00 (-, 3.68)	0.00 (-, 4.34)	0.00 (-, 24.39)	0.72 (0.02, 3.99)
	PY	754.37	1901.23	1617.92	283.31	2655.6
0-2 years	n	2	0	0	0	2
	n/PY*1000	2.65 (0.32, 9.58)	0 (-, 1.94)	0 (-, 2.28)	0 (-, 13.02)	0.75 (0.09, 2.72)
	PY	1075.29	2696.71	2299.63	397.08	3772
0-3 years	n	4	4	4	0	8
	n/PY*1000	3.72 (1.01, 9.52)	1.48 (0.40, 3.80)	1.74 (0.47, 4.45)	0 (-, 9.29)	2.12 (0.92, 4.18)
	PY	1351.42	3367.75	2875	492.75	4719.17
0-4 years	n	6	10	9	1	16
	n/PY*1000	4.44 (1.63, 9.66)	2.97 (1.42, 5.46)	3.13 (1.43, 5.94)	2.03 (0.05, 11.31)	3.39 (1.94, 5.51)
	PY	1579.93	3920.81	3357.22	563.59	5500.75
0-5 years	n	8	15	12	3	23
	n/PY*1000	5.06 (2.19, 9.98)	3.83 (2.14, 6.31)	3.57 (1.85, 6.24)	5.32 (1.10, 15.56)	4.18 (2.65, 6.27)
	PY	1761.86	4356.82	3740.73	616.1	6118.68
0-6 years	n	10	16	12	4	26
	n/PY*1000	5.68 (2.72, 10.44)	3.67 (2.10, 5.96)	3.21 (1.66, 5.60)	6.49 (1.77, 16.62)	4.25 (2.78, 6.23)
	PY	1901	4689.66	4039.48	650.18	6590.67
0-7 years	n	12	21	17	4	33
	n/PY*1000	6.31 (3.26, 11.03)	4.48 (2.77, 6.85)	4.21 (2.45, 6.74)	6.15 (1.68, 15.75)	5.01 (3.45, 7.03)
	PY	1990.13	4925.81	4254.77	671.03	6915.93

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
0-8 years	n	16	22	18	4	38
	n/PY*1000	8.04 (4.60, 13.06)	4.47 (2.80, 6.76)	4.23 (2.51, 6.69)	5.96 (1.62, 15.26)	5.49 (3.89, 7.54)
	PY	2040.7	5067.25	4384.37	682.88	7107.95
0-9 years	n	17	25	21	4	42
	n/PY*1000	8.33 (4.85, 13.34)	4.93 (3.19, 7.28)	4.79 (2.96, 7.32)	5.86 (1.60, 15.00)	5.91 (4.26, 7.99)
	PY	2055.84	5108.58	4422.37	686.21	7164.42
0-10 years	n	17	25	21	4	42
	n/PY*1000	8.27 (4.82, 13.24)	4.89 (3.17, 7.22)	4.75 (2.94, 7.26)	5.83 (1.59, 14.92)	5.86 (4.23, 7.92)

NDD: neurodevelopmental disorders; PY: Person-Years
Legend: Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) were presented. It was not always possible to estimate the lower bound of the 95% CI for the corresponding incidence rate

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

This section supersedes section 10.5.1.4 from the final study report v1.1.

Association between potential covariates (risk factors and confounders) for NDD including ASD and paternal exposure group was assessed in the Primary outcome cohort for comparative analyses. Results of the crude associations are shown in Table 15, Table 16, and Table 17.

Offspring exposed to AEDs and/or diagnosed with epilepsy after birth were included in the Primary outcome for descriptive analyses but excluded from the Primary outcome for comparative analyses, hence the absence of a summary for epilepsy in Table 15. Epilepsy was an exclusion criterion for selecting the population for the comparative analyses because it was a strong risk factor for NDD including ASD (see Table 4 of the final study report v1.1) and offspring with epilepsy or receiving AEDs are already at risk of NDD including ASD regardless of paternal exposure.

All the variables examined were initially selected based on literature review and clinical expert opinion (see study protocol v6.0, section 9.3.3).

For the offspring, none of the characteristics identified from the literature as risk factors or confounders were associated with paternal exposure (Table 15).

Maternal characteristics identified as risk factors or confounders (see Table 4 of the final study report v1.1, Table 16), that were statistically significantly associated with paternal exposure in the offspring were:

- Affective disorder (p=0.0099), less frequent in the valproate paternal exposure group.
- Smoking during pregnancy (p=0.0301), more frequent in the valproate paternal exposure group.
- Concomitant medications associated with valproate-indicated psychiatric condition during pregnancy (p=0.0194), higher percentage in the valproate paternal exposure group.

Paternal characteristics identified as risk factors or confounders (see Table 4 of the final study report v1.1, Table 17) that were statistically significantly associated with paternal exposure were:

- Affective disorder (excluding bipolar affective disorder and mania) (p<0.0001), bipolar affective disorder (p<0.0001), and neurotic disorder (p<0.0001), 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), less frequent in the valproate exposure group.
- Concomitant medications associated with neuropsychiatric adverse events (p=0.0084), less frequent in the valproate exposure group.
- Age (p<0.0043), younger fathers in the valproate group.

Table 15 Association between potential offspring risk factors/confounders for NDD by paternal exposure group; Primary outcome cohort in Norway

	Paternal exposure group										Comparison
NDD	**Valproate**		**Lamotrigine/ Levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**	**Valproate vs Lamotrigine /levetiracetam**	
Number of pregnancies	**N=398**		**N=1018**		**N=863**		**N=155**		**N=1416**	-	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Offspring risk factors/ confounders											
Gender [a]											
Male	198	49.75	539	52.95	445	51.56	94	60.65	737	52.05	-
Female	200	50.25	479	47.05	418	48.44	61	39.35	679	47.95	-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	1.17 (0.2789)
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	-
Fetal 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	-

CMV: Cytomegalovirus; NDD: Neurodevelopmental disorders

Legend: Number of pregnancies represented the total number of offspring with linked mother and father. The same mother/father could 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 was tested using Chi-square independence test; however, if the frequency of any of the categories analyzed was <5 Fischer's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.

a) at index (childbirth)

b) between index and exit date

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

Table 16 Association between potential maternal risk factors/confounders for NDD by paternal exposure group; Primary outcome cohort in Norway

	Paternal exposure group										Comparison
NDD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=398**		**N=1018**		**N=863**		**N=155**		**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	1.29	22	1.55	-
21-25	60	15.08	134	13.16	115	13.33	19	12.26	194	13.70	-
26-30	137	34.42	337	33.10	275	31.87	62	40.00	474	33.47	-
31-35	137	34.42	340	33.40	295	34.18	45	29.03	477	33.69	-
36-40	50	12.56	151	14.83	135	15.64	16	10.32	201	14.19	-
>40	8	2.01	40	3.93	29	3.36	11	7.10	48	3.39	-
Test statistics	-	-	-	-	-	-	-	-	-	-	5.16 (0.3971)
Mother's age [a] (continuous)											
Mean (SD)	30.37 (4.84)	-	30.95 (5.11)	-	30.98 (5.08)	-	30.76 (5.30)	-	30.79 (5.04)	-	270488.50 (0.0960)*
Median (25th - 75th percentile)	30.00 (27.00, 34.00)	-	31.00 (27.00, 35.00)	-	31.00 (27.00, 35.00)	-	30.00 (27.00, 33.00)	-	31.00 (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	5.78	103	10.12	98	11.36	5	3.23	126	8.90	6.65 (0.0099)
Diabetes [b]	6	1.51	21	2.06	21	2.43	0	0.00	27	1.91	0.47 (0.4922)
Gestational diabetes [c]	21	5.28	67	6.58	61	7.07	6	3.87	88	6.21	0.84 (0.3605)
Neurotic disorder [b]	50	12.56	137	13.46	124	14.37	13	8.39	187	13.21	0.20 (0.6548)
Schizophrenia, schizotypal and	1	0.25	0	0.00	0	0.00	0	0.00	1	0.07	0.28 (0.2811)*

NDD	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=398		N=1018		N=863		N=155		N=1416		-
	N	%	N	%	N	%	N	%	N	%	
delusional disorders [b]											
Obesity [d]	6	1.51	10	0.98	10	1.16	0	0.00	16	1.13	0.71 (0.4006)
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 (0.4833)*
Substance abuse prior to LMP2 [d]	2	0.50	4	0.39	4	0.46	0	0.00	6	0.42	0.67 (0.6759)*
Substance abuse during pregnancy [c]	2	0.50	2	0.20	2	0.23	0	0.00	4	0.28	0.31 (0.3150)*
Smoking prior to LMP2 [d]											
No	273	68.59	772	75.83	645	74.74	127	81.94	1045	73.80	-
Yes	59	14.82	121	11.89	110	12.75	11	7.10	180	12.71	-
Missing	66	16.58	125	12.28	108	12.51	17	10.97	191	13.49	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	3.44 (0.0636)
Smoking during pregnancy [c]											
No	317	79.65	871	85.56	733	84.94	138	89.03	1188	83.90	-
Yes	27	6.78	43	4.22	42	4.87	1	0.65	70	4.94	-
Missing	54	13.57	104	10.22	88	10.20	16	10.32	158	11.16	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	4.70 (0.0301)

NDD	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=398		N=1018		N=863		N=155		N=1416		-
	N	%	N	%	N	%	N	%	N	%	
Maternal polypharmacy index prior to LMP2 [e] (categorical)											
0	262	65.83	648	63.65	547	63.38	101	65.16	910	64.27	-
1-4	125	31.41	349	34.28	298	34.53	51	32.90	474	33.47	-
5-10	10	2.51	21	2.06	18	2.09	3	1.94	31	2.19	-
>10	1	0.25	0	0.00	0	0.00	0	0.00	1	0.07	-
Test statistics	-	-	-	-	-	-	-	-	-	-	3.74 (0.2910)
Maternal polypharmacy index prior to LMP2 [e] (continuous)											
Mean (SD)	0.70 (1.36)	-	0.65 (1.14)	-	0.66 (1.15)	-	0.63 (1.11)	-	0.67 (1.21)	-	279386.50 (0.6595)*
Median (25th - 75th percentile)	0.00 (0.00, 1.00)	-	0.00 (0.00, 1.00)	-	0.00 (0.00, 1.00)	-	0.00 (0.00, 1.00)	-	0.00 (0.00, 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	211	53.02	513	50.39	430	49.83	83	53.55	724	51.13	-
1-4	178	44.72	476	46.76	407	47.16	69	44.52	654	46.19	-
5-10	9	2.26	29	2.85	26	3.01	3	1.94	38	2.68	-
>10	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-	-	-	-	-	-	1.01 (0.6038)

NDD	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=398		N=1018		N=863		N=155		N=1416		-
	N	%	N	%	N	%	N	%	N	%	
Maternal polypharmacy index during pregnancy [c] (continuous)											
Mean (SD)	0.87 (1.23)	-	0.95 (1.32)	-	0.98 (1.35)	-	0.83 (1.16)	-	0.93 (1.30)	-	274948.00 (0.2693)*
Median (25th - 75th percentile)	0.00 (0.00, 1.00)	-	0.00 (0.00, 1.00)	-	1.00 (0.00, 1.00)	-	0.00 (0.00, 1.00)	-	0.00 (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	7.79	111	10.90	99	11.47	12	7.74	142	10.03	3.08 (0.0794)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	12	3.02	62	6.09	58	6.72	4	2.58	74	5.23	5.46 (0.0194)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at	270	67.84	693	68.07	593	68.71	100	64.52	963	68.01	0.01 (0.9320)

	Paternal exposure group										Comparison
NDD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam - **
Number of pregnancies	**N=398**		**N=1018**		**N=863**		**N=155**		**N=1416**		
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
least one prescription											
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	162	40.70	439	43.12	379	43.92	60	38.71	601	42.44	0.69 (0.4075)

NDD: Neurodevelopmental disorders; SD: Standard deviation; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks
Legend: Number of offspring represented the total number of offspring with linked mother and father. The same mother/father could 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 analyzed was <5 Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) all available data prior to index date
c) during pregnancy (from LMP2 until index date)
d) 12 months lookback from LMP2
e) 3 months lookback from LMP2
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed

Table 17 Association between potential paternal risk factors/confounders for NDD by paternal exposure group; Primary outcome cohort in Norway

NDD	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=398		N=1018		N=863		N=155		N=1416		-
	N	%	N	%	N	%	N	%	N	%	
Paternal risk factors/confounders											
Affective disorder excluding bipolar affective disorder and mania [a]	31	7.79	227	22.30	226	26.19	1	0.65	258	18.22	40.43 (<.0001)
Bipolar affective disorder [a]	57	14.32	282	27.70	282	32.68	0	0.00	339	23.94	28.13 (<.0001)
Mania [a]	6	1.51	7	0.69	7	0.81	0	0.00	13	0.92	2.11 (0.1459)
Neurotic disorder [a]	30	7.54	156	15.32	154	17.84	2	1.29	186	13.14	15.20 (<.0001)
Schizophrenia, schizotypal and delusional disorders [a]	11	2.76	18	1.77	18	2.09	0	0.00	29	2.05	1.41 (0.2344)
Substance abuse [c]	10	2.51	22	2.16	22	2.55	0	0.00	32	2.26	0.16 (0.6891)
Paternal polypharmacy index [d] (categorical)											
0	255	64.07	520	51.08	415	48.09	105	67.74	775	54.73	-
1-4	137	34.42	465	45.68	418	48.44	47	30.32	602	42.51	-
5-10	6	1.51	31	3.05	28	3.24	3	1.94	37	2.61	-
>10	0	0.00	2	0.20	2	0.23	0	0.00	2	0.14	-
Test statistics	-	-	-	-	-	-	-	-	-	-	20.72 (0.0001)
Paternal polypharmacy index [d] (continuous)											
Mean (SD)	0.65 (1.14)		1.01 (1.49)		1.08 (1.53)		0.57 (1.17)		0.91 (1.41)		252616.50 (<.0001)*

NDD	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=398		N=1018		N=863		N=155		N=1416		-
	N	%	N	%	N	%	N	%	N	%	
Median (25th - 75th percentile)	0.00 (0.00, 1.00)		0.00 (0.00, 1.00)		1.00 (0.00, 2.00)		0.00 (0.00, 1.00)		0.00 (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 [c] – fathers with at least one prescription	85	21.36	361	35.46	353	40.90	8	5.16	446	31.50	26.38 (<.0001)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription	226	56.78	655	64.34	585	67.79	70	45.16	881	62.22	6.95 (0.0084)
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	7.29	69	6.78	57	6.60	12	7.74	98	6.92	-
26-30	106	26.63	225	22.10	185	21.44	40	25.81	331	23.38	-
31-35	142	35.68	330	32.42	275	31.87	55	35.48	472	33.33	-
36-40	85	21.36	240	23.58	211	24.45	29	18.71	325	22.95	-
>40	34	8.54	151	14.83	133	15.41	18	11.61	185	13.06	-
Test statistics	-	-	-	-	-	-	-	-	-	-	13.16 (0.0219)
Father's age [e] (continuous)											
Mean (SD)	32.94 (5.63)		34.05 (6.25)		34.22 (6.30)		33.15 (5.91)		33.74 (6.10)		262268.50 (0.0043)*

NDD	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=398		N=1018		N=863		N=155		N=1416		-
	N	%	N	%	N	%	N	%	N	%	
Median (25th - 75th percentile)	32.00 (29.00, 37.00)		34.00 (30.00, 38.00)		34.00 (30.00, 38.00)		33.00 (29.00, 37.00)		33.00 (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		-
Year of offspring conception [f,g]											
2009-2013	194	48.74	456	44.79	399	46.23	57	36.77	650	45.90	-
2014-2019	204	51.26	562	55.21	464	53.77	98	63.23	766	54.10	-
Test statistics	-	-	-	-	-	-	-	-	-	-	1.80 (0.1800)

NDD: Neurodevelopmental disorders; LMP2: Last menstrual period date plus 2 weeks; SD: Standard Deviation
Legend: Number of offspring represented the total number of offspring with linked mother and father. The same mother/father could 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 was tested using Chi-square independence test; however, if the frequency of any of the categories analyzed was <5 Fisher's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) all available data prior to index date (childbirth)
c) 12 months lookback from LMP2
d) 3 months lookback from LMP2
e) at index (childbirth)
f) at mother's LMP2
g) calendar years were grouped in each country according to the length of the study period
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed

3.2.1.5 Association between potential risk factors/confounders and NDD including ASD

This section supersedes section 10.5.1.5 from the final study report v1.1.

Association between covariates (potential risk factors / confounders) and occurrence of NDD was assessed in the Primary outcome cohort for comparative analyses. Results of crude associations are shown in Table 18, Table 19 and Table 20.

These variables were initially selected based on literature review and clinical expert opinion (see Table 4 of the final study report v1.1).

For offspring characteristics, only gender (OR: 0.49, 95% CI: 0.25, 0.98; p=0.0446) was associated with NDD including ASD (Table 18); the proportion of events among females were significantly lower than the proportion of events among males.

For maternal characteristics identified as risk factors or confounders (see Table 4 of the final study report v1.1, and Table 19) the following variables were statistically significantly associated with the occurrence of NDD including ASD events:

- Maternal age (p=0.0057); Offspring from mothers aged 26-30 years had a lower risk of NDD including ASD when compared with offspring from mothers aged 31-35 years (OR: 0.24, 95% CI: 0.08, 0.73).
- Substance abuse during pregnancy (OR: 12.4, 95% CI: 1.26, 121.9; p=0.0310).
- Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 (OR: 3.88, 95% CI: 1.88, 8.00; p=0.0002).

For paternal characteristics identified as risk factors or confounders (see Table 4 and Table 6 of the final study report v1.1), only categories of calendar year of offspring conception were associated with the occurrence of NDD, including ASD events. A lower OR was observed for the offspring conceived between 2014-2019 (OR: 0.25, 95% CI: 0.12, 0.54; p=0.0004) when compared to those conceived between 2009-2013 (reference category) (Table 20).

Table 18 Association between potential offspring risk factors/confounders and NDD; Primary outcome cohort in Norway

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Offspring risk factors/confounders								
Gender [a]								
Male	737	52.05	26	3.53	711	96.47	Reference	-
Female	679	47.95	12	1.77	667	98.23	0.49 (0.25, 0.98)	-
Missing	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	4.03, 0.0446
Congenital CMV [b]								
No	1416	100.00	38	2.68	1378	97.32	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital rubella [b]								
No	1416	100.00	38	2.68	1378	97.32	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Fetal alcohol syndrome [b]								
No	1416	100.00	38	2.68	1378	97.32	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Fragile X syndrome [b]								
No	1416	100.00	38	2.68	1378	97.32	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Lejeune/cri du chat syndrome [b]								
No	1416	100.00	38	2.68	1378	97.32	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Tuberous sclerosis [b]								
No	1416	100.00	38	2.68	1378	97.32	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-

CI: Confidence interval; CMV: Cytomegalovirus; NDD: Neurodevelopmental disorders; OR: Odds ratio

Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, 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 19 Association between potential maternal risk factors/confounders and NDD; Primary outcome cohort in Norway

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Maternal risk factors/confounders								
Mother's age [a] (categorical)								
≤20 years	22	1.55	0	0.00	22	100.00	0.00 (0.00, I)	-
21-25	194	13.70	11	5.67	183	94.33	1.72 (0.78, 3.78)	-
26-30	474	33.47	16	3.38	458	96.62	Reference	-
31-35	477	33.69	4	0.84	473	99.16	0.24 (0.08, 0.73)	-
36-40	201	14.19	3	1.49	198	98.51	0.43 (0.12, 1.51)	-
>40	48	3.39	4	8.33	44	91.67	2.60 (0.83, 8.12)	-
Wald test	-	-	-	-	-	-	-	16.42 (0.0057)
Affective disorder [b]								
No	1290	91.10	35	2.71	1255	97.29	Reference	-
Yes	126	8.90	3	2.38	123	97.62	0.87 (0.27, 2.88)	0.05 (0.8258)
Diabetes [b]								
No	1389	98.09	38	2.74	1351	97.26	Reference	-
Yes	27	1.91	0	0.00	27	100.00	0.00 (0.00, I)	0.00 (0.9868)
Gestational diabetes [c]								
No	1328	93.79	36	2.71	1292	97.29	Reference	-
Yes	88	6.21	2	2.27	86	97.73	0.83 (0.20, 3.52)	0.06 (0.8058)

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Neurotic disorder [b]								
No	1229	86.79	35	2.85	1194	97.15	Reference	-
Yes	187	13.21	3	1.60	184	98.40	0.56 (0.17, 1.83)	0.93 (0.3337)
Schizophrenia, schizotypal and delusional disorders [b]								
No	1415	99.93	38	2.69	1377	97.31	Reference	-
Yes	1	0.07	0	0.00	1	100.00	0.00 (0.00, I)	0.00 (0.9912)
Obesity [d]								
No	1400	98.87	38	2.71	1362	97.29	Reference	-
Yes	16	1.13	0	0.00	16	100.00	0.00 (0.00, I)	0.00 (0.9898)
CMV [c]								
No	1416	100.00	38	2.68	1378	97.32	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Rubella [c]								
No	1416	100.00	38	2.68	1378	97.32	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse prior to LMP2 [d]								
No	1413	99.79	38	2.69	1375	97.31	Reference	-
Yes	3	0.21	0	0.00	3	100.00	0.00 (0.00, I)	0.00 (0.9899)
Alcohol abuse during pregnancy [c]								
No	1414	99.86	38	2.69	1376	97.31	Reference	-
Yes	2	0.14	0	0.00	2	100.00	0.00 (0.00, I)	0.00 (0.9917)
Substance abuse prior to LMP2 [d]								
No	1410	99.58	37	2.62	1373	97.38	Reference	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Yes	6	0.42	1	16.67	5	83.33	7.42 (0.85, 65.11)	3.27 (0.0704)
Substance abuse during pregnancy [c]								
No	1412	99.72	37	2.62	1375	97.38	Reference	-
Yes	4	0.28	1	25.00	3	75.00	12.39 (1.26, 121.91)	4.65 (0.0310)
Smoking prior to LMP2 [d]								
No	1045	73.80	27	2.58	1018	97.42	Reference	-
Yes	180	12.71	5	2.78	175	97.22	1.08 (0.41, 2.83)	-
Missing	191	13.49	6	3.14	185	96.86	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	0.02 (0.8802)
Smoking during pregnancy [c]								
No	1188	83.90	34	2.86	1154	97.14	Reference	-
Yes	70	4.94	1	1.43	69	98.57	0.49 (0.07, 3.65)	-
Missing	158	11.16	3	1.90	155	98.10	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	0.48 (0.4877)
Maternal polypharmacy index prior to LMP2 [e] (categorical)								
0	910	64.27	20	2.20	890	97.80	Reference	-
1-4	474	33.47	15	3.16	459	96.84	1.45 (0.74, 2.87)	-
5-10	31	2.19	2	6.45	29	93.55	3.07 (0.68, 13.75)	-
>10	1	0.07	1	100.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	2.81 (0.4219)
Maternal polypharmacy index during pregnancy [c] (categorical)								
0	724	51.13	15	2.07	709	97.93	Reference	-

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
1-4	654	46.19	20	3.06	634	96.94	1.49 (0.76, 2.94)	-
5-10	38	2.68	3	7.89	35	92.11	4.05 (1.12, 14.65)	-
>10	0	0.00	0	0.00	0	0.00	-	-
Wald test	-	-	-	-	-	-	-	4.84 (0.0887)
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription								
No	1274	89.97	27	2.12	1247	97.88	Reference	-
Yes	142	10.03	11	7.75	131	92.25	3.88 (1.88, 8.00)	13.47 (0.0002)
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription								
No	1342	94.77	35	2.61	1307	97.39	Reference	-
Yes	74	5.23	3	4.05	71	95.95	1.58 (0.47, 5.25)	0.55 (0.4575)
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription								
No	453	31.99	11	2.43	442	97.57	Reference	-
Yes	963	68.01	27	2.80	936	97.20	1.16 (0.57, 2.36)	0.17 (0.6837)

NDD	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	815	57.56	17	2.09	798	97.91	Reference	-
Yes	601	42.44	21	3.49	580	96.51	1.70 (0.89, 3.25)	2.57 (0.1088)

CI: Confidence interval; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; NDD: Neurodevelopmental disorders; OR: Odds ratio
Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (NDD) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, 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) 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 20 Association between potential paternal risk factors/confounders and NDD; Primary outcome cohort in Norway

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Paternal risk factors/confounders								
Affective disorder [a]								
No	1158	81.78	30	2.59	1128	97.41	Reference	-
Yes	258	18.22	8	3.10	250	96.90	1.20 (0.55, 2.66)	0.21, 0.6469

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Bipolar affective disorder [a]								
No	1077	76.06	31	2.88	1046	97.12	Reference	-
Yes	339	23.94	7	2.06	332	97.94	0.71 (0.31, 1.63)	0.65, 0.4216
Mania [a]								
No	1403	99.08	38	2.71	1365	97.29	Reference	-
Yes	13	0.92	0	0.00	13	100.00	0.00 (0.00, I)	0.00, 0.9908
Neurotic disorder [a]								
No	1230	86.86	36	2.93	1194	97.07	Reference	-
Yes	186	13.14	2	1.08	184	98.92	0.36 (0.09, 1.51)	1.95, 0.1629
Schizophrenia, schizotypal and delusional disorders [a]								
No	1387	97.95	37	2.67	1350	97.33	Reference	-
Yes	29	2.05	1	3.45	28	96.55	1.30 (0.17, 9.84)	0.07, 0.7969
Substance abuse [c]								
No	1384	97.74	37	2.67	1347	97.33	Reference	-
Yes	32	2.26	1	3.13	31	96.88	1.17 (0.16, 8.83)	0.02, 0.8759
Paternal polypharmacy index [d] (categorical)								
0	775	54.73	19	2.45	756	97.55	Reference	-
1-4	602	42.51	18	2.99	584	97.01	1.23 (0.64, 2.36)	-
5-10	37	2.61	1	2.70	36	97.30	1.11 (0.14, 8.49)	-
>10	2	0.14	0	0.00	2	100.00	0.00 (0.00, I)	-
Wald test	-	-	-	-	-	-	-	0.37, 0.9454

NDD	Overall		Event		Non-event		Association	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Concomitant medications associated with valproate-indicated psychiatric conditions [c] -fathers with at least one prescription								
No	970	68.50	26	2.68	944	97.32	Reference	-
Yes	446	31.50	12	2.69	434	97.31	1.00 (0.50, 2.01)	0.00, 0.9912
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription								
No	535	37.78	15	2.80	520	97.20	Reference	-
Yes	881	62.22	23	2.61	858	97.39	0.93 (0.48, 1.80)	0.05, 0.8275
Father's age [e] (categorical)								
≤20 years	5	0.35	0	0.00	5	100.00	0.00 (0.00, I)	-
21-25	98	6.92	4	4.08	94	95.92	2.47 (0.73, 8.36)	-
26-30	331	23.38	14	4.23	317	95.77	2.56 (1.06, 6.18)	-
31-35	472	33.33	8	1.69	464	98.31	Reference	-
36-40	325	22.95	5	1.54	320	98.46	0.91 (0.29, 2.80)	-
>40	185	13.06	7	3.78	178	96.22	2.28 (0.82, 6.38)	-
Wald test	-	-	-	-	-	-	-	7.46, 0.1887
Year of offspring conception [f,g]								
2009-2013	650	45.90	29	4.46	621	95.54	Reference	-
2014-2019	766	54.10	9	1.17	757	98.83	0.25 (0.12, 0.54)	-
Wald test	-	-	-	-	-	-	-	12.60, 0.0004

CI: Confidence interval; CMV: Cytomegalovirus; NDD: Neurodevelopmental disorders; OR: Odds ratio

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

a) all available data prior to index date (childbirth)

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

3.2.1.6 Variable estimates from propensity score

This section supersedes section 10.5.1.6 from the final study report v1.1.

Variables found to be associated with the outcome were included in the PS models for the analyses of the Primary outcome cohort. This means all specified confounders for which an association with both the outcome and the exposure was observed and all specified risk factors (associated with the outcome but not the exposure) are included in the PS models (see section 9.7.3.2.3 of the study protocol for more details). If any unbalance for these variables remained after performing PS weighting, they were also included in the final Cox regression model if they were statistically significantly associated with both the exposure and the outcome, and if the number of events allowed it.

In the PS model estimated from logistic regression Table 21, offspring gender was not associated with the paternal exposure to valproate when compared to lamotrigine/levetiracetam (OR: 1.07, 95% CI: 0.82, 1.40, p=0.5956). From maternal risk factors/confounders, smoking during pregnancy (OR: 1.95, 95% CI: 1.09, 3.48, p=0.0235), and concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy (OR: 0.26, 95% CI: 0.09, 0.80, p=0.0192) were associated with the study exposure: offspring of mothers who smoked during pregnancy were more likely to have a father exposed to valproate; offspring of mothers who took concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy, were more likely to have a father exposed to lamotrigine/levetiracetam. Offspring with fathers with affective disorders (OR: 0.36, 95% CI: 0.22, 0.60, p<0.0001), bipolar affective disorder (OR: 0.53, 95% CI: 0.36, 0.79, p=0.0019), and neurotic disorders (OR: 0.48, 95% CI: 0.28, 0.85, p=0.0110), had a lower probability of being in the valproate exposure group. A random forest PS was performed to identify variable importance metrics, ie, two-way interactions, and variables presenting low index importance were not included in the PS logistic informed by random forest model (Table 57 in the Appendix).

Variables or interactions associated with NDD including ASD in the PS model from logistic regression informed by random forest were smoking during pregnancy (OR: 1.94, 95% CI: 1.09, 3.46, p=0.0246), concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy (OR: 0.27, 95% CI: 0.09, 0.82, p=0.0211), paternal affective disorder (OR: 0.37, 95% CI: 0.22, 0.61, p<0.0001), bipolar affective disorder (OR: 0.53, 95% CI: 0.36, 0.79, p=0.0017), and neurotic disorder (OR: 0.44, 95% CI: 0.25, 0.78, p=0.0050) (Table 58 in the Appendix).

Plots of each PS model are depicted in Figure 5, Figure 7 and Figure 8.

The PS model that best achieved a balance in the weighted exposure groups after using inverse probability of treatment weights was the PS model estimated from logistic regression, please see Table 59 and Figure 5. Thus, the logistic regression model was used to apply inverse probability of treatment weights in the effect estimation analysis (presented in Section 3.2.1.7).

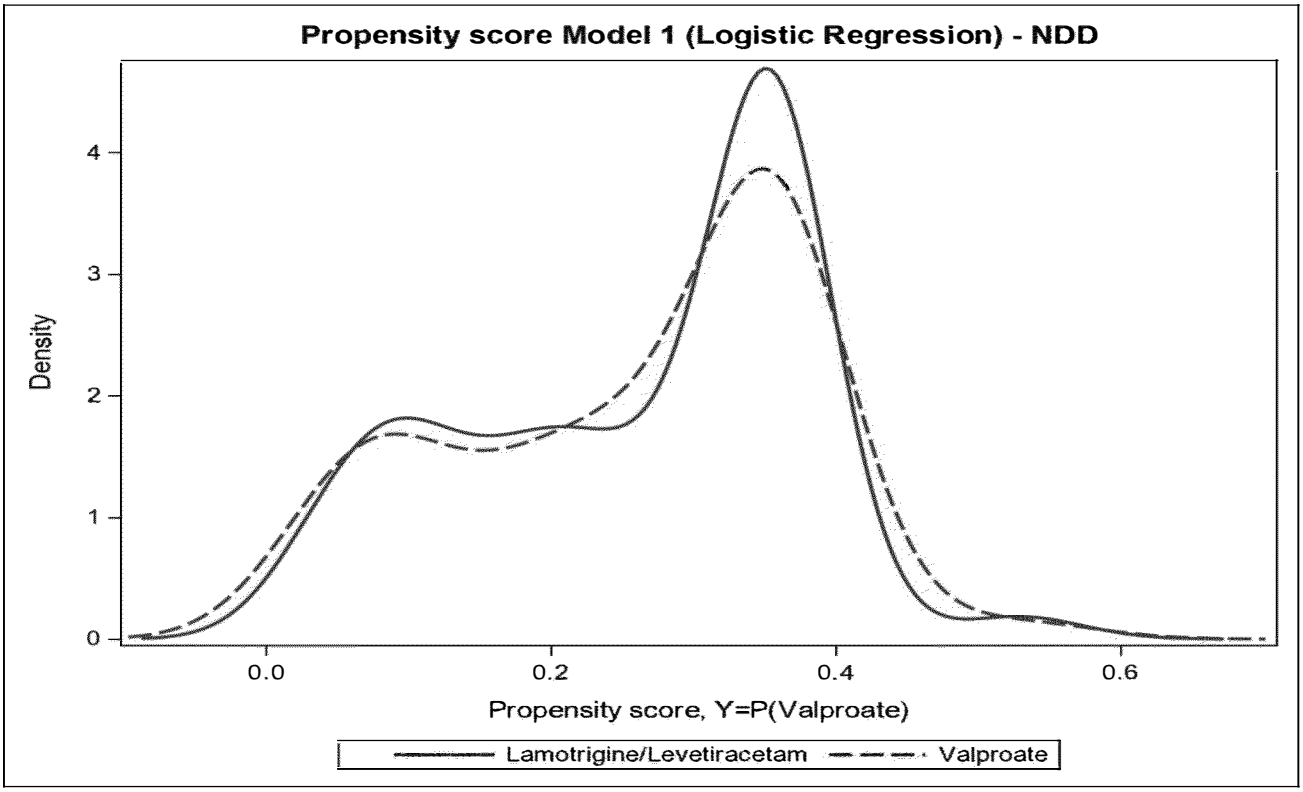
Table 21 Variable estimates from logistic regression propensity score model; Primary outcome cohort in Norway

NDD	Estimate		
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
Offspring risk factors/confounders			
Gender [b]			
Male	Reference	-	-
Female	1.07	0.82, 1.40	0.5956
Maternal risk factors/confounders			
Mother's age [b] (categorical)			
≤20 years	1.11	0.39, 3.13	0.8408
21-25	0.97	0.64, 1.46	0.8703
26-30	Reference	-	-
31-35	0.96	0.70, 1.32	0.7967
36-40	0.78	0.50, 1.21	0.2620
>40	0.43	0.17, 1.07	0.0696
Affective disorder [d]	0.62	0.34, 1.15	0.1278
Diabetes [d]	0.85	0.23, 3.15	0.8053
Gestational diabetes [e]	0.74	0.36, 1.53	0.4205
Neurotic disorder [d]	1.16	0.76, 1.79	0.4864
Obesity [f]	1.10	0.30 - 4.08	0.8896
Smoking during pregnancy [e]			
No	Reference	-	-
Yes	1.95	1.09, 3.48	0.0235
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.79	0.44, 1.42	0.4246
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.26	0.09, 0.80	0.0192
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] -mothers with at least one prescription	1.10	0.81, 1.48	0.5446
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.96	0.73, 1.28	0.7979
Paternal risk factors/confounders			
Affective disorder [d,g]	0.36	0.22, 0.60	<.0001
Bipolar affective disorder [d]	0.53	0.36, 0.79	0.0019
Neurotic disorder [d]	0.48	0.28, 0.85	0.0110
Schizophrenia, schizotypal and delusional disorders [d]	0.65	0.17, 2.45	0.5240
Substance abuse [f]	0.49	0.11, 2.22	0.3537

NDD		Estimate	
Variable (or interaction)[a]	**OR**	**95% CI**	**P-value**
Year of offspring conception [i,j]			
2009-2013	Reference	-	-
2014-2019	0.97	0.74, 1.27	0.8072

NDD: Neurodevelopmental disorders; CI: Confidence Interval; LMP2: Last menstrual period date plus 2 weeks; OR: Odds ratio
Legend: Odds ratios (OR), 95% confidence intervals (CI) and p-values were represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model were listed here, however some of the variables might not be included in the final set of variables.

a) candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful.
b) at index (childbirth)
c) between index and exit date
d) all available data prior to index date
e) during pregnancy (from LMP2 until index date)
f) 12 months lookback from LMP2
g) excluding bipolar affective disorder and mania
h) 3 months lookback from LMP2
i) at mother's LMP2
j) calendar years were grouped in each country according to the length of the study period



NDD: Neurodevelopmental disorders; PS: propensity score

Figure 5 Balance of PS Model 1- Logistic Regression; Primary outcome cohort in Norway

3.2.1.7 Effect estimation for NDD including ASD

This section supersedes section 10.5.1.7 from the final study report v1.1.

The effect estimation for NDD, including ASD, was assessed using a crude Cox regression model as per protocol (Table 22). In this model 1,401 offspring were included, 383 offspring in the valproate group and 1,018 in the lamotrigine/levetiracetam group, after the exclusion of 15 influential subjects. However, all those 15 influential subjects were offspring who experienced NDD including ASD events and were from the valproate group; their exclusion is due to the dfbeta[2] for each of the 15 offspring being above the desired threshold. This is due to the small number of events, especially in the valproate group, which causes instability in the model estimates when including or removing each of the offspring experiencing the outcome in the valproate group. Thus, the crude model was rerun without considering the dfbetas criterion (Table 23). This was a deviation from the protocol, but was decided to be performed though 1) due to the invalid HR estimate obtained from the crude Cox regression model, as all events in the valproate group were excluded (Table 22); and 2) to ensure comparability of the crude models across countries, the same methodology was applied for Denmark and Sweden, even though no influential subjects were identified in the crude models (see sections 10.3.1.7 and 10.4.1.6.1 of the final study report v1.1, respectively).

Consequently, the crude model was adapted, not considering the dfbetas criterion; it consisted of a total of 1,416 offspring (398 in the valproate group and 1,018 in the lamotrigine/levetiracetam group). Respectively, 3.8% (N=15) of offspring of the valproate group and 2.3% (N=23) of the lamotrigine/levetiracetam group presented a NDD including ASD event. In the crude analysis, no increased risk for NDD including ASD was observed in the offspring of fathers exposed to valproate compared to offspring of fathers exposed to lamotrigine/levetiracetam (HR: 1.60, 95% CI: 0.81, 3.15).

The effect estimation for NDD including ASD using PS-weighted Cox regression model was assessed in a total of 1,235 offspring, 325 offspring of valproate group and 910 of lamotrigine/levetiracetam group. Respectively, 4.0% (N=13) of offspring of the valproate group and 2.3% (N=21) of the lamotrigine/levetiracetam group presented an NDD including ASD event. In the PS-weighted Cox regression model, no increased risk for NDD including ASD was observed in offspring of fathers exposed to valproate compared to offspring of fathers exposed to the lamotrigine/levetiracetam group (HR: 1.76, 95% CI: 0.83, 3.71) (Table 24).

Table 25 presents the effect estimation for NDD including ASD using PS-weighted Cox regression model adjusted for the K-means exposure cluster (ie, trajectories with constant high exposure (A), and with constant low exposure (B), for further details on the K-means cluster please see Figure 3 and Table 12). In order to obtain estimates of the effect of valproate *vs* lamotrigine/levetiracetam in each cluster identified by the K-means algorithm, an interaction term between the K-means clusters variable and the main exposure variable was included in the model. The effect estimation was assessed in a total of 1,235 offspring. No increased risk for

[2] Dfbeta is a metric for evaluating the influence of a given observation on a covariate coefficient in the model: it measures the change in a regression coefficient when the i^{th} offspring is removed from the regression model. In the crude model, the only regression coefficient is the one related to the exposure group (valproate vs lamotrigine/levetiracetam): in this model therefore, dfbeta for i^{th} offspring = |regression coefficient calculated using all the data - regression_coefficient calculated excluding the i^{th} offspring|.
A commonly used criterion to consider one unit "influential" uses a threshold of ±2/sqrt(n) for the dfbeta (Belsley et al., 1980, p. 28) (1). This is a size-adjusted threshold, ie, in a sample of 1000, a given point will have less influence than in a sample of 100, all else equal.
In Norway, because of the small number of events and total offspring included in the model, all the offspring in the valproate paternal exposure group experiencing the outcome event had a dfbeta value above the desired threshold.

NDD including ASD was observed, for offspring of fathers exposed to valproate compared to offspring of fathers exposed to lamotrigine/levetiracetam, in the different cluster of exposure. Likewise, no interaction between exposure and paternal K-means cluster was observed.

In the analysis of effect estimation in cluster A (ie, trajectories with constant high exposure) 230 offspring from the valproate group, of which 3.9% (N=9) presented an NDD including ASD event and 702 from lamotrigine/levetiracetam, of which 2.1% (N=15) presented an NDD including ASD event, were considered. In cluster A, no increased risk for NDD including ASD was observed for offspring from fathers exposed to the valproate compared to offspring from fathers exposed to lamotrigine/levetiracetam (HR: 1.72, 95% CI: 0.69, 4.29). The effect estimated in cluster B (ie, constant low exposure) considered 95 offspring from the valproate group, of which 4.2% (N=4) presented an NDD including ASD event and 208 from lamotrigine/levetiracetam, of which 2.9% (N=6) presented an NDD including ASD event. In cluster B, no increased risk for NDD including ASD was observed for offspring from fathers exposed to the valproate compared to offspring from fathers exposed to lamotrigine/levetiracetam (HR: 1.79, 95% CI: 0.48-6.72) (Table 25).

Table 22 Effect estimation for neurodevelopmental disorders (NDD) using crude Cox regression model; Primary outcome cohort in Norway (considering the dfbetas criterion)

Variable	Total N	Number of events	Number of subjects included in the model (after excluding influential subjects) [a]		Model estimates		
	N	N	N	%	HR	95% CI	P-value
Valproate	383	0					
Lamotrigine/levetiracetam	1018	23					
Paternal exposure: valproate vs lamotrigine/levetiracetam	1416		1401	98.94	—	(0.00, 0.00)	<.0001

ASD: Autism Spectrum Disorder; CI: Confidence interval; HR: Hazard ratio; NDD: Neurodevelopmental Disorders
Legend: a) Influential subjects were identified using the dfbetas for the main exposure coefficient
Out of the total N = 1416 offspring, N = 15 influential subjects were identified using the dfbetas and excluded, resulting in a sample size of N = 1401 offspring. The N = 15 excluded offspring included all NDD, including ASD events in the valproate group. The exclusion of these events led to an invalid crude HR (95% CI) estimate.

Table 23 Effect estimation for neurodevelopmental disorders (NDD) using crude Cox regression model; Primary outcome cohort in Norway[1]

Variable	Total N	Number of events	Number of subjects included in the model		Model estimates		
	N	N	N	%	HR	95% CI	P-value
Valproate	398	15					
Lamotrigine/levetiracetam	1018	23					
Paternal exposure: valproate vs lamotrigine/levetiracetam	1416		1416	100.00	1.60	(0.81, 3.15)	0.178

CI: Confidence interval; HR: Hazard ratio
Legend: [1] The results reported in this table comprise the crude HR (95% CI) without excluding influential subjects and this approach represented a deviation from the study protocol

Table 24 Effect estimation for neurodevelopmental disorders (NDD) using Propensity Score weighted Cox regression model; Primary outcome cohort in Norway

Variable	Total N	Number of events	Model estimates[1]		
			HR	95% CI	P-value
Valproate	325	13			
Lamotrigine/levetiracetam	910	21			
Paternal exposure: valproate vs Lamotrigine/levetiracetam	1235		1.76	(0.83, 3.71)	0.139

CI: Confidence interval; HR: Hazard ratio; LMP2: Last menstrual period date plus 2 weeks
Legend: [1] **The logistic regression PS model includes all variables from Table 21, as follows: Offspring risk factors/confounders:** "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2, "Year of offspring conception"

Table 25 Effect estimation for neurodevelopmental disorders (NDD) using Propensity Score weighted Cox regression model adjusted for K-means exposure cluster; Primary outcome cohort in Norway

Variable	Total N	Number of events	Model estimates		
			HR	95% CI	P-value
Valproate – cluster A	230	9			
Lamotrigine/levetiracetam – cluster A	702	15			
Valproate – cluster B	95	4			
Lamotrigine/levetiracetam – cluster B	208	6			
Paternal exposure: valproate vs lamotrigine/levetiracetam	1235		-	-	0.244
K-means exposure cluster:					
K-means exposure cluster B	-		-	-	0.8155
Paternal exposure * cluster:					
Valproate * cluster B	-		-	-	0.963
Effect of valproate across K-means cluster:					
Valproate vs lamotrigine/levetiracetam in cluster A	-		1.72	(0.69, 4.29)	-
Valproate vs lamotrigine/levetiracetam in cluster B	-		1.79	(0.48, 6.72)	-

CI: Confidence interval; HR: Hazard ratio; LMP2: Last menstrual period date plus 2 weeks
Legend: Cluster A: constant high exposure; Cluster B: constant low exposure.
[1]**The logistic regression PS model includes all variables from Table 21, described as follows: Offspring risk factors/confounders:** "Gender"; **Maternal risk factors/confounders:** "Mother's age"; "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception"

3.2.1.8 Case assessment

This section supersedes section 10.5.1.8 from the final study report v1.1.

Overall, considering all the groups of paternal exposure, 2.9% of the offspring were identified as cases of NDD including ASD, of which the majority (71.4%) were considered in the case assessment as a probable case (meeting the criteria of multiple diagnosis for NDD including ASD recorded during the follow-up). The same was observed considering valproate and lamotrigine/levetiracetam group, with a slightly higher percentage of NDD including ASD being observed in the valproate group. Considering the valproate group, 4.1% of the offspring were identified as cases of NDD including ASD, of which 70.6% were classified in the case assessment as probable cases. Considering the lamotrigine/levetiracetam group, 2.4% of the offspring were identified as cases of NDD including ASD, of which 72.0% were classified in the case assessment as probable cases (Table 26).

Table 26 Case assessment in Norway

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of pregnancies	**N=413**		**N=1058**		**N=896**		**N=162**		**N=1471**	
Number of offspring identified as cases of NDD including ASD*	17	4.12%	25	2.36%	21	2.34%	4	2.47%	42	2.86%
Case assessment										
Possible**	5	29.41%	7	28.00%	6	28.57%	1	25.00%	12	28.57%
Probable**	12	70.59%	18	72.00%	15	71.43%	3	75.00%	30	71.43%

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

3.2.1.9 Exploratory Analyses – NDD including ASD cohort

This section supersedes section 10.5.1.9 from the final study report v1.1.

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

This section supersedes section 10.5.1.9.1 from the final study report v1.1.

Results from exploratory analysis 5 are presented in Table 60 to Table 68 in Section 8.1.6 (see Appendix). The analyses were performed in order to answer Exploratory Objective 5, which aimed to describe the risk factors and frequency of NDD, including ASD in offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine/levetiracetam) and lamotrigine/levetiracetam (in combination with other AEDs excluding valproate) at the time of the conception. The analysis was performed in the Primary outcome cohort for explorative objective 5. Findings were compared to results obtained from the Primary cohort for comparative analysis (main analysis).

For the exploratory analyses 5, the inclusion criterion was all offspring from the Primary outcome cohort (N=3,300). After additional exclusions, a total of 204 offspring were included in this analysis, with 45 in valproate and 159 in lamotrigine/levetiracetam group (Figure 9 and Table 60).

None of the offspring was born extremely preterm (gestational age <28 weeks) or had extremely low (<1000 g) birth weight in the valproate polytherapy group, while these counts were 1 (0.6%) and 2 (1.3%) offspring in the lamotrigine/levetiracetam polytherapy group, respectively. Gestational age and birth weight were similarly distributed between the exposure groups. Compared with the valproate monotherapy in the main analysis (Table 15), a higher proportion of females were observed in the valproate polytherapy group (57.8% vs. 48.0% female in the main analyses) (Table 60).

The proportion of NDD including ASD was higher in the offspring paternally exposed to valproate polytherapy (6.7% vs 3.8% in lamotrigine/levetiracetam group) (Table 61) compared with those on monotherapy in the main analysis (3.8% valproate and 2.3% lamotrigine/levetiracetam) (Section 3.2.1.7).

Compared with the main analyses (Table 16), in this exploratory analysis mothers presented similar median age (30 years) (Table 62), and lower proportion of comorbidities was also observed in the lamotrigine/levetiracetam polytherapy (when compared to lamotrigine/levetiracetam monotherapy group) such as neurotic disorders (6.3% vs. 13.5%) and affective disorders (6.3% vs 10.1%). The frequency of these comorbidities was similar in this exploratory analysis compared with the main analysis in the valproate group (Table 63).

Compared to those included in the main analyses, fathers included in this exploratory analysis (Table 17) presented similar median age in the valproate (32 years vs. 34 years, respectively) and in the lamotrigine/levetiracetam groups (34 years vs. 33 years, respectively) (Table 64). Higher proportion of comorbidities was observed in the valproate group in the main analysis as compared with the valproate group in the exploratory analysis 5: bipolar disorder (14.3% vs. 2.2%), and neurotic disorder (7.5% vs. 4.4%). Similar observation was also noted in the lamotrigine/levetiracetam monotherapy (main analysis) and lamotrigine/levetiracetam polytherapy (exploratory analysis 5): affective disorder excluding bipolar affective

disorder and mania (22.3% vs. 5.7%), bipolar affective disorder (27.7% vs. 3.8%), and neurotic disorder (15.3% vs. 8.8%). The most frequent indication for AED treatment was epilepsy in the exploratory analysis 5 (valproate 82.2% and lamotrigine/levetiracetam polytherapy 83.7%) (Table 66). The distribution of potential risk factors and confounders for NDD including ASD by paternal exposure of polytherapy group were examined for the Primary outcome cohort for Explorative Objective 5. Results of univariable analyses are presented in Table 66 to Table 68.

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 of the final study report v1.1 for an overview.

As observed in the main analyses (Table 15), none of the offspring characteristics were associated with paternal polytherapy exposure (Table 66).

When compared to the main analysis (Table 16), less maternal characteristics were associated to paternal exposure in the exploratory analyses 5 (Table 67). One maternal risk factor was statistically associated with paternal polytherapy exposure: age (categorical, p=0.0189).

Also, less paternal characteristics were associated to paternal exposure in the exploratory analyses 5 (Table 68), when compared to the main analyses (Table 17). One paternal characteristic, concomitant medications associated with valproate-indicated psychiatric conditions – fathers with at least one prescription (p=0.0094) was statistically associated with paternal polytherapy exposure.

The distribution of potential risk factors and confounders were examined by NDD including ASD group in the Primary outcome cohort for explorative objective 5. Due to a low number of NDD events (<10), the following tables were not produced: Association between potential offspring risk factors/confounders and NDD; primary outcome; Association between potential maternal risk factors/confounders and NDD; primary outcome; and Association between potential paternal risk factors/confounders and NDD; primary outcome.

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

This section supersedes section 10.5.1.9.2 from the final study report v1.1.

Results from exploratory analysis 6 are presented in Table 69 to Table 77 in Section 8.1.7. The analysis was performed in the Primary outcome cohort for explorative objective 6. This objective aimed to describe the risk factors and frequency of NDD including ASD, in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception. Findings were compared to results obtained from the Primary cohort for comparative analysis (main analyses).

For the exploratory analyses 6, the inclusion criterion was all offspring from the Primary outcome cohort for comparative analysis (N=1,416). After additional exclusions, a total of 2 offspring were included in this analysis, with 1 in valproate and 1 in lamotrigine/levetiracetam group (Figure 10 and Table 69).

In exploratory analysis 6, the sample size was significantly lower than the main analysis, hence direct comparison with the main analysis may not be ideal. But overall, both offspring were born at term in the valproate group and the lamotrigine/levetiracetam group (Table 69). In exploratory analysis 6, the mean

follow-up time was longer for the offspring in the valproate group (4.9 years) than lamotrigine/levetiracetam group (1.9 years) (Table 69). Regarding clinical characteristics, none of the offspring had comorbidities, which might be attributed to the small sample size (Table 70).

In this cohort, no event of NDD including ASD was observed (Table 70).

The mother's age at childbirth was lower in the valproate than in the lamotrigine/levetiracetam group (30 vs 33, respectively) (Table 71). Neither of the mothers in the valproate group or lamotrigine/levetiracetam group had any comorbidities. Maternal polypharmacy index prior to LMP2 was 0.0 in both valproate and lamotrigine/levetiracetam group (Table 72).

The father's age was lower in the valproate than in the lamotrigine/levetiracetam group (31 vs. 34, respectively) (Table 73). The father in the valproate group did not have any comorbidities, and in the lamotrigine/levetiracetam group, the father had neurotic disorder. Paternal polypharmacy index prior to LMP2 was 0.0 in valproate and 2.0 in lamotrigine/levetiracetam group (Table 74). Due to small sample size (n=2), comparing these findings with the main analysis may not be informative.

The distribution of potential risk factors and confounders for NDD including ASD by paternal exposure to valproate and levetiracetam were examined for the Primary outcome cohort for explorative objective 6. Results of univariable analyses are presented in Table 75 to Table 77).

All the variables examined were initially selected based on literature review and clinical expert opinion, see section 9.4.4 in the final study report v1.1 for an overview.

As observed in the main analyses (Table 15), none of the offspring characteristics were associated with paternal exposure (Table 75).

Also, none of the maternal and paternal characteristics were associated with paternal exposure to valproate or lamotrigine/levetiracetam (Table 76 and Table 77).

3.2.1.10 Sensitivity Analyses for NDD including ASD

This section supersedes section 10.5.1.10 from the final study report v1.1.

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

Findings from extending the exposure window for the primary outcome to 6 months (sensitivity analysis 1), excluding offspring with low birth weight or born prior to 8th month for the primary cohort (sensitivity analysis 3), simple pairwise comparisons for the exposure groups (valproate vs lamotrigine, sensitivity analysis 5), comparing PS-matched model with covariate adjusted model for the primary cohort (sensitivity analysis 6), examining the effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy (sensitivity analysis 7) and using a narrow definition of the outcome (sensitivity analysis 11) were similar with the results observed in the main analyses (see Table 27).

After the exclusion of influential subjects, the crude Cox regression models for sensitivity analyses 1, 3, 5, 7, and 11 led to invalid HR estimates due to the exclusion of all NDD including ASD events in the valproate group. The crude model was rerun without considering the dfbetas criterion for sensitivity analysis 11 (which is a deviation from the protocol, and the model was adapted due to very small numbers). In sensitivity analysis 5, offspring in the levetiracetam exposure group had no NDD event resulting non-interpretable HR for crude Cox regression model and PS-weighted Cox regression model adjusted for K-means exposure model (cluster B). See Table 27 for further details.

Table 27 Summary of main analysis and sensitivity analysis of Neurodevelopmental Disorders (NDD) including Autism Spectrum Disorders (ASD) in Norway

Analyses*	Population considered	HR (95% CI) estimates		HR (95% CI) estimates by cluster of exposure	
		Crude	Adjusted*	Cluster A	Cluster B
Main analysis N sample = 1416	See Figure 1	1.60 (0.81, 3.15)[1]	1.76 (0.83, 3.71)	1.72 (0.69, 4.29)	1.79 (0.48, 6.72)
Sensitivity analysis 1 N sample = 1479	Extended risk window of paternal valproate exposure (6 months)	NA[2]	1.86 (0.87, 3.99)	1.83 (0.66, 5.04)	1.91 (0.60, 6.13)
Sensitivity analysis 3 N sample = 1403	Exclusion of offspring with low birth weight or born prior to 8th months	NA[2]	1.84 (0.87, 3.88)	1.85 (0.74, 4.61)	1.78 (0.47, 6.69)
Sensitivity analysis 5[A] N sample = 1261	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	NA[2]	1.68 (0.77, 3.67)	1.77 (0.68, 4.63)	1.47 (0.39, 5.52)
Sensitivity analysis 5[B] N sample = 553	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	NA[3]	1.75 (0.40, 7.73)	1.46 (0.32, 6.72)	NA[4]
Sensitivity analysis 6 N sample = 1416	Comparison of PS-weighted model with covariate adjustment model	–	1.60 (0.81, 3.15)[1]	–	–
Sensitivity analysis 7 N sample = 1436	Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy	NA[6]	1.92 (0.97, 3.81)	NA[6]	NA[6]
Sensitivity analysis 11 N sample = 1415	Narrow definition of NDD	1.63 (0.80, 3.32)[7]	1.87 (0.86, 4.08)	1.82 (0.69, 4.83)	1.85 (0.49, 6.94)

AED: Antiepileptic drug; ASD: Autism Spectrum Disorder; CI: Confidence interval; HR: Hazard Ratio; NA: Not available; NDD: Neurodevelopment disorders; PS: Propensity score; 5[A] analysis comparing valproate and lamotrigine; 5[B] analysis comparing valproate and levetiracetam

Legend: [1] Out of the total N = 1416 offspring, N = 15 influential subjects were identified using the dfbetas and excluded, resulting in a sample size of N = 1401 offspring. The N = 15 excluded offspring included all NDD, including ASD events in the valproate group. The exclusion of these events led to an invalid HR (95% CI) estimate. The model was rerun without considering the dfbetas criterion, and the findings were reported.

[2] Influential subjects were identified using the dfbetas and excluded (N = 15). The N = 15 excluded offspring included all NDD, including ASD events in the valproate group. The exclusion of these events led to an invalid crude HR (95% CI) estimate.

[3] Due to the sample size, the estimated HR was not interpretable (>100,000). Crude and adjusted models do not always use the same population leading to differences in the sample size and number of events in the models.

[4] In cluster B there are no events in the levetiracetam group, which gives a very high HR for valproate vs. levetiracetam.

[5] Effect estimation for NDD using crude Cox regression model and propensity score weighted Cox regression model adjusted for K-means exposure cluster could not be produced due to the low number of events (less than 30 and 50 events, respectively).

[6] Out of the total N = 1415 offspring, N = 14 influential subjects were identified using the dfbetas and excluded, resulting in a sample size of N = 1401 offspring. The N = 14 excluded offspring included all NDD, including ASD events in the valproate group. The exclusion of these events led to an invalid crude HR (95% CI) estimate. The crude model was rerun without considering the dfbetas criterion, which represents a deviation from the protocol, and the findings were reported.

***The logistic regression PS models used in sensitivity analysis include variables following described:**

Sensitivity analysis 1: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's Age", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy"; mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Neurotic disorder", "Substance abuse prior to LMP2"; fathers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions", "Year of offspring conception"

Sensitivity analysis 3: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders**: "Mother's Age", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy"; mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of "Concomitant medications associated with neuropsychiatric adverse events", "Year of offspring conception"

Sensitivity analysis 5[A]: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's Age", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity" ", "Smoking during pregnancy"; mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", fathers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions", "Year of offspring conception"

Sensitivity analysis 5[B]: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Neurotic disorder", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Year of offspring conception". Unbalanced variables after PS weighting were not added to this model due to the small number of NDD events in the cohort.

Sensitivity analysis 6: No covariates were significantly associated with both the exposure and the outcome and therefore none of them was included in the model; the resulting model was therefore the same as the crude one, and it was not estimated due to the small number of events after removal of outliers and influential subjects.

Sensitivity analysis 7: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's Age", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy"; "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2"; "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy"; "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2"; "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Bipolar affective disorder"; "Neurotic disorder"; "Schizophrenia, schizotypal and delusional disorders"; Concomitant medications associated with neuropsychiatric adverse events prior to LMP2"; "Year of offspring conception"

Sensitivity analysis 11: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders**: "Mother's Age", "Diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy"; mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Substance abuse prior to LMP2", "Year of offspring conception"

Validation of the assumption that individuals are exposed to one DDD per day (sensitivity analysis 8) was performed among fathers who had prescriptions of AED for epilepsy, the estimated treatment durations (estimated from the number of prescriptions as described in section 9.9.4.8 of the final study report v1.1) was longer for fathers treated with levetiracetam 194.2 (±140.8) days followed by those treated with lamotrigine 186.1 (±131.4) days and valproate 135.9 (±83.1) days. The actual observed time between prescriptions was longer for fathers prescribed with valproate 99.6 (±33.6) days followed by levetiracetam 88.8 (±33.5) days and lamotrigine 87.0 (±34.4) days. The ratio (expected vs observed) was 0.99 for valproate, 0.75 for lamotrigine, and 0.70 for levetiracetam. Under the assumption of perfect compliance of each father, the ratio for valproate was within the approximation range 0.8-1.20 which indicate the real daily dose prescribed in congruence with the World Health Organisation (WHO) DDD. However, the ratio for lamotrigine and levetiracetam depart from the range indicating the real daily dose prescribed diverge from the WHO DDD (see Table 28 for further details).

Sensitivity analysis 8 was also performed among fathers who had prescriptions of AED without indication for epilepsy, the estimated treatment durations (expected) was longer for fathers treated with lamotrigine 182.9 (±158.5) days followed by those treated with levetiracetam 149.3 (±72.8) days, and valproate 132.2 (±112.2) days. Time between prescriptions (observed) was longer for fathers prescribed with lamotrigine 92.9 (±33.7) days, valproate 89.9 (±30.5) days, and levetiracetam 82.0 (±41.8) days. The ratio (expected vs observed) was 1.16 for valproate, 0.92 for lamotrigine and 0.67 for levetiracetam (Table 28). Under the assumption of perfect compliance of each father, the ratios for valproate and lamotrigine were within the approximation range 0.80-1.20 which indicate the real daily dose prescribed was in congruence with the WHO DDD. However, the ratio for levetiracetam depart from the range indicating the real daily dose prescribed diverge from the WHO DDD (see Table 28 for further details).

Table 28 Distribution of estimated treatment durations and time between prescriptions for fathers with/without an indication for epilepsy; Primary outcome cohort in Norway

	Distribution of estimated treatment durations and time between prescriptions for fathers with an indication for epilepsy			**Distribution of estimated treatment durations and time between prescriptions for fathers without an indication for epilepsy; primary outcome**		
	Paternal exposure group			**Paternal exposure group**		
NDD	**Valproate**	**Lamotrigine**	**Levetiracetam**	**Valproate**	**Lamotrigine**	**Levetiracetam**
Number of offspring	**N=239**	**N=291**	**N=148**	**N=174**	**N=605**	**N=14**
Estimated treatment durations (expected)	135.94 (83.11)	186.09 (131.42)	194.24 (140.76)	132.16 (112.18)	182.93 (158.46)	149.33 (72.84)
Time between prescriptions (observed)	99.57 (33.58)	86.97 (34.40)	88.79 (33.52)	89.87 (30.50)	92.92 (33.73)	82.00 (41.76)
Ratio (expected vs observed)	0.99	0.75	0.70	1.16	0.92	0.67

NDD: Neurodevelopmental disorders.
The expected and observed treatment duration and ratio is calculated separately for each offspring, and then the average is calculated and reported.

In sensitivity analysis 10, the mean paternal cumulative exposure to valproate was 64.8 (±23.7) days, while in the lamotrigine/levetiracetam group mean paternal cumulative exposure 69.6 (±22.6) days (See Table 29). The low number of events per covariate (n<10) after the exclusion of influential subjects prevented the Cox covariate adjustment model to be conducted. Therefore, the following tables were not produced: Effect estimation for NDD using Cox covariate adjustment model, Primary outcome cohort in Norway; Effect estimation for NDD using Cox covariate adjustment model for valproate and lamotrigine treatment group, Primary outcome cohort in Norway; and Primary outcome cohort in Norway Effect estimation for NDD using Cox covariate adjustment model for levetiracetam treatment group, Primary outcome cohort in Norway.

Table 29 Paternal cumulative exposure to Antiepileptic Drugs (AEDs) by paternal exposure group; Primary outcome cohort in Norway

	Paternal exposure group									
NDD	**Valproate**		**Lamotrigine/levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of pregnancies	**N=398**		**N=1018**		**N=863**		**N=155**		**N=1416**	
Cumulative exposure to AEDs	N	%	N	%	N	%	N	%	N	%
Low	129	32.41	340	33.40	289	33.49	50	32.26	476	33.62
Medium	95	23.87	69	6.78	70	8.11	105	67.74	157	11.09
High	174	43.72	609	59.82	504	58.40	0	0.00	783	55.30
Mean (SD)	64.75 (23.67)		69.55 (22.57)		68.87 (22.87)		73.34 (20.51)		68.20 (22.98)	
Median (25^{th} - 75^{th} percentile)	75.50 (48.00, 84.00)		84.00 (58.00, 84.00)		84.00 (57.00, 84.00)		84.00 (73.00, 84.00)		84.00 (56.00, 84.00)	
Min, max	1.00, 84.00		2.00, 84.00		2.00, 84.00		2.00, 84.00		1.00, 84.00	

AED: antiepileptic drugs; NDD: neurodevelopmental disorders; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of pregnancies represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics will be described in relationship to the exposure window for each individual offspring. Percentages are calculated over the total number of offspring.

3.2.2 Congenital Malformations

This section supersedes section 10.5.2 from the final study report v1.1.

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

This section supersedes section 10.5.2.1 from the final study report v1.1.

The results presented below (Table 30 to Table 35) are of analyses performed in the Secondary outcome cohort for descriptive analyses (Flowchart presented Figure 2).

Overall, the majority of offspring were male (52.1%; 49.5% in those paternally exposed to valproate and 53.1% in those paternally exposed to lamotrigine/levetiracetam), born at term between 37-41 weeks of gestational age (89.6%; 87.5% in those paternally exposed to valproate and 90.4% in those paternally exposed to lamotrigine/levetiracetam) and weighing ≥2500 g (96.1%, similar in both exposure groups (Table 30). Regarding CM, 14.7% were diagnosed with CM during the overall study follow-up. In the group paternally exposed to valproate, 7.0% had a major CM, 9.4% had a diagnosis of minor CM. In the lamotrigine/levetiracetam paternally exposed group, 8.3% had a major CM, 8.4% had a diagnosis of minor CM (Table 31).

The most frequent adverse pregnancy outcome associated with a diagnosis of CM was intrauterine growth retardation (IUGR), both for the valproate paternal exposure group (14.3%) and the lamotrigine/levetiracetam paternal exposure group (9.7%) (Table 31).

Overall, the median (IQR) age of mothers from the Secondary outcome cohort for descriptive analyses at childbirth was 30.0 (27.0, 34.0) years, similar in both exposure groups (Table 32).

The most prevalent clinical characteristics recorded in mothers prior to childbirth were gestational diabetes (observed in 1.9% and in 2.3% of mothers of offspring from fathers exposed to valproate and of offspring from fathers exposed to lamotrigine/levetiracetam, respectively) and diabetes (observed in 1.7% and in 2.0% of mothers of offspring from fathers exposed to valproate and of offspring from fathers exposed to lamotrigine/levetiracetam, respectively) (Table 33).

Smoking prior to LMP2 was recorded in 15.1% and in 12.3% of mothers of offspring from fathers exposed to valproate and of offspring from fathers exposed to lamotrigine/levetiracetam, respectively; it is to be noted that the corresponding proportions of missing values were 15.9% and 12.5%, respectively for this maternal covariate. Smoking during pregnancy was recorded in 6.7% and in 4.5% of mothers of offspring from fathers exposed to valproate and from fathers exposed to lamotrigine/levetiracetam, respectively (Table 33); the corresponding proportions of missing values were 13.0% and 10.1%. Exposure to AEDs in mothers prior to LMP2 and during pregnancy was very low.

Concomitant medications associated with teratogenic activity/fetal toxicity prior to LMP2 were reported in 28.1% and 29.5% of mothers of offspring from fathers exposed to valproate and of offspring from fathers exposed to lamotrigine/levetiracetam, respectively. Correspondingly, concomitant medications associated with teratogenic activity/fetal toxicity during pregnancy were reported in 27.9% and in 32.5% of mothers of offspring from fathers

exposed to valproate and of offspring from fathers exposed to lamotrigine/levetiracetam respectively (Table 33). These exposures were considered as risk factors for CM and excluded for the comparative analysis.

Regarding fathers' demographic characteristics, the overall median (IQR) age of fathers at childbirth was 33.0 (29.0, 37.0) years; (32.0 [29.0-36.0] in the valproate group and 33.0 [29.0-37.0] in the lamotrigine/levetiracetam group). A larger proportion of offspring in the lamotrigine/levetiracetam group were conceived in the latest year of the study time period, compared with the valproate group (Table 34). Regarding fathers' indication for AED treatment, epilepsy was reported in 57.7% of paternal valproate exposed group and in 41.6% of paternal lamotrigine/levetiracetam exposed group (Table 35).

The K-means algorithm, analyzing DDD trajectories in fathers exposed to AEDs 3 months prior to conception (ie, prior to LMP2) identified 2 different clusters (Figure 6), one with constant high exposure (cluster A) and one with constant low exposure to AEDs (cluster B). A higher proportion of fathers were in cluster A (70.0%) as compared to cluster B (30.1%) in the valproate exposed group. In the lamotrigine/levetiracetam exposed group, similar distribution was observed among clusters (76.4% in cluster A and 23.6% in cluster B) (Table 35).

The proportion of fathers exposed to drugs with teratogenic activity/fetal toxicity in the 3 months lookback from LMP2 was 29.1% in the valproate group and 39.8% in the lamotrigine/levetiracetam group (Table 35). Nevertheless, this exposure was considered as risk factor for CM and offspring from parents being exposed to these teratogenic drugs were excluded for the comparative analysis.

Table 30 Offspring demographic characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=1,476)

	Paternal exposure group									
CM	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of pregnancies	**N=416**		**N=1060**		**N=897**		**N=163**		**N=1476**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Gestational age (weeks)										
<28 (extremely preterm)	2	0.48	5	0.47	5	0.56	0	0.00	7	0.47
28-31 (very preterm)	3	0.72	6	0.57	5	0.56	1	0.61	9	0.61
32-36 (moderate to late preterm)	24	5.77	44	4.15	36	4.01	8	4.91	68	4.61
37-41 (at term)	364	87.50	958	90.38	812	90.52	146	89.57	1322	89.57
≥42 (post-term)	23	5.53	47	4.43	39	4.35	8	4.91	70	4.74
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Birth weight (g)										
<1000 (extremely low)	3	0.72	8	0.75	7	0.78	1	0.61	11	0.75
1000-1499 (very low)	1	0.24	4	0.38	3	0.33	1	0.61	5	0.34
1500-2499 (low)	15	3.61	27	2.55	22	2.45	5	3.07	42	2.85
≥2500	397	95.43	1021	96.32	865	96.43	156	95.71	1418	96.07
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gender										
Male	206	49.52	563	53.11	466	51.95	97	59.51	769	52.10
Female	210	50.48	497	46.89	431	48.05	66	40.49	707	47.90
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM: Congenital malformation

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

Table 31 Offspring clinical characteristics paternal exposure group; Secondary outcome cohort in Norway (N=1,476)

CM	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of pregnancies	N=416		N=1060		N=897		N=163		N=1476	
	N	%	N	%	N	%	N	%	N	%
Comorbidities [a]										
Congenital CMV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital Herpes Simplex	0	0.00	1	0.09	1	0.11	0	0.00	1	0.07
Congenital rubella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Congenital varicella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Fœtal alcohol syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Outcomes										
CM	63	15.14	154	14.53	129	14.38	25	15.34	217	14.70
Major CM (at any time)	29	6.97	88	8.30	75	8.36	13	7.98	117	7.93
Minor CM (at any time)	39	9.38	89	8.40	72	8.03	17	10.43	128	8.67
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]										
Stillbirth	3	4.76	3	1.95	2	1.55	1	4.00	6	2.76
Spontaneous abortion [c]	0	0.00	2	1.30	2	1.55	0	0.00	2	0.92
Intrauterine growth retardation	9	14.29	15	9.74	13	10.08	2	8.00	24	11.06
Perinatal mortality	4	6.35	3	1.95	2	1.55	1	4.00	7	3.23

CM: Congenital malformations; CMV: Cytomegalovirus

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

a) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date

b) denominator for the percentage is the number of offspring with CM.

Table 32 Maternal demographic characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=1,476)

CM Number of pregnancies	Paternal exposure group									
	Valproate N=416		Lamotrigine/ levetiracetam N=1060		Lamotrigine N=897		Levetiracetam N=163		Total (valproate + lamotrigine/ levetiracetam) N=1476	
	N	%	N	%	N	%	N	%	N	%
Mother's age [a]										
≤20 years	11	2.64	21	1.98	19	2.12	2	1.23	32	2.17
21-25	66	15.87	160	15.09	133	14.83	27	16.56	226	15.31
26-30	150	36.06	372	35.09	303	33.78	69	42.33	522	35.37
31-35	135	32.45	324	30.57	284	31.66	40	24.54	459	31.10
36-40	49	11.78	156	14.72	139	15.50	17	10.43	205	13.89
>40	5	1.20	27	2.55	19	2.12	8	4.91	32	2.17
Mean (SD)	29.89 (4.90)		30.42 (5.12)		30.49 (5.10)		30.04 (5.26)		30.27 (5.07)	
Median (25^{th} - 75^{th} percentile)	30 (27.00, 33.00)		30 (27.00, 34.00)		30 (27.00, 34.00)		29 (26.00, 33.00)		30 (27.00, 34.00)	
Min, max	18.00, 43.00		17.00, 45.00		17.00, 45.00		17.00, 43.00		17.00, 45.00	
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM: Congenital malformations; Min: Minimum; Max: Maximum; SD: Standard deviation.
Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (12^{th} week of gestation in Norway, 22^{nd} week of gestation in Denmark)

Table 33 Maternal clinical characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=1,476)

	Paternal exposure group									
CM	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of pregnancies	**N=416**		**N=1060**		**N=897**		**N=163**		**N=1476**	
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**
Comorbidities										
Diabetes [a]	7	1.68	21	1.98	21	2.34	0	0.00	28	1.90
Epilepsy [a]	7	1.68	15	1.42	12	1.34	3	1.84	22	1.49
Obesity [b]	6	1.44	10	0.94	10	1.11	0	0.00	16	1.08
CMV [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Folate deficiency [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Gestational diabetes [c]	8	1.92	24	2.26	23	2.56	1	0.61	32	2.17
Herpes simplex virus [c]	1	0.24	1	0.09	1	0.11	0	0.00	2	0.14
Rubella [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Toxoplasmosis [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Varicella [c]	0	0.00	1	0.09	1	0.11	0	0.00	1	0.07
Lifestyle characteristics										
Alcohol abuse prior to LMP2 [b]	1	0.24	2	0.19	2	0.22	0	0.00	3	0.20
Alcohol abuse during pregnancy [c]	1	0.24	1	0.09	1	0.11	0	0.00	2	0.14
Substance abuse prior to LMP2 [b]	2	0.48	4	0.38	4	0.45	0	0.00	6	0.41
Substance abuse during pregnancy [c]	2	0.48	1	0.09	1	0.11	0	0.00	3	0.20
Smoking prior to LMP2 [b]										
Yes	63	15.14	130	12.26	118	13.15	12	7.36	193	13.08
No	287	68.99	798	75.28	666	74.25	132	80.98	1085	73.51
Missing	66	15.87	132	12.45	113	12.60	19	11.66	198	13.41
Smoking during pregnancy [c]										

CM	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of pregnancies	N=416		N=1060		N=897		N=163		N=1476	
	N	%	N	%	N	%	N	%	N	%
Yes	28	6.73	48	4.53	47	5.24	1	0.61	76	5.15
No	334	80.29	905	85.38	760	84.73	145	88.96	1239	83.94
Missing	54	12.98	107	10.09	90	10.03	17	10.43	161	10.91
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	15	1.42	15	1.67	0	0.00	15	1.02
Levetiracetam	0	0.00	2	0.19	2	0.22	0	0.00	2	0.14
Barbiturates and derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Benzodiazepine derivatives	1	0.24	0	0.00	0	0.00	0	0.00	1	0.07
Carboxamide derivatives	3	0.72	2	0.19	1	0.11	1	0.61	5	0.34
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	0	0.00	18	1.70	17	1.90	1	0.61	18	1.22
Exposure to AEDs during pregnancy [c]										
Valproate	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Lamotrigine	0	0.00	13	1.23	13	1.45	0	0.00	13	0.88
Levetiracetam	0	0.00	2	0.19	2	0.22	0	0.00	2	0.14
Barbiturates and derivatives	1	0.24	0	0.00	0	0.00	0	0.00	1	0.07
Hydantoin derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00

CM	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of pregnancies	N=416		N=1060		N=897		N=163		N=1476	
	N	%	N	%	N	%	N	%	N	%
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	3	0.72	2	0.19	1	0.11	1	0.61	5	0.34
Fatty acid derivatives	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Other antiepileptics	0	0.00	16	1.51	15	1.67	1	0.61	16	1.08
K means cluster prior to LMP2 [d]										
Unexposed	413	99.28	1041	98.21	880	98.10	161	98.77	1454	98.51
Group A[1]	2	0.48	14	1.32	12	1.34	2	1.23	16	1.08
Group B[1]	1	0.24	5	0.47	5	0.56	0	0.00	6	0.41
K means cluster during pregnancy [c]										
Unexposed	412	99.04	1042	98.30	881	98.22	161	98.77	1454	98.51
Group A[2]	2	0.48	11	1.04	9	1.00	2	1.23	13	0.88
Group B[2]	2	0.48	7	0.66	7	0.78	0	0.00	9	0.61
Maternal exposure to teratogenic activity/fetal toxicity prior to LMP2 [d] - mothers with at least one prescription	117	28.13	313	29.53	267	29.77	46	28.22	430	29.13
Maternal exposure to teratogenic activity/fetal toxicity during pregnancy [d] - mothers with at least one prescription	116	27.88	344	32.45	294	32.78	50	30.67	460	31.17

AED: Antiepileptic Drug; CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks
Legend: Cluster A[1]: constant moderate exposure, Cluster B[1]: constant low exposure
Cluster A[2]: constant low exposure, Cluster B[2]: moderate to low exposure

Table 34 Paternal demographic characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=1,476)

	Paternal exposure group									
CM Number of pregnancies	Valproate N=416		Lamotrigine/ levetiracetam N=1060		Lamotrigine N=897		Levetiracetam N=163		Total (valproate + lamotrigine/ levetiracetam) N=1476	
	N	%	N	%	N	%	N	%	N	%
Father's age [a]										
≤20 years	4	0.96	7	0.66	5	0.56	2	1.23	11	0.75
21-25	37	8.89	82	7.74	67	7.47	15	9.20	119	8.06
26-30	116	27.88	266	25.09	219	24.41	47	28.83	382	25.88
31-35	142	34.13	340	32.08	283	31.55	57	34.97	482	32.66
36-40	86	20.67	229	21.60	204	22.74	25	15.34	315	21.34
>40	31	7.45	136	12.83	119	13.27	17	10.43	167	11.31
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00
Mean (SD)	32.45 (5.67)		33.47 (6.25)		33.66 (6.29)		32.42 (5.91)		33.19 (6.11)	
Median (25^{th} - 75^{th} percentile)	32 (29.00, 36.00)		33 (29.00, 37.00)		33 (29.00, 38.00)		32 (28.00, 36.00)		33 (29.00, 37.00)	
Min, max	19.00, 52.00		17.00, 63.00		17.00, 63.00		20.00, 51.00		17.00, 63.00	
Year of offspring conception [b]										
2009	24	5.77	63	5.94	57	6.35	6	3.68	87	5.89
2010	46	11.06	118	11.13	109	12.15	9	5.52	164	11.11
2011	43	10.34	89	8.40	78	8.70	11	6.75	132	8.94
2012	51	12.26	110	10.38	95	10.59	15	9.20	161	10.91
2013	42	10.10	104	9.81	83	9.25	21	12.88	146	9.89
2014	47	11.30	114	10.75	96	10.70	18	11.04	161	10.91
2015	49	11.78	116	10.94	93	10.37	23	14.11	165	11.18
2016	40	9.62	111	10.47	96	10.70	15	9.20	151	10.23
2017	34	8.17	101	9.53	81	9.03	20	12.27	135	9.15
2018	32	7.69	109	10.28	89	9.92	20	12.27	141	9.55

CM	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of pregnancies	N=416		N=1060		N=897		N=163		N=1476	
	N	%	N	%	N	%	N	%	N	%
2019	8	1.92	25	2.36	20	2.23	5	3.07	33	2.24

CM: Congenital malformations; Min: Minimum; Max: Maximum; SD: Standard deviation.
Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at index (12th week of gestation in Norway, 22nd week of gestation in Denmark)
b) at mother's LMP2

Table 35 Paternal clinical characteristics by paternal exposure group; Secondary outcome cohort in Norway (N=1,476)

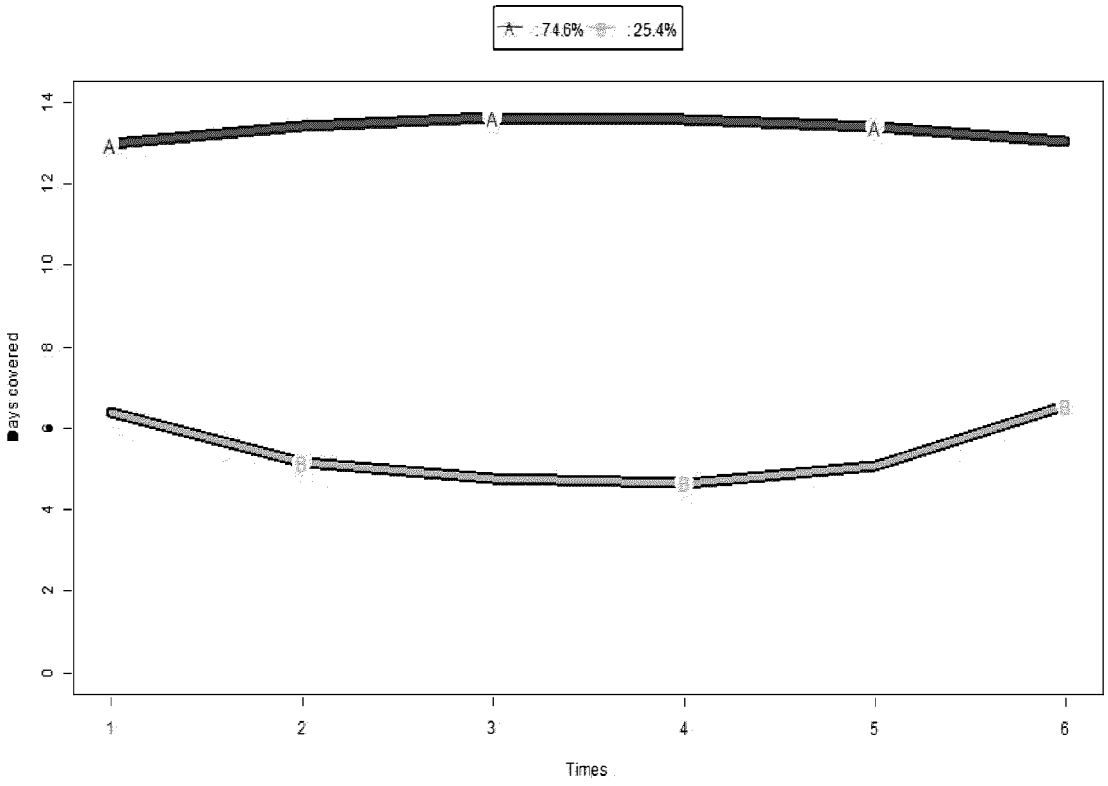
CM	Paternal exposure group									
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)	
Number of pregnancies	N=416		N=1060		N=897		N=163		N=1476	
	N	%	N	%	N	%	N	%	N	%
Medication use										
AED indication										
Epilepsy	240	57.69	441	41.60	292	32.55	149	91.41	681	46.14
Bipolar affective disorder and mania	56	13.46	290	27.36	290	32.33	0	0.00	346	23.44
Other/unknown	120	28.85	329	31.04	315	35.12	14	8.59	449	30.42
K means cluster [a]										
Cluster A	291	69.95	810	76.42	675	75.25	135	82.82	1101	74.59
Cluster B	125	30.05	250	23.58	222	24.75	28	17.18	375	25.41
Paternal exposure to teratogenic activity/fetal toxicity [a]	121	29.09	422	39.81	382	42.59	40	24.54	543	36.79

AED: Antiepileptic drugs; CM: Congenital malformations; LMP2: Last menstrual period date plus 2 weeks

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

a) 3-months lookback from LMP2

Cluster A: constant high exposure; Cluster B: constant low exposure



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

Figure 6 Mean defined daily dose (DDD) trajectories for fathers exposed to Antiepileptic Drugs (AEDs) in the 3 months lookback prior to Last Menstrual Period Date Plus 2 weeks LMP2 in Norway

3.2.2.2 Cumulative incidence proportion

This section supersedes section 10.5.2.2 from the final study report v1.1.

Considering the overall study follow-up, the incidence proportion of CM (major and minor as composite) among offspring paternally exposed to valproate (n=63, 15.1%, 95% CI: 11.7, 18.6) appeared to be higher than those paternally exposed to lamotrigine/levetiracetam (n=154, 14.5, 95% CI: 12.4, 16.7). The CIs were slightly overlapping, which does not support differences between exposure groups (Table 36).

Table 36 Cumulative incidence proportion (risk) of CM by paternal exposure group; Secondary outcome cohort in Norway (N=1,476)

		Paternal exposure group				
CM		**Valproate**	**Lamotrigine /levetiracetam (composite)**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up in years from index date						
	N	416	1060	897	163	1476
0-1 years	n	45	102	85	17	147
	n/N*100	10.82 (7.83, 13.80)	9.62 (7.85, 11.40)	9.48 (7.56, 11.39)	10.43 (5.74, 15.12)	9.96 (8.43, 11.49)
	N	360	907	770	137	1267
1-2 years	n	7	22	19	3	29
	n/N*100	1.94 (0.52, 3.37)	2.43 (1.42, 3.43)	2.47 (1.37, 3.56)	2.19 (-0.26, 4.64)	2.29 (1.47, 3.11)
	N	323	795	681	114	1118
2-3 years	n	4	8	7	1	12
	n/N*100	1.24 (0.03, 2.44)	1.01 (0.31, 1.70)	1.03 (0.27, 1.79)	0.88 (-0.83, 2.59)	1.07 (0.47, 1.68)
	N	287	699	602	97	986
3-4 years	n	1	6	4	2	7
	n/N*100	0.35 (-0.33, 1.03)	0.86 (0.17, 1.54)	0.66 (0.02, 1.31)	2.06 (-0.77, 4.89)	0.71 (0.19, 1.23)
	N	249	594	512	82	843
4-5 years	n	1	2	2	0	3
	n/N*100	0.40 (-0.38, 1.19)	0.34 (-0.13, 0.80)	0.39 (-0.15, 0.93)	0.00 (0.00, 0.00)	0.36 (-0.05, 0.76)
	N	207	502	438	64	709
5-6 years	n	3	5	5	0	8
	n/N*100	1.45 (-0.18, 3.08)	1.00 (0.13, 1.86)	1.14 (0.15, 2.14)	0.00 (0.00, 0.00)	1.13 (0.35, 1.91)
	N	168	391	342	49	559
6-7 years	n	0	1	1	0	1
	n/N*100	0.00 (0.00, 0.00)	0.26 (-0.24, 0.76)	0.29 (-0.28, 0.86)	0.00 (0.00, 0.00)	0.18 (-0.17, 0.53)
	N	130	299	266	33	429

		Paternal exposure group				
CM		**Valproate**	**Lamotrigine /levetiracetam (composite)**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up in years from index date						
7-8 years	n	1	4	2	2	5
	n/N*100	0.77 (-0.73, 2.27)	1.34 (0.04, 2.64)	0.75 (-0.29, 1.79)	6.06 (-2.08, 14.20)	1.17 (0.15, 2.18)
	N	82	209	191	18	291
8-9 years	n	1	4	4	0	5
	n/N*100	1.22 (-1.16, 3.60)	1.91 (0.06, 3.77)	2.09 (0.06, 4.12)	0.00 (0.00, 0.00)	1.72 (0.23, 3.21)
	N	49	126	118	8	175
9-10+ [a] 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	416	1060	897	163	1476
Overall (0-10 years)	n	63	154	129	25	217
	n/N*100	15.14 (11.70, 18.59)	14.53 (12.41, 16.65)	14.38 (12.08, 16.68)	15.34 (9.81, 20.87)	14.70 (12.90, 16.51)

CM: Congenital malformations

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

a) For countries where the index date was the 12th or 22nd week of pregnancy, follow-up time in years was longer than age in years, therefore some offspring were >10 years of follow-up by the time they were censored upon 10th birthday. For this reason, the table shows '10+ years'.

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

This section supersedes section 10.5.2.3 from the final study report v1.1.

Association between potential covariates (risk factors and confounders) for CM and paternal exposure group was assessed in the Secondary outcome cohort for comparative analyses. Results of the crude associations are shown in Table 37 to Table 39.

For the offspring, none of the characteristics a priori considered as potential risk factor/confounder was associated with paternal exposure (Table 37).

None of the maternal characteristics a priori considered as potential risk factors or confounders (see Table 5 of the final study report v1.1) was significantly associated with paternal exposure to valproate or lamotrigine/levetiracetam (Table 38).

Likewise, none of the paternal characteristics a priori considered as a potential risk factor or confounder was significantly associated with paternal exposure (Table 39).

Table 37 Association between potential offspring risk factors/confounders for CM by paternal exposure group; Secondary outcome cohort in Norway (N=513)

	Paternal exposure group										Comparison
CM	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/levetiracetam)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=169**		**N=344**		**N=277**		**N=67**		**N=513**		**N=513**
	N	**%**	**N**	**%**	**N**	**%**	**N**	**%**	**N**	**%**	
Offspring risk factors/ confounders[a]											
Congenital CMV	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital Herpes Simplex	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital rubella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital toxoplasmosis	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Congenital varicella	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Fetal alcohol syndrome	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-

CM: Congenital malformations; CMV: Cytomegalovirus
Legend: Number of 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 analyzed 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) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 38 Association between potential maternal risk factors/confounders for CM by paternal exposure group; Secondary outcome cohort in Norway (N=513)

	Paternal exposure group										Comparison
CM	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=169		N=344		N=277		N=67		N=513		N=513
	N	%	N	%	N	%	N	%	N	%	
Maternal risk factors/ confounders											
Mother´s age [a] (categorical)											
≤20 years	1	0.59	7	2.03	5	1.81	2	2.99	8	1.56	-
21-25	21	12.43	50	14.53	39	14.08	11	16.42	71	13.84	-
26-30	73	43.20	123	35.76	92	33.21	31	46.27	196	38.21	-
31-35	56	33.14	105	30.52	90	32.49	15	22.39	161	31.38	-
36-40	18	10.65	51	14.83	45	16.25	6	8.96	69	13.45	-
>40	0	0.00	8	2.33	6	2.17	2	2.99	8	1.56	-
Test statistics	-	-	-	-	-	-	-	-	-	-	9.16 (0.1027)
Mother´s age [a] (continuous)											
Mean (SD)	30.09 (4.12)		30.35 (5.03)		30.59 (5.01)		29.36 (5.03)		30.26 (4.75)		42666.00 (0.6264)*
Median (25th - 75th percentile)	30 (28.00, 33.00)		30 (27.00, 34.00)		31 (27.00, 34.00)		29 (26.00, 32.00)		30 (27.00, 33.00)		-
Min, max	20.00, 40.00		17.00, 43.00		17.00, 43.00		17.00, 43.00		17.00, 43.00		-
Missing	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Diabetes [b]	0	0.00	2	0.58	2	0.72	0	0.00	2	0.39	1.00 (1.0000)*
Obesity [c]	2	1.18	2	0.58	2	0.72	0	0.00	4	0.78	0.60 (0.6015)*
Alcohol abuse prior to LMP2 [c]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Alcohol abuse during pregnancy [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-

CM	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=169		N=344		N=277		N=67		N=513		N=513
	N	%	N	%	N	%	N	%	N	%	
Substance abuse prior to LMP2 [c]	0	0.00	1	0.29	1	0.36	0	0.00	1	0.19	1.00 (1.0000)*
Substance abuse during pregnancy [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Smoking prior to LMP2 [c]											
No	123	72.78	264	76.74	211	76.17	53	79.10	387	75.44	-
Yes	19	11.24	34	9.88	28	10.11	6	8.96	53	10.33	-
Missing	27	15.98	46	13.37	38	13.72	8	11.94	73	14.23	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	0.35 (0.5526)
Smoking during pregnancy [d]											
No	138	81.66	289	84.01	230	83.03	59	88.06	427	83.24	-
Yes	11	6.51	15	4.36	14	5.05	1	1.49	26	5.07	-
Missing	20	11.83	40	11.63	33	11.91	7	10.45	60	11.70	-
Test statistics without 'Missing' category	-	-	-	-	-	-	-	-	-	-	1.11 (0.2925)
CMV [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Folate deficiency [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Gestational diabetes [d]	2	1.18	2	0.58	2	0.72	0	0.00	4	0.78	0.60 (0.6015)*
Herpes simplex virus [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Rubella [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-

CM	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=169		N=344		N=277		N=67		N=513		N=513
	N	%	N	%	N	%	N	%	N	%	
Toxoplasmosis [d]	0	0.00	0	0.00	0	0.00	0	0.00	0	0.00	-
Varicella [d]	0	0.00	1	0.29	1	0.36	0	0.00	1	0.19	1.00 (1.0000)*

CM: Congenital malformations; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; 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 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 analyzed 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 (12th week of gestation in Norway, 22nd week of gestation in Denmark)
b) all available data prior to index date
c) 12-months lookback from LMP2
d) during pregnancy (from LMP2 until the earliest of the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)

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

Table 39 Association between potential paternal risk factors/confounders for CM by paternal exposure group; Secondary outcome cohort in Norway (N=513)

CM	Paternal exposure group										Comparison
	Valproate		Lamotrigine/ levetiracetam		Lamotrigine		Levetiracetam		Total (valproate + lamotrigine/ levetiracetam)		Valproate vs Lamotrigine /levetiracetam
Number of pregnancies	N=169		N=344		N=277		N=67		N=513		N=513
	N	%	N	%	N	%	N	%	N	%	
Paternal risk factors/confounders											
Father´s age [a] (categorical)											
≤20 years	0	0.00	4	1.16	2	0.72	2	2.99	4	0.78	-
21-25	8	4.73	27	7.85	18	6.50	9	13.43	35	6.82	-
26-30	54	31.95	90	26.16	71	25.63	19	28.36	144	28.07	-

CM	Paternal exposure group										Comparison
Number of pregnancies	Valproate N=169		Lamotrigine/ levetiracetam N=344		Lamotrigine N=277		Levetiracetam N=67		Total (valproate + lamotrigine/ levetiracetam) N=513		Valproate vs Lamotrigine /levetiracetam N=513
	N	%	N	%	N	%	N	%	N	%	
31-35	57	33.73	107	31.10	82	29.60	25	37.31	164	31.97	-
36-40	40	23.67	79	22.97	70	25.27	9	13.43	119	23.20	-
>40	10	5.92	37	10.76	34	12.27	3	4.48	47	9.16	-
Test statistics	-	-	-	-	-	-	-	-	-	-	8.09 (0.1511)
Father´s age [a] (continuous)											
Mean (SD)	32.90 (5.11)	-	33.12 (5.99)	-	33.61 (6.05)	-	31.09 (5.33)	-	33.04 (5.71)	-	42633.50 (0.6120)*
Median (25^{th} - 75^{th} percentile)	32.00 (29.00, 36.00)	-	33.00 (29.00, 37.00)	-	33.00 (29.00, 38.00)	-	32.00 (27.00, 35.00)	-	32.00 (29.00, 37.00)	-	-
Min, max	22.00, 52.00	-	20.00, 53.00	-	20.00, 53.00	-	20.00, 44.00	-	20.00, 53.00	-	-
Year of offspring conception [b,c]											
2009-2013	79	46.75	168	48.84	138	49.82	30	44.78	247	48.15	-
2014-2019	90	53.25	176	51.16	139	50.18	37	55.22	266	51.85	-
Test statistics	-	-	-	-	-	-	-	-	-	-	0.20 (0.6559)

CM: Congenital malformations; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; 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 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 analyzed 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 (12^{th} week of gestation in Norway, 22^{nd} week of gestation in Denmark)
b) at mother's LMP2
c) calendar years will be grouped in each country according to the length of the study period

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

3.2.2.4 Association between potential offspring risk factors/confounders and CM

This section supersedes section 10.5.2.4 from the final study report v1.1.

Association between covariates (potential risk factors/confounders) and occurrence of CM was assessed in the Secondary outcome cohort for comparative analyses. Results of crude associations are shown in Table 40 to Table 42.

None of the offspring or paternal characteristics were found to be associated with CM event in Norway (Table 40 and Table 42).

For maternal characteristics (Table 41), only smoking during pregnancy (OR: 3.21, 95% CI: 1.33, 7.74, p=0.0096) was associated with CM.

Table 40 Association between potential offspring risk factors/confounders and CM; Secondary outcome cohort in Norway (N=513)

CM	Overall		Event		Non-event		Event vs non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Offspring risk factors/confounders [a]								
Congenital CMV								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital Herpes Simplex								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital rubella								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital toxoplasmosis								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Congenital varicella								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Fetal alcohol syndrome								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-

CM: Congenital malformations; CMV: Cytomegalovirus; OR: Odds ratio; CI: Confidence interval

Legend: Percentages were calculated over the total number of offspring. The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, 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.

Table 41 Association between potential maternal risk factors/confounders and CM; Secondary outcome cohort in Norway

CM	Overall		Event		Non-event		Event vs Non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Maternal risk factors/confounders								
Mother's age [a] (categorical)								
≤20 years	8	1.56	1	12.50	7	87.50	0.86 (0.10, 7.24)	-
21-25	71	13.84	8	11.27	63	88.73	0.76 (0.33, 1.76)	-
26-30	196	38.21	28	14.29	168	85.71	Reference	-
31-35	161	31.38	22	13.66	139	86.34	0.95 (0.52, 1.73)	-
36-40	69	13.45	10	14.49	59	85.51	1.02 (0.47, 2.22)	-
>40	8	1.56	1	12.50	7	87.50	0.86 (0.10, 7.24)	-
Wald test	0	0.00	0	0.00	0	0.00	-	0.47, 0.9933
Diabetes [b]								
No	511	99.61	69	13.50	442	86.50	Reference	-
Yes	2	0.39	1	50.00	1	50.00	6.41 (0.40, 103.61)	1.71, 0.1909
Obesity [c]								
No	509	99.22	69	13.56	440	86.44	Reference	-
Yes	4	0.78	1	25.00	3	75.00	2.13 (0.22, 20.73)	0.42, 0.5163
Alcohol abuse prior to LMP2 [c]								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Alcohol abuse during pregnancy [d]								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Substance abuse prior to LMP2 [c]								
No	512	99.81	70	13.67	442	86.33	Reference	-
Yes	1	0.19	0	0.00	1	100.00	0.00 (0.00, I)	0.00, 0.9914

CM	Overall		Event		Non-event		Event vs Non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Substance abuse during pregnancy [d]								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Smoking prior to LMP2 [c]								
No	387	75.44	48	12.40	339	87.60	Reference	-
Yes	53	10.33	10	18.87	43	81.13	1.64 (0.77, 3.48)	-
Missing	73	14.23	12	16.44	61	83.56	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	1.67, 0.1957
Smoking during pregnancy [d]								
No	427	83.24	52	12.18	375	87.82	Reference	-
Yes	26	5.07	8	30.77	18	69.23	3.21 (1.33, 7.74)	-
Missing	60	11.70	10	16.67	50	83.33	-	-
Wald test without 'Missing' category	-	-	-	-	-	-	-	6.70, 0.0096
CMV [d]								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Folate deficiency [d]								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Gestational diabetes [d]								
No	509	99.22	70	13.75	439	86.25	Reference	-
Yes	4	0.78	0	0.00	4	100.00	0.00 (0.00, I)	0.00, 0.9888
Herpes simplex virus [d]								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-

CM	Overall		Event		Non-event		Event vs Non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics, p-value
Rubella [d]								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Toxoplasmosis [d]								
No	513	100.00	70	13.65	443	86.35	-	-
Yes	0	0.00	0	0.00	0	0.00	-	-
Varicella [d]								
No	512	99.81	70	13.67	442	86.33	Reference	-
Yes	1	0.19	0	0.00	1	100.00	0.00 (0.00, I)	0.00, 0.9914

CM: Congenital malformations; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; OR: Odds ratio; CI: Confidence interval

Legend: The overall column represents the number and percentage of offspring with each characteristic (percentage was calculated over the total number of offspring). The columns Event/Non-Event represent the number and percentage of events and non-events (CM) in each subgroup defined by the characteristic (percentage was calculated over the number of offspring with the characteristic, 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 (12th week of gestation in Norway, 22nd week of gestation in Denmark)

b) all available data prior to index date

c) 12-months lookback from LMP2

during pregnancy (from LMP2 until the earliest of the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)

Table 42 Association between potential paternal risk factors/confounders and CM; Secondary outcome cohort in Norway

CM	Overall		Event		Non-event		Event vs non-event	
	N	%	N	%	N	%	OR (95% CI)	Test statistics (p-value)
Paternal risk factors / confounders for CM								
Father's age [a] (categorical)								
≤20 years	4	0.78	0	0.00	4	100.00	0.00 (0.00, I)	-
21-25	35	6.82	3	8.57	32	91.43	0.64 (0.18, 2.27)	-
26-30	144	28.07	23	15.97	121	84.03	1.29 (0.68, 2.45)	-
31-35	164	31.97	21	12.80	143	87.20	Reference	-
36-40	119	23.20	15	12.61	104	87.39	0.98 (0.48, 2.00)	-
>40	47	9.16	8	17.02	39	82.98	1.40 (0.57, 3.39)	-
Wald test	-	-	-	-	-	-	-	2.04, 0.8439
Year of offspring conception [b,c]								
2009-2013	247	48.15	34	13.77	213	86.23	Reference	-
2014-2019	266	51.85	36	13.53	230	86.47	0.98 (0.59, 1.62)	-
Wald test	-	-	-	-	-	-	-	0.01, 0.9392

CI: Confidence interval; CM: Congenital malformations; LMP2: Last menstrual period date plus 2 weeks; 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 (CM) 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 (12th week of gestation in Norway, 22nd week of gestation in Denmark)

b) at mother's LMP2

calendar years will be grouped in each country according to the length of the study period

3.2.2.5 Variable estimates from propensity score

This section supersedes section 10.5.2.5 from the final study report v1.1.

The PS logistic model did not converge due to a quasi-complete separation exacerbated by the low event numbers. Also, in the random forest model, all values for variable importance were 0 after the exclusion of outliers. For these reasons it was not possible to produce the following results and tables: Variable estimates from logistic regression PS model; Variable importance metric from random forest PS model; Variable estimates from logistic regression informed by random forest PS model; Balance of risk factors/confounders between offspring weighted using PS scores obtained with logistic regression; Balance of risk factors/confounders between offspring weighted using PS scores obtained with random decision forest PS model; Balance of risk factors/confounders between offspring weighted using PS scores obtained with logistic regression informed by random forest PS model; Effect estimation for CM using PS-weighted logistic model; and Effect estimation for CM using PS-weighted logistic model on offspring with concordant K-means exposure cluster. Likewise, the following figure was also not produced: Balance of PS Model 1- Logistic Regression; Secondary outcome cohort in Norway.

Only the effect estimation for CM using the crude logistic regression was generated and is presented in Table 43.

3.2.2.6 Effect estimation for Congenital Malformation

This section supersedes section 10.5.2.6 from the final study report v1.1.

The effect estimation for CM was assessed by using crude logistic regression model as presented in Table 43. In this model 513 subjects were included, with 169 offspring in the valproate group and 344 in the lamotrigine/levetiracetam group. The number of offspring with CM in the valproate and lamotrigine/levetiracetam group was 24 (14.2%) and 46 (13.4%), respectively. The OR of CM was 1.06 (95% CI: 0.62, 1.82) between offspring of fathers exposed to valproate when compared to offspring of fathers exposed to lamotrigine/levetiracetam.

Table 43 Effect estimation for congenital malformations (CM) using crude logistic model; Secondary outcome cohort in Norway.

Variable	Total N	Number of events	Model estimates		
	N	N	OR	95% CI	P-value
Valproate	169	24			
Lamotrigine/levetiracetam	344	46			
Paternal exposure: valproate vs lamotrigine/levetiracetam	513		1.06	(0.62, 1.82)	0.8326

OR: Odds ratio; CI: Confidence interval

3.2.2.7 Exploratory Analyses - CM cohort

This section supersedes section 10.5.2.7 from the final study report v1.1.

3.2.2.7.1 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Exploratory analysis 5 for CM)

This section supersedes Section 10.5.2.7.1 from the final study report v1.1.

Results from exploratory analysis 5 are presented in Table 78 to Table 86 in Section 8.1.8. The analysis was performed in the Secondary outcome cohort for explorative objective 5, in order to answer Exploratory Objective 5, which aimed to describe the risk factors and frequency of CM in offspring paternally exposed to valproate (in combination with other AEDs excluding lamotrigine/levetiracetam) and lamotrigine/levetiracetam (in combination with other AEDs excluding valproate) at the time of the conception.

For the exploratory analyses 5, the inclusion criterion was all offspring from the Secondary outcome cohort (N=3,315). After additional exclusions, a total of 35 offspring were included in this analysis, with 3 in valproate and 32 in lamotrigine/levetiracetam group (Figure 11).

In exploratory analysis 5, the sample size was significantly lower than the main analysis, hence direct comparison with the main analysis may not be ideal. Overall, all offspring were born at term in the valproate polytherapy group (100%) while 90.6% born at term in the lamotrigine/levetiracetam polytherapy (Table 78). Majority of offspring in the main analysis was also born at term (Table 30). Regarding clinical characteristics, none of the offspring had comorbidities which might be attributed to the small sample size (Table 79).

Median age of mothers at childbirth was lower in the valproate polytherapy than in the lamotrigine/levetiracetam polytherapy (26.0, IQR 21.0, 30.0 vs. 28.5, IQR 26.0, 33.0, respectively) (Table 80). None of the mothers in the valproate polytherapy had comorbidities, and in the lamotrigine/levetiracetam polytherapy, one mother had gestational diabetes in exploratory analysis 5. Smoking prior to LMP2 was 0.0% in both valproate and lamotrigine/levetiracetam polytherapy. Smoking during pregnancy was 0.0% in the valproate polytherapy and 3.1% in the lamotrigine/levetiracetam polytherapy (Table 81). Due to small sample size (N=35), comparing these findings with the main analysis may not be informative.

Median age of fathers was lower in the valproate polytherapy than in the lamotrigine/levetiracetam polytherapy (27.0, IQR 25.0, 32.0 vs. 32.0, IQR 28.0, 34.5, respectively) in exploratory analysis 5 (Table 82). Epilepsy was the most common indication for valproate (100.0%) polytherapy and lamotrigine/levetiracetam polytherapy (90.6%) (Table 83).

The distribution of potential risk factors and confounders for CM by paternal exposure to valproate polytherapy and lamotrigine/levetiracetam polytherapy were examined for the Secondary outcome cohort for explorative objective 5. Results of univariable analyses are presented in Table 84 to Table 86.

All the variables examined were initially selected based on literature review and clinical expert opinion, see Section 9.4.4 in the study report v1.1 for an overview.

As observed in the main analyses (Table 37, Table 38, and Table 39), none of the offspring, maternal and paternal characteristics were associated with paternal exposure (Table 84, Table 85, and Table 86).

3.2.2.7.2 Paternal exposure to valproate or lamotrigine/levetiracetam in discordant siblings (Exploratory analysis 6)

This section supersedes Section 10.5.2.7.2 from the final study report v1.1.

Results from exploratory analysis 6 are presented in Table 87 to Table 92 in Section 8.1.9. The analysis was performed in the Secondary outcome cohort for explorative objective 6. This objective aimed to describe the risk factors and frequency of CM, in paternally and maternally matched exposure-discordant (valproate vs lamotrigine/levetiracetam monotherapy) siblings at conception.

For the exploratory analyses 6, the inclusion criterion was all offspring from the Secondary outcome cohort for comparative analysis (N=513). After additional exclusions, a total of 1 offspring were included in this analysis, with 0 in valproate and 1 in lamotrigine/levetiracetam group (Figure 12 and Table 87).

In exploratory analysis 6, the sample size is significantly lower than the main analysis and there was no single offspring in the valproate group, hence direct comparison with the main analysis may not be ideal. But overall, the 1 offspring included in the lamotrigine/levetiracetam group, was born at term, had birth weight ≥2500 gram, and was female (Table 87). No comorbidities were reported in this exploratory analysis (Table 88).

The mother's age at childbirth was 25 years in the lamotrigine/levetiracetam group (Table 89). No maternal comorbidities and no smoking was reported in either prior to LMP2 or during pregnancy (Table 90).

The father's age at childbirth was 30 years in the lamotrigine/levetiracetam group (Table 91). The father had an AED indication for epilepsy in the lamotrigine/levetiracetam group (Table 92).

Results for exploratory analysis 8 are not reported in this final report. For further details, please see the addendum to the final study report v1.1.

3.2.2.8 Sensitivity analyses for CM

This section supersedes section 10.5.2.8 from the final study report v1.1.

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

Sensitivity analysis 4 was performed for the CM handling missing CM diagnosis comparing valproate with lamotrigine/levetiracetam. Overall, the findings in the crude logistic regression model (OR: 1.06, 95% CI: 0.62, 1.82) and PS-weighted logistic model on offspring with concordant K-means exposure cluster (cluster A (constant high exposure to AEDs): OR 0.58, 95% CI: 0.14, 2.29; and cluster B (constant low exposure to AEDs): OR 0.83, 95% CI: 0.40, 1.73) were consistent with the main analyses. No increase in the risk of CM observed in the PS-weighted adjusted logistic regression model (OR: 0.76, 95% CI: 0.40, 1.44).

Sensitivity analysis 5 was performed for the CM outcome comparing valproate with lamotrigine, and valproate with levetiracetam separately as presented in Table 44. The crude logistic regression model estimation for CM in the sensitivity analysis 5, for both simple pairwise comparison between valproate and lamotrigine, and valproate and levetiracetam, was consistent with the estimate observed in the main analysis. See Table 44 for further detail.

In the PS adjusted logistic regression model, the simple pairwise comparisons between valproate and lamotrigine showed a non-significant lower risk of CM in the offspring (OR of valproate and lamotrigine 0.86, 95% CI: 0.46, 1.59), but a non-significant higher risk of CM when comparing offspring exposed to valproate and levetiracetam (OR of valproate and levetiracetam 1.60, 95% CI: 0.57, 4.52). The number of offspring with CM in the simple pairwise comparison between valproate and lamotrigine was 19 and 35, respectively. For simple pairwise comparison between valproate and levetiracetam the number of offspring with CM was 20 and 5, respectively (Data not shown). See Table 44 for further details.

In sensitivity analysis 6, there were zero patients with CM in the valproate exposure group after removing outliers. Therefore, the logistic regression model did not converge, and the OR estimation was not possible. OR, 95% CI and p-values were not presented.

Sensitivity analysis 9 focused on live births for CM outcome. Findings from this analysis produced similar estimates as with the main analysis (live-birth or non-live-birth) in the crude logistic regression model, PS adjusted logistic regression model and PS-weighted logistic model on offspring with concordant K-means exposure cluster. See Table 44 for further details.

In sensitivity analysis 10, the mean paternal cumulative exposure to valproate was 66.4 (±22.7) days, while in the lamotrigine/levetiracetam group mean paternal cumulative exposure 69.0 (±23.4) days reported (see Table 45). Due to the low number of events per covariate (or covariate category), the following tables were not produced: Effect estimation for CM using logistic covariate adjustment model; secondary outcome; Effect estimation for CM using logistic covariate adjustment model for valproate treatment group; secondary outcome; Effect estimation for CM using logistic covariate adjustment model for lamotrigine treatment group; secondary outcome; and Effect estimation for CM using logistic covariate adjustment model for levetiracetam treatment group; secondary outcome.

The number of events reported in the valproate group and lamotrigine/levetiracetam group were 12 and 25, respectively (data not shown).

Among fathers exposed to valproate, all CM events were observed in offspring of fathers with high cumulative exposure to valproate (12 events). However, no CM event was reported for low cumulative exposure and medium exposure groups. Hence, the logistic regression covariate adjustment model did not converge, and the CI and p-values were not created. The OR were not possible to interpret (Table not shown).

Likewise, among fathers exposed to lamotrigine, all CM events were observed in offspring of fathers with high cumulative exposure to lamotrigine (19 events). However, no CM event was reported for low cumulative exposure and medium exposure groups. Hence, the logistic covariate adjustment model did not converge, and the CI and p-values were not created. The OR were not possible to interpret (Table not shown).

Table 44 Summary of main analysis and sensitivity analyses for the Secondary outcome cohort in Norway

Analyses*	Population considered	OR (95% CI) estimates		OR (95% CI) estimates by cluster of exposure	
		Crude	Adjusted*	Cluster A	Cluster B
Main analysis N sample = 513	Please check Section 3.2.2.6	1.06 (0.62, 1.82)	NA	NA	NA
Sensitivity analysis 4 N sample = 513	Handling of missing CM diagnosis	1.06 (0.62, 1.82)	0.76 (0.40, 1.44)	0.58 (0.14, 2.29)	0.83 (0.40, 1.73)
Sensitivity analysis 5[A] N sample = 446	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	1.02 (0.58, 1.79)	0.86 (0.46, 1.59)	0.50 (0.14, 1.78)	1.03 (0.51, 2.11)
Sensitivity analysis 5[B] N sample = 236	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	1.23 (0.52, 2.89)	1.60 (0.57, 4.52)	NA[1]	NA[1]
Sensitivity analysis 9 N sample = 513	Narrow case definition for secondary outcome	1.06 (0.62, 1.82)	0.76 (0.40, 1.44)	0.58 (0.14, 2.29)	0.83 (0.40, 1.73)

OR: Odds ratio; CI: confidence intervals; LMP2: Last Menstrual Period Plus 2 weeks; NA: not available; 5[A] analysis comparing valproate and lamotrigine; 5[B] analysis comparing valproate and levetiracetam

Legend: [1] The logistic regression model did not converge. The odds ratios of valproate across K-means cluster were not shown.

***The logistic regression PS models used in sensitivity analysis include variables following described:**

Sensitivity analysis 4: Maternal risk factors/confounders: "Diabetes", "Substance abuse prior to LMP2", "Smoking during pregnancy", "Varicella during pregnancy"

Sensitivity analysis 5[A]: Maternal risk factors/confounders: "Smoking during pregnancy"; **Paternal risk factors/confounders:** "Year of offspring conception"

Sensitive analysis 5[B]: Paternal risk factors/confounders: "Year of offspring conception". In sensitivity analysis 5[B], unbalanced confounders ("Smoking during pregnancy") were not entered into the model because they were not retained in the PS model.

Sensitivity analysis 9: Maternal risk factors/confounders: "Diabetes", "Substance abuse prior to LMP2", "Smoking during pregnancy", "Varicella during pregnancy"

Table 45 Paternal cumulative exposure to Antiepileptic drugs (AEDs) by paternal exposure group; Secondary outcome cohort in Norway

	Paternal exposure group									
CM	**Valproate**		**Lamotrigine/ levetiracetam**		**Lamotrigine**		**Levetiracetam**		**Total (valproate + lamotrigine/ levetiracetam)**	
Number of pregnancies	**N=169**		**N=344**		**N=277**		**N=67**		**N=513**	
Cumulative exposure to AEDs										
Low	56	33.14	114	33.14	93	33.57	22	32.84	170	33.14
Medium	33	19.53	25	7.27	17	6.14	7	10.45	58	11.31
High	80	47.34	205	59.59	167	60.29	38	56.72	285	55.56
Mean (SD)	66.41 (22.65)		68.97 (23.36)		69.27 (23.11)		67.72 (24.50)		68.12 (23.14)	
Median (25^{th} - 75^{th} percentile)	80.00 (52.00, 84.00)		84.00 (58.00, 84.00)		84.00 (58.00, 84.00)		84.00 (55.00, 84.00)		84.00 (56.00, 84.00)	
Min, max	1.00, 84.00		2.00, 84.00		5.00, 84.00		2.00, 84.00		1.00, 84.00	

AED: Antiepileptic drugs; CM: Congenital malformations; Min: Minimum; Maximum; 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.

4. Discussion

This section supersedes section 11 from the final study report v1.1.

Valproate-containing medicines are approved in the European Union to treat epilepsy and bipolar disorder (2). In October 2014, PRAC published an assessment report (AR, EMEA/H/A-31/1387) with a review of all available information from non-clinical, clinical, and pharmaco-epidemiological studies, published literature, spontaneous reports, and the opinions of the relevant experts on the safety and efficacy of valproate use (3). In this review, the teratogenic effect of valproate use during pregnancy suggested that children born to women who received valproate during pregnancy had a significantly higher risk of CM involving various body system.

Besides, the PRAC reviewed the evidence from a number of prospective and retrospective observational studies on the effects of valproate on cognitive development in pregnancy, despite limited data available on long-term outcomes (3). The available data showed that valproate exposure during pregnancy may harm a child's mental and physical development (4). Whereas AED may have potential teratogenic effects, the precise mode of action of valproate causing NDD, including ASD, or CM, is still unclear. As suggested by Christensen and colleagues, potential mechanisms include neuronal death or plasticity, impairment of folic acid metabolism, histone deacetylase inhibition, interference with neurotransmitter function (4). Therefore, due to the observed increased risk of CM and of NDD in offspring after valproate exposure in utero, the use of valproate in women of childbearing potential (suffering of epilepsy and bipolar disorder) and in pregnant women suffering of epilepsy has been restricted to circumstances where there is no other effective alternative treatment available, and it has been contraindicated during pregnancy for bipolar disorder (2,3). Despite the increased attention for the role of maternal exposure there have been few studies on the effects of paternal AED exposure on offspring (5–8). So far, only 4 studies have been published addressing the paternal exposure to AEDs on birth outcomes (5–8). Engeland et al. found a higher risk of birth defects of the urinary system in offspring paternally exposed to AEDs, though they could not differentiate among this class of medications (5). In a Danish nationwide cohort study, Yang et al. observed no higher risk of CM in the offspring paternally exposed to AEDs though these authors also did not differentiate among AED classes (7). Velby and colleagues found no evidence of negative effects of paternal exposure to AEDs on the NDD risk of the offspring, though the study did not differentiate between various AEDs (6). Only the study of Tomson and colleagues assessed the risk of major CM as well as risk of different subtypes of NDDs (diagnoses of (i) ASD, (ii) attention deficit hyperactivity disorder [ADHD] and (iii) intellectual disability, separately) in the offspring from fathers exposed to valproate, on monotherapy, for epilepsy, during conception, compared with offspring from fathers with epilepsy unexposed to AEDs during conception (8). The authors found no association between paternal exposure to valproate, or other AEDs, at the time of conception, and major CM or NDDs in the offspring.

The potential impact of paternal use of valproate was discussed during the PRAC referral conducted in 2018, and in an effort to increase knowledge on the association between paternal exposure to valproate and the risk of congenital anomalies and neurodevelopmental disorders, including autism, in offspring, a retrospective observational study was recommended (9).

Therefore, a PASS was conducted, to assess the risk of NDD, including ASD, and CM in the offspring from fathers exposed to valproate in monotherapy at conception, compared to offspring from fathers exposed to lamotrigine/levetiracetam in monotherapy. This final report presents the results of this PASS. Paternal exposure to valproate (monotherapy) was compared to paternal exposure to lamotrigine/levetiracetam (composite

monotherapy). The primary outcome of interest was NDD including ASD and the secondary outcome was CM (minor and major). The multivariable adjusted associations were described independently of potential impact of measured clinical and demographic characteristics of the study population. This study was conducted in 3 countries, Sweden, Norway and Denmark, as these were the only available databases with father-offspring linkage.

4.1 Key Results

This section supersedes section 11.1 from the final study report v1.1.

4.1.1 Primary outcome cohort – Neurodevelopmental disorder including autism spectrum disorder

This section supersedes section 11.1.1 from the final study report v1.1.

Country-specific results pooled in a meta-analysis were computed to achieve a more precise summary estimate of the observed effect size. Pooled risk ratios and hazard ratios of NDD including ASD in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam were calculated across the 3 countries.

The pooled hazard ratios were estimated, and no higher risk was observed in the crude pooled estimate (HR 1.13, 95% CI: 0.85-1.49), but after pooling the PS-adjusted HRs, a significantly higher risk of NDD including ASD among offspring from fathers exposed to valproate in comparison to lamotrigine/levetiracetam group (HR 1.50, 95% CI: 1.09-2.07) was observed.

Main analysis – Effect estimation of the association between paternal exposure to valproate and NDD including ASD

When assessing the association of paternal exposure to valproate in each of the 3 study countries separately, no difference in the risk of experiencing NDD including ASD events was observed in offspring from the valproate group compared with the lamotrigine/levetiracetam group.

The crude Cox regression models showed a non-significant HR of 0.94 (95% CI: 0.60, 1.46, N=1,950) in Denmark, 1.16 (95% CI: 0.76, 1.76, N=2,355) in Sweden, and 1.60 (95% CI: 0.81, 3.15, N=1,416) in Norway.

These results showed that for all countries, in earlier years of the study a higher proportion of offspring was conceived in the valproate group, while in more recent years, a higher proportion of offspring was conceived in the lamotrigine/levetiracetam group, although the variation observed for Norway was minor. For example, in Denmark: year of offspring conception 1996-2001: valproate 26.1%, N=207 versus lamotrigine/levetiracetam 5.0%, N=58, and year of offspring conception 2013-2018: valproate 15.6%, N=124 versus lamotrigine/levetiracetam 39.2%, N=381. In Sweden: year of offspring conception 2006-2010: valproate 39.8%, N=370 versus lamotrigine/levetiracetam 21.8%, N=311, and year of offspring conception 2016-2019: valproate 19.6%, N=182 versus lamotrigine/levetiracetam 36.6%, N=521. However, in Norway, the number of offspring conceived between the 2 groups is comparable: 48.7%, N=194 of offspring in the valproate group, were conceived between 2009-2013 versus 44.8%, N=456 in the lamotrigine/levetiracetam group, and 51.3%, N=204

of offspring in the valproate group were conceived between 2014-2019 versus 55.2%, N=562 in the lamotrigine/levetiracetam group. This could be attributed to the fact that the study period started in 2010, a time when lamotrigine/levetiracetam therapy had already been established in the market. Therefore, fathers (and consequently their offspring) are more evenly distributed between the 2 groups. Moreover, the follow-up time in Norway is shorter in comparison to Denmark and Sweden. Besides, in Sweden, 83% of offspring in the valproate group were identified as probable cases *versus* 63.5% in the lamotrigine/levetiracetam group. This may be attributed to a shorter follow-up period in the lamotrigine/levetiracetam group leading to the detection of fewer probable cases than in the valproate group. In Norway, the proportion of offspring identified as probable cases in the valproate and lamotrigine/levetiracetam groups is comparable (70.6% and 72.0%, respectively). For Denmark, an opposite trend was observed, with 60% of offspring in the valproate group identified as probable cases versus 70% in the lamotrigine/levetiracetam group. Also, compared to Sweden and Norway, in Denmark the maternal risk factor profile was worse in the lamotrigine/levetiracetam groups (eg, more smokers, a higher percentage of IUGR, higher exposure to teratogens), which might also contribute to the divergent findings.

To reduce the follow-up bias, due to the shorter follow-up period in the lamotrigine/levetiracetam group compared to the valproate group, as well as to account for other confounders, a PS-weighted Cox proportional hazards regression model was used to estimate the HR of NDD. This model was adjusted for differences in follow-up time, and the year of conception was considered in the PS model. Yet, the HR may change over time and by reporting a single average HR, the distribution of events during follow-up was not taken into consideration (10). Therefore, the different length of the follow-up may have significantly influenced these findings. Adjusted survival curves, or adjusted cumulative risk curves, would have been more informative than the average HR measure (10). Over the study period, the frequency of events was lower than 10% in the 3 study countries, thus making the adjusted Kaplan-Meier curve difficult to compute and interpret.

Besides, considering the observational nature of the study, the potential biases caused by confounding by indication were unavoidable. Indeed, different AEDs are prescribed for different types and severity of epilepsy (and bipolar disorders). However, measures of severity of the treated disorders were not available in the data sources precluding adjustment for this in the regression models.

In line with the findings observed in the crude models, no significant higher risk of NDD, including ASD, in offspring from fathers exposed to valproate versus those from fathers exposed to lamotrigine/levetiracetam was observed in the PS-weighted Cox regression models, in each of the 3 study countries: HR of 1.34 (95% CI: 0.79, 2.25) in Denmark, 1.54 (95% CI: 0.95, 2.51) in Sweden, and of 1.76 (95% CI: 0.83, 3.71) in Norway. For Denmark, the PS-weighted Cox regression model was additionally adjusted for variables considered as risk factors and/or confounders that were still unbalanced after PS weighting (ie, maternal affective disorder, and maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy). For maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy that remained unbalanced after weighting, the HR was 3.29 (95% CI: 1.38, 7.83). Despite the fact that when unbalanced covariates are included in PS-weighted models, double adjustment, as performed in the current study, reduces residual confounding (11). Given the magnitude of the effect observed for maternal concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy, either stratification or exclusion would have provided both an evaluation and a control for this confounder. Finally, an analysis adjusted for clusters of exposure was performed to account for intensity and evolution of exposure over time. No higher risk of NDD including ASD was observed whatever the trajectories of exposure, but higher

estimates, though not significant, were observed at higher doses and prolonged treatment trajectories in Denmark and Sweden, as opposed to Norway in which a higher HR was observed at lower doses (HR for cluster A: 1.72, 95% CI (0.69, 4.29) versus HR for cluster B: 1.79, 95% CI (0.48, 6.72). However, the sample size in Cluster A was larger than the sample size in Cluster B. This difference in sample sizes may have impacted the accuracy of the HR estimates. As observed for cluster B, with its smaller sample size, the wider CI result in increased uncertainty around the HR estimate.

Stronger associations were observed in adjusted models compared with crude models for all 3 countries. This trend moving the point estimates away from the null, may reflect handling of confounding effects in the PS models. In particular, since the crude non-significant association no longer captures the partial effect of the omitted confounders (ie, omitted variable bias), as suggested by higher rates of confounding factors in the levetiracetam/lamotrigine group than in the valproate group, after adjustment, it rather reflects the “less biased” effect of the association between the exposure and the outcome (12).

Additionally, to assess the impact of the PS-weighted model computed for each country, a Cox regression model adjusted for the set of identified confounders in each country was computed to estimate the HR of NDD, including ASD. Results from this sensitivity analysis (sensitivity analysis 6) showed similar aHRs compared to those obtained from the PS-weighted models, in Denmark and Sweden. However, this comparison was not possible for Norway since the exclusion of influential subjects led to aHR impossible to estimate. The Cox covariate adjustment model was rerun without considering the dfbetas criterion, and, no covariates were associated with both the exposure and the outcome, which resulted in the same model as the one in the crude main analysis of NDD, including ASD. Not considering the dfbetas criterion implies that outliers and influential subjects were not removed from the analysis. However, it is important to note that the removal of influential subjects encompassed all events in the valproate group. This is likely due to the small numbers observed in this analysis. Consequently, the model estimates derived are likely not very robust as they are based on very few cases. Several other sensitivity analyses were performed aiming to explore the robustness of the estimated risk of the study outcomes. For most of the sensitivity analyses, the results overall described similar results when compared to those observed in the main analysis.

An association between paternal valproate exposure and the occurrence of NDD, was also found in another sensitivity analysis (sensitivity analysis 11), in which a narrow composite NDD case definition was used. In this definition, major NDD diagnoses only (excluding mental disorder, not otherwise specified, other specified behavioral and emotional disorders with onset usually occurring in childhood and adolescence disorders, tic disorders, stereotyped movement disorders, essential tremor, other specified forms of tremor, myoclonus, other chorea, other specified extrapyramidal and movement disorders, extrapyramidal and movement disorder, unspecified, Idiopathic nonfamilial dystonia, spasmodic torticollis, idiopathic orofacial dystonia, blepharospasm, other dystonia, dystonia, unspecified, extrapyramidal and movement disorders in diseases classified elsewhere), including ASD, were considered. A significant, moderate, association was observed between paternal exposure to valproate in the 3 months before conception and the occurrence of diagnoses of major NDD, including ASD in Sweden (PS-weighted HR: 1.70, 95% CI: 1.02, 2.81), a similar but non-significant point estimates were observed in Norway (PS-weighted HR: 1.87, 95% CI: 0.86, 4.08), and a non-significant but stronger than the main analysis result in Denmark (PS-weighted HR: 1.59, 95% CI: 0.89, 2.86). Results from the main analysis, considering all NDD, including ASD showed a gradient toward risk dilution (in Denmark, PS-weighted, HR: 1.34 [95% CI: 0.79, 2.25]; in Sweden, HR: 1.54 [95% CI: 0.95, 2.51]; in Norway, HR: 1.76 [95% CI: 0.83, 3.71]). However, most of the "minor NDD diagnoses" did not have any events recorded. In the

valproate group in Norway, after using a narrow composite case definition, the number of events decreased from 15 events (in the main analysis) to 14 events (in sensitivity analysis 11) out of 398 offspring. In the lamotrigine/levetiracetam group, there were 23 events out of 1,018 offspring in the main analysis and 21 events out of 1,017 offspring in sensitivity analysis 11. Additionally, in each country, the "tic disorder" was frequently excluded from the analysis, and interestingly, this disorder was more prevalent in the lamotrigine/levetiracetam group. This may have resulted in an increased risk when this disorder was excluded from the analysis. When assessing a wider exposure window (6 months) to investigate whether there was an effect of valproate beyond the spermatogenic cycle, the results, although not statistically significant, were similar to those observed in the main analysis as presented in section 10.3.1.10 for Denmark and 10.4.1.9 for Sweden in the final study report v1.1, and section 3.2.1.10 for Norway in this corrigendum. However, in Denmark, offspring born to fathers who had constant low valproate exposure had a non-significantly lower risk of NDD, including ASD (when compared to those who had constant high valproate exposure).

We furthermore investigate the possibility of a mediator effect of preterm birth in the association between exposure to AEDs and NDD occurrence could be present. Thus, a sensitivity analysis excluding extremely low birth weight, very preterm and extremely preterm new-born was done to explore the potential impact introduced in the main analysis by inclusion of this subpopulation of offspring, because conditioning on mediators may lead to a biased estimate. This sensitivity analysis produced very similar results compared to the main results. Since low birth weight, very preterm, and extremely preterm new-born were used as proxies for IUGR, the likelihood that bias was introduced as a consequence of the inclusion of this subpopulation in the Primary outcome comparative cohort in the 3 study countries cannot be ruled out. Nevertheless, considering that ultrasound biometry is essential for the diagnosis of IUGR (13) and the difficulty of obtaining good quality data in real-world studies, low birth weight, very preterm, and extremely preterm are reasonable proxies, and have been used in several perinatal epidemiological studies (14–16).

For the main analysis, the comparator group included irrespective exposure to either lamotrigine or levetiracetam. Thus, a sensitivity analysis was performed comparing valproate paternal exposure to separately lamotrigine (sensitivity analysis 5^{A}) and levetiracetam (sensitivity analysis 5^{B}) paternal exposure to evaluate differential effect of using one or the other comparator. The 3 AEDs are usually used for different type of epilepsy or potentially for other indications. For instance, lamotrigine may be prescribed for depression in the setting of bipolar disorder, but levetiracetam is not. Valproate could be used in acute mania in the context of bipolar disorder. Additionally, levetiracetam is approved and used in monotherapy for focal epilepsy and, despite not being approved, is used in monotherapy for generalized seizures, while valproate is now essentially used as a first-line treatment in cases of idiopathic generalized epilepsy and lamotrigine in cases of refractory partial epilepsy and generalized epilepsy not responding to valproate. Another issue relates to the different periods of licensing, resulting in systematic differences in the treated populations. The results of the comparison between those exposed to valproate and those exposed to lamotrigine were similar to the association estimated in the main analysis. When the HRs were estimated by clusters of exposure, the same trend was observed, although the association in Cluster A, constant high exposure in Sweden was even stronger than the one observed in the main analysis. The comparison results with the levetiracetam exposure group were difficult to interpret, with contradictory findings between the 3 countries. It should be noted that this was the smallest group of exposure in all 3 countries, and the number of events in this exposure group was also very small.

The WHO DDD is the assumed average maintenance dose per day for a drug used for its main indication, ie, epilepsy for the studied AEDs, in adults. However, this may not represent the suggested or prescribed daily

dose. Due to individual characteristics (such as indication, age, weight, ethnic variations, kind and severity of disease), pharmacokinetic considerations, and other factors, therapeutic doses for certain patients and patient groups will commonly deviate from the DDD. In this study, a comparison between the estimated treatment durations and time between prescriptions was provided, acknowledging that this would necessarily be affected by the DDD methodology approximation. To better provide an estimate of the impact of this approach, a sensitivity analysis (sensitivity Analysis 8) was performed. stratifying patients with and without epilepsy, the main indication used by the WHO DDD. Overall, this sensitivity analysis showed a lower agreement with the WHO DDD among fathers with AED prescription without an indication of epilepsy, especially in the lamotrigine group for Denmark and Sweden. In Norway, a lower agreement with the WHO DDD was observed among fathers with AED prescription, especially in the levetiracetam group, regardless of the indication for epilepsy.

Finally, a sensitivity analysis (sensitivity 10) was done to investigate the risk of NDD, including ASD using a cumulative exposure to treatment. Cumulative exposure was calculated as the total amount of DDD intake that a father was exposed to over the 3 months' time window prior to conception (this corresponded to the sum of the DDD in all 14-day intervals). As a continuous variable, the cumulative exposure to valproate was not associated with a higher risk of NDD including ASD in Denmark and Sweden. Similarly, when the cumulative exposure was categorized, cumulative higher doses of valproate were also not associated to higher risk of NDD, including ASD in Denmark and Sweden. The low number of events per covariate after the exclusion of influential subjects prevented the models to be conducted for Norway. In the main analysis' multivariate K-Means adjusted Cox regression model, the associations in cluster with higher exposure were numerically stronger than those in clusters with lower exposure in Denmark and Sweden, but not in Norway, where a higher HR was observed in the lower exposure cluster. The analyses were limited by the loss of power when subdividing into strata. The dose-effect association thus remains unclear; besides, considering the small number of events in each of the cumulative exposure categories, no conclusion can be drawn.

4.1.2 Secondary outcome cohort - Congenital malformations

This section supersedes section 11.1.2 from the final study report v1.1.

Meta-analysis

Country-specific results were pooled in a meta-analysis to achieve a more precise summary estimate of the observed effect size. Pooled OR of CM in offspring paternally exposed to valproate compared with offspring paternally exposed to lamotrigine/levetiracetam were calculated across 2 countries, Denmark and Norway.

No higher risk of CM in the valproate versus the lamotrigine/levetiracetam groups was observed in any of the follow-up periods and for the overall study period in both countries.

The crude pooled results suggested no higher risk of CM associated with paternal exposure to valproate 3 months prior to conception compared to lamotrigine/levetiracetam exposure (OR: 0.81, 95% CI: 0.48, 1.36). However, it was not possible to provide the pooled results for the adjusted model, as in Norway, the PS logistic model did not converge due to a quasi-complete separation exacerbated by the low event numbers. Therefore, it was not possible to produce the PS-weighted adjusted OR. It should be noted, however, that considerable heterogeneity was observed between country-specific cumulative incidence proportion estimates for the overall period of study follow-up and for 0-1 years of follow-up. Hence, the pooled results should be interpreted with caution since they are crude data that have not been adjusted for other variables and may reflect this heterogeneity, explained by the small sample size (only 2 countries are included and only the crude results are pooled) but also by the diverging results observed (crude OR of 0.62 [95% CI: 0.37, 1.04] for Denmark, and OR of 1.06 [95% CI: 0.62, 1.82] for Norway).

Main analysis – Effect estimation of the association between paternal exposure to valproate and CM

When assessing the association of paternal exposure to valproate in the 2 study countries, Denmark and Norway, no difference in the risk of CM was observed in offspring from the valproate group compared with the lamotrigine/levetiracetam group. Considering the overall study follow-up, the incidence proportion of the first CM event (major and minor as composite) among offspring paternally exposed to valproate appeared to be lower than that of those paternally exposed to either lamotrigine or levetiracetam in Denmark (respectively, 9.3%, [95% CI: 6.9, 11.7] vs. 14.1%, [95% CI: 12.1, 16.2]). In Norway, it was the opposite (respectively, 15.1%, 95% CI: 11.7, 18.6 vs. 14.5%, [95% CI: 12.4, 16.7]). In Denmark, when focusing on the first year of follow-up - due to the small number of events and masking rules, the incidence proportion of first CM event was 5.3% (95% CI: 3.4, 7.2, n=29) among offspring paternally exposed to valproate and 9.1% (95% CI: 7.4, 10.8, n=101) in those paternally exposed to lamotrigine/levetiracetam. In Norway, in the first year of follow-up, the incidence proportion of first CM event was 10.8% (95% CI: 7.8, 13.8, n=45) among offspring paternally exposed to valproate and 9.6% (95% CI: 7.9, 11.4, n=102) among those paternally exposed to lamotrigine/levetiracetam. Nonetheless, these figures should be interpreted with caution, even though the overlapping CIs do not support differences between exposure groups. It is worth mentioning that the incidence proportions estimated in these descriptive cohorts, refer to offspring born from fathers and/or mothers exposed to teratogenic drugs in the preconception period or during pregnancy, thus an overestimation of the incidence of CM is highly probable.

For the crude logistic regression models, it was observed a non-significant OR of 0.62 (95% CI: 0.37, 1.04) in Denmark, and 1.06 (95% CI: 0.62, 1.82) in Norway. The opposite direction in the OR observed between Denmark and Norway may be explained by the higher risk factors potentially linked to CM observed in the

lamotrigine/levetiracetam group versus the valproate group. Similar to what was observed for the crude models, in the PS-weighted logistic regression models, no higher risk of CM was observed in offspring from fathers of valproate group compared with lamotrigine/levetiracetam group, in Denmark, OR of 0.61 (95% CI: 0.36, 1.06). In Norway, the PS logistic model did not converge due to a quasi-complete separation exacerbated by the low event numbers. Therefore, it was not possible to produce the PS-weighted adjusted OR.

Finally, in Denmark, no higher risk of CM was observed in the analysis adjusted for clusters of exposure to account for intensity and evolution of exposure over time, regardless of exposure trajectories. The OR for CM was 0.68 (95% CI: 0.31, 1.48) for cluster A and 0.54 (95% CI: 0.26, 1.12) for cluster B, when comparing paternal exposure to valproate to those exposed to lamotrigine/levetiracetam. However, in Norway, it was not possible to provide these estimates due to the issue reported above.

The evaluation of CM described above, comprised a population of live births, stillbirths, and spontaneous abortions during gestation, for Norway and Denmark. In Sweden, as linkage with fathers was only possible for live births, no information was available on stillbirths, and spontaneous abortions during gestation. Thus, an exploratory objective (exploratory analysis 7) was designed in Sweden to assess the risk of CM in offspring paternally exposed to valproate compared to lamotrigine or levetiracetam at the time of conception. Also, for this exploratory analysis no association was observed between exposure to valproate at the time of conception and the occurrence of a CM when compared to live offspring from fathers exposed to lamotrigine or levetiracetam. A crude OR of 1.01 (95% CI: 0.66, 1.55) and a PS-weighted adjusted OR of 0.92 (95% CI: 0.59, 1.44) were observed. Furthermore, no higher risk of CM was observed regardless of the trajectories of exposure. Additionally, to confirm the robustness of the results, a sensitivity analysis (sensitivity analysis 9) was performed on the live-birth population for Norway and Denmark, as we expect that the distribution of CM observed in this population likely reflected functional defects and minor morphological abnormalities. Results from this sensitivity analysis were also similar to the ones observed in the main analysis, confirming the main observed association.

Additional sensitivity analyses were performed in this study aiming to explore the risk of CM in offspring born to fathers exposed to valproate, in different study populations. These analyses can be used to challenge the robustness of the study results, which can then be compared to the main findings to provide a quantitative assessment of the robustness of the original analysis. The following sensitivity analysis results overall describe similar associations when compared to the those observed in the main analysis.

As several diagnoses for spontaneous abortions and stillbirths could be missing due to under-reporting, a sensitivity analysis was performed to investigate the risk of CM using a broader definition of the outcome.

For this sensitivity analysis (sensitivity analysis 4) all the ICD-10 codes of interest for live births and spontaneous abortions or stillbirths as well as all spontaneous abortions or stillbirths without an ICD-10 code for the diagnosis were included. In both countries, similar results as to the estimated risk of CM were observed when this broader definition of CM was applied. However, this comparison is limited for Norway, considering only the crude model was produced in the main analysis of the secondary outcome due to non-convergence of the PS-weighted model. Nevertheless, the expected under-reporting does not seem to have impacted the results reported in the main analysis.

The comparator group in the main analysis included, irrespectively, exposure to either lamotrigine or levetiracetam in monotherapy. As for the primary outcome, to evaluate differential effect of using lamotrigine or

levetiracetam, a sensitivity analysis was performed comparing paternal exposure to valproate to paternal exposure to lamotrigine (sensitivity analysis 5^A) and levetiracetam (sensitivity analysis 5^B), separately. The results for the comparison between the offspring exposed to valproate versus those exposed to lamotrigine, and between the offspring exposed to valproate versus those exposed to levetiracetam, were similar to the associations estimated in the main analysis. However, the comparison is limited for Norway due to the issue reported above. In addition, because of the very small number of events, in this sensitivity analysis the estimation of the association by clusters of exposure was not possible for the comparison between valproate and levetiracetam.

A sensitivity analysis was planned to assess the impact of the PS-weighted model computed for each country, by computing a logistic regression model adjusted for a set of identified confounders in each country (sensitivity analysis 6). Since no PS weighting is applied in this analysis, the dfbetas (statistics that indicate the effect that deleting each observation has on the estimates for the regression coefficients) for the exposure coefficient was calculated for each offspring after fitting the adjusted model to identify influential subjects, and excluded them from the model, before re-estimating the model. However, this sensitivity analysis was not possible to compute as there were no observed CM events in the population after removing outliers.

Finally, a sensitivity analysis was done to investigate the risk of CM using a cumulative exposure to treatment (sensitivity analysis 10), similar to what was computed for the Primary outcome cohort. Also, for this analysis, due to the small number of events, no conclusions could be drawn.

4.2 Limitations and strengths

This section supersedes section 11.2 from the final study report v1.1.

This observational retrospective study was conducted in 3 Nordic countries using data sources that were not primarily collected to address the study objectives, therefore, the following limitations must be acknowledged.

- Data were collected only for administrative purposes in Denmark and Sweden, therefore, some medical information not directly related to reimbursement may be incomplete or not available at all. In Norway, most of the confounders assessed were from the birth registry, a database designed for research purposes, although we also used data from the patient registry, a database established for administrative purposes.
- As the data was extracted from different country registries, some differences were expected in terms of variables collected, coverage and missing data patterns. This was indeed the case as presented above, however many of the descriptive analyses showed similar trends.
- Paternal linkage might be incorrectly classified when the registered father is not the child's biological father. The ability to identify adoption or in vitro fertilization (IVF) is available in the registers of all countries of interest. Children born through IVF or adoption are not considered in this study. However, this proportion is likely not to be different between AEDs.
- Information about spontaneous abortions and stillbirths (linked to mother and father) were not available for Denmark before 22nd week of pregnancy and for Norway before the 12th week of pregnancy. Accordingly, diagnoses of CM leading to a spontaneous abortion and elective

terminations of pregnancies which occurred before these weeks of gestation were not detectable and not included in this study. This may have led to a selection of cases and to a survivor bias as the distribution of type of CM and severity is likely to be different.

- Information on medicines without a prescription purchased were not available in the databases. This is an important limitation, particularly regarding folic acid, which has a significative impact on frequency of neural tube defects and congenital heart defects. Randomized trial evidence indicate that periconceptional folic acid supplementation prevented a major proportion (about 90%) of neural tube defects as well as a certain proportion (about 40%) of congenital heart defects (17). The impact of failing to account for folic acid supplementation could bias risk estimates in the comparative analyses of CM, if exposure differed across to exposure groups.
- Despite paternal exposure to medications has not been associated with birth defects, offspring from fathers exposed to drugs with known teratogenic effects 3 months prior to conception, were excluded from the comparative, sensitivity and exploratory objective analyses. The exclusion of a large number of patients may have introduce a bias and decreased the precision of the effect size estimates.
- Misclassification of exposure can also not be ruled out. In this study, paternal exposure to antiepileptic drugs was defined using a risk window of 3 months prior to the estimated date of conception. First, the date of conception could have been incorrectly estimated. Second, and related to AED's, given the longest half-life (no longer than 118 hours) and the estimated five half-life's (not more than 1 month), the window of exposure of 3 months prior to conception used in this study may have been conservative, and exposed males at the time of conception could have been classified as unexposed. Offspring exposed to AEDs and/or diagnosed with epilepsy after birth are included in the primary outcome for descriptive analysis but excluded from the primary outcome for comparative analysis. Epilepsy and bipolar disorders are strong risk factors for NDD, and offspring with epilepsy or receiving AEDs are already at increased risk of NDD regardless of paternal exposure. Other known risk factors for NDD include genetic disorders, some congenital infectious disease, and perinatal asphyxia. It was assumed that these characteristics were balanced between the 2 exposure groups, though we could not verify this. There could have been a difference in the distribution of these characteristics between the 2 exposure groups, resulting in bias in the HR estimate.
- Indications for medications were not available in all the data sources used for this study. Epilepsy was assumed to be the primary indication for the 3 AEDs of interest (valproate, lamotrigine, and levetiracetam) at the time of study design and protocol development. The indication for paternal epilepsy was considered a proxy for the AED's prescription; hence, this clinical characteristic was not accounted for in the comparative analyses. Nonetheless, our results showed that epilepsy was the AED indication in 63.5%, 55.8%, and 35.1% of the cases in Denmark, Sweden, and Norway, respectively. Thus, a confounding effect of the paternal epilepsy indication cannot be ruled out based on the estimates.
- It should also be considered that some AEDs may be continued or discontinued more frequently than others. Fathers with more severe epilepsy are more likely to continue their AED intake. In the present study, patients switching or discontinuing their medication were considered as polytherapy,

and the offspring of these fathers were excluded from the main analyses, which might have introduced selection bias.

- In the present study, no information was available on the type of epilepsy in fathers. This is, particularly relevant for genetic epilepsies, which could be associated with NDD.
- Bipolar disorders in the parents can have an impact on offspring development. Bipolar disorders in fathers were taken into account in the primary outcome analyses, but bipolar disorders in mothers were not.
- Lifestyle factors (such as paternal and maternal smoking, substance abuse or alcohol consumption) were missing in a high proportion in both countries. The exception is smoking before pregnancy which was well recorded in Sweden. The negative effects of prenatal alcohol exposure on the developing brain and the resulting neurological and/or cognitive, behavioral, emotional, and adaptive functioning deficits in offspring maternally exposed *in utero* are well recognized (18). It is also well established that prenatal nicotine exposure, even though maternal smokeless tobacco use, is associated with numerous post-natal adverse health outcomes in new-born – not only low birth weight, preterm delivery, and sudden infant death syndrome but also severe neuropsychiatric disorders (Tourette syndrome and chronic tic disorder, as well as Tourette syndrome with comorbid psychiatric conditions including ADHD) (19). The limited information on these factors will preclude complete adjustment in the final model, however, this misclassification is anticipated to be non-differential, affecting both exposed groups equally.
- For Denmark, when the outcome for a specific analysis had <5 cases/observations, the specific result and other potentially related results that could lead to the identification of those patients were masked by the data provider. This might sometimes lead to incomplete descriptive analyses, for example, the minimum and maximum values could not be reported, as well as strata with very few counts.
- The major malformations were defined per protocol based on the exclusion of minor using EUROCAT classification. This approach is well described and accepted. However, the list of exclusions (minor) was based on the British Paediatric Association extension of ICD-10. Country-specific adaptations of ICD-10 in Denmark and Norway may have led to a failure in excluding minor malformations, and consequently, a high proportion of overall CM was observed.
- Offspring with CM are more at risk of NDD. Not having excluding offspring suffering from CM in the primary outcome cohorts might have biased the estimate of the association between exposure and risk of NDD.
- NDD was considered as a composite outcome therefore it may be challenging to understand the clinical relevance of the observed findings. The main issue is the potential of misinterpretation when there is heterogeneity of response among components of composite endpoints. For instance, less clinically significant endpoint(s) included in the definition of the composite outcome may drive the overall observed effect (ie, less important outcomes may account for the majority of events). This may have had an impact on the estimate in the main analysis.
- The incidence proportions and the incidence rates estimated in the descriptive cohort are unadjusted, therefore should be interpreted with caution. Yet, the interpretation of the findings for

the effect of paternal exposure to valproate (compared with lamotrigine/levetiracetam) on NDD, including ASD or CM risk, was based on the results from the PS-weighted adjusted Cox regression models. However, despite the very comprehensive and through adjustments implemented in the multivariable models, residual confounding cannot be completely ruled out.

Also, results were pooled in a meta-analysis and, the following limitations should be considered when interpreting the findings:

- In some instances the I^2 statistic suggested low heterogeneity, however, very broad CI were observed suggesting large uncertainty in this assessment, added to which the meta-analysis is conducted only using 3 and 2 sets of results, ie, Denmark, Sweden, and Norway, and Denmark and Norway, respectively for primary and secondary outcome. Specifically, in the pooled results of the secondary outcome analysis, significant heterogeneity and risk estimates in opposite directions in the 2 countries make the results difficult to interpret.
- There are differences in the healthcare systems and healthcare policy, such as the screening for the outcomes of interest, as well as country-specific risk factors and confounders considered in the PS adjusted model.
- The study-specific results from which the pooled HR were derived may be biased due to residual confounding because the degree of adjustment may differ by country depending on the availability of the selected variables and the strength of the relationships between exposure and outcome(s).
- In crude analyses no risk for NDD including ASD was observed in offspring from the paternal exposure to valproate group compared to the paternal exposure to lamotrigine/levetiracetam group. A slight and non-significant higher HR was observed, which may be attributable to paternal underlying psychiatric indications that were not considered in the crude analysis.

With regard to the research methods the following strengths should also be acknowledged:

- Data sources are based on live births with medical record linkage to mother and father available in multiple registry databases in Denmark, Sweden, and Norway for NDD including ASD. The choice of minimal inclusion and exclusion criteria were applied in this study to minimize potential selection bias and capture a comprehensive sample that could represent the nationwide real practice.
- The study is based on data of offspring with linkage data to both parents from national health registries in Denmark, Norway and Sweden.
- An adequate number of offspring was reached for each study cohort in all study countries. This provided 80% power, to observe a minimum HR of 2.0 for the composite NDD, including ASD. The follow-up of the study was up to 10 years of age of the offspring in Norway, and up to 12 years of age of the offspring in Denmark and Sweden, enabling the identification of the safety outcomes of interest during the infancy and childhood period.
- In the present study paternal exposure to valproate was compared to paternal exposure to lamotrigine/levetiracetam, a comparator group with similar indications without evidence, so far, of an association with NDD nor CM. Therefore, the threat of a systematic bias was minimized by the choice of a robust active comparator group. Also, the implementation of appropriate statistical techniques (PS weighting, double adjustment, adjustment for K-means cluster of exposure) likely

reduced the likelihood of confounding. The observed findings regarding higher incidence rates in specific age groups, corresponding with "Real life practice": less than 2 years correspond to the most severe cases, 5-6 years first years of mandatory school, 7-8 years age of first national school learning level tests (Europewide aligned).

- The robustness of the main findings was corroborated by the consistency of the largely similar findings observed in sensitivity and exploratory analyses across the 3 study countries.

4.3 Interpretation

This section supersedes section 11.3 from the final study report v1.1.

It is well recognized that maternal exposure to valproate during pregnancy significantly increases the risk of CM, including neural tube, cardiac, skeletal and limb, or-facial cleft, and craniofacial deformities (20). Results from a Danish population-based study of children born alive, Christensen and colleagues (4), investigated potential association of prenatal exposure to valproate with risk of ASD. They observed a higher risk of ASD and childhood autism, and the association was observed among offspring of mothers with and without epilepsy, and after further adjustment for parental psychiatric disease. According to the animal model study, maternal valproate therapy in mice increases the occurrence of features similar to ASD at the molecular, cellular, and behavioral levels. Besides, offspring with in utero exposure to valproate presented health and behavioral outcomes such as NDD, including ASD-related deficits (21–24). On the other hand, it is unclear how exposure to paternal valproate will affect the behaviors of the offspring, and human studies investigating this association among offspring from fathers exposed are still scarce (25). Nevertheless, recent findings suggest that paternal exposure to valproate during the spermatogenesis of mice may disturb the histone acetylation balance in the brain of offspring through changes in the germline epigenome, leading to behavioral alterations in offspring (26). However, whether the same mechanisms apply to humans is not yet known. There are indeed concerns whether paternally exposed offspring to valproate, during conception may be at increased risk of NDD including ASD and CM.

So far, only 4 population-based studies have been published assessing the paternal exposure to AEDs on birth outcomes (6–8,27). In a prospective population base-cohort study, children born to parents with epilepsy and treated with AEDs had a significantly higher risk of scores on tests of personal social skills (OR: 2.3, 95% CI: 1.3, 4.1) and a measure of autistic traits compared to children whose parents had epilepsy but were untreated. However, the study did not differentiate between the various AEDs; therefore, the findings cannot be extended to valproate (6). Interestingly, all the groups exposed to AEDs, including lamotrigine, were associated with more autistic traits at 36 months. Results from a cohort study based on the Norwegian Prescription Database and the MBR of Norway, suggest no association between paternal exposure to AEDs and higher risk of unfavorable pregnancy outcomes (5). Further results from a cohort study based on Danish national registers found that children whose fathers used AEDs during the 3 months before conception had a 23% higher risk of congenital anomalies (adjusted OR 1.23, 95% CI: 1.10, 1.37), compared to those unexposed (7). Despite this study did not differentiate between AEDs, the results of the negative-control analysis suggested that the higher risk was also observed in children whose fathers were former users (ie, those using AEDs only from 1 year to 3 months before conception) (OR 1.29, 95% CI: 1.03, 1.61) and later users (ie, those using AEDs only during pregnancy) (OR 1.35, 95% CI: 1.12, 1.65). The authors concluded that the risk of congenital anomalies in the offspring

paternally exposed to AEDs before conception may be attributable to the underlying condition rather than to the effects of AEDs (7). Yet, so far, only one study has examined potential associations between valproate exposure and major CM or NDD in offspring (8). This study was conducted using the Swedish registries to investigate the association between paternal use of AEDs and adverse neurodevelopmental outcomes and major CM in the offspring (8). The results found that offspring of fathers exposed to AEDs did not show a higher risk of autism (aHR 0.9, [95% CI: 0.5, 1.7]), ADHD (aHR 1.1, [95% CI: 0.7, 1.9]), or intellectual disability (aHR 1.3, 95% CI: 0.6, 2.8) compared with offspring of fathers with epilepsy who were not exposed to AEDs. Among offspring of fathers with epilepsy who used valproate in monotherapy during conception, rates of autism and intellectual disability up to 11 years of follow-up were slightly higher compared to those of the offspring of fathers with epilepsy who did not use AEDs during conception. However, after adjustment for PS the estimated risk lost its statistical significance, leading the authors to conclude that exposure to valproate, or other AEDs, during conception was not associated with a higher risk of major CM or NDD in the offspring. From a supplementary analysis, the authors found that compared to offspring from mothers without epilepsy, offspring from mothers with epilepsy had higher risk of CM (aHR 1.4, 95%CI 1.2, 1.5), ASD (aHR 1.5, 95%CI 1.2, 1.9), ADHD (aHR 1.6, 95%CI 1.3, 2.) and ID (aHR 2.4, 95%CI 1.8, 3.1). And among offspring from mothers with epilepsy, those from mothers treated with AEDs had a higher risk of CM (aHR 1.3, 95%CI 1.0, 1.7), ASD (aHR 1.8, 95%CI 1.1, 3.0), ADHD (aHR 1.1, 95%CI 0.7, 1.7) and ID (aHR 4.8, 95%CI 2.1, 10.8), compared to those from mother not treated with AEDs (8). From these results, the authors concluded that the higher risk of NDD was more likely caused by factors associated with epilepsy and partly genetically determined (8).

To the best of our knowledge, this study is the first extensive population-based study, comprising 3 countries, showing a significantly increased risk of neurodevelopmental disorders in children from fathers with epilepsy exposed to valproate, compared to those from fathers with epilepsy exposed to lamotrigine/levetiracetam. However, whereas the aHR for ASD from the PS-weighted Cox model was 0.76 (95% CI: 0.30, 1.89) in Denmark, in Norway, it was not possible to provide this estimate due to the low number of ASD events (<10) (please see Addendum v2.0 to Final Report v1.1). Since the outcome investigated was a composite of any NDD it was not possible to evaluate neither the proportion of the different type of NDDs nor the comparative risk for each NDD subtype. Besides, this study was not designed to fully characterize this risk, rather to identify if one existed. Yet, interpreting the findings of the present study (showing a significant higher risk of composite NDD, in offspring paternally exposed to valproate compared to offspring paternally exposed to lamotrigine/levetiracetam), and compare to those observed by Tomson and colleagues (no association with NDD), both in Sweden, is challenging. Only one study based on Danish national registers has reported an increased risk of ASD following paternal use of selective serotonin reuptake inhibitors (SSRIs) before conception (28). Offspring of fathers who used SSRIs before conception had a 1.62-fold greater risk of developing ASD than those who did not. The risk was reduced after controlling for possible confounders, particularly fathers' mental disorders (HR: 1.43; 95% CI: 1.18, 1.74). Extending the exposure window to 3 months before conception did not change the observed higher risk, but no risk was observed for the offspring of fathers who only used SSRIs during the last 3 months before conception. The authors concluded that the increased risk of ASD in the offspring associated with paternal SSRI use before conception may be attributable to paternal underlying psychiatric indications related to SSRI use or other unmeasured confounding factors (28).

In the study of Tomson et al., performed in Sweden in live-born singleton children between 2006-2016, 1.7% of offspring paternally exposed to valproate (n=8) were diagnosed with an ASD versus 1.3% of offspring paternally

unexposed (n=32) (8). In the present study, also in Sweden ASD as the first NDD diagnosis - although maybe not reliable as methods of diagnosis may have changed over time - during all the study period (2007-2019), was observed in 1.6% of offspring paternally exposed to valproate and in 0.6% of offspring paternally exposed to lamotrigine/levetiracetam. All ASD diagnoses (ie, not only as a first diagnosis) were observed in 2.2% of offspring paternally exposed to valproate and in 0.9% of offspring paternally exposed to lamotrigine/levetiracetam. However, in the study by Tomson et al., no information about lamotrigine or levetiracetam was available, making comparison difficult.

Considering the observational nature of the studies, several biases might have affected the findings, the most important of which related to the choice of the comparator group. In the current study, the risk of systematic bias was reduced by using a robust active comparator group (ie, paternal exposure to lamotrigine/levetiracetam with basically similar indications as valproate, but with no robust evidence of an association with NDD or CM, based on data for in utero exposure, at the time when the current study was designed), as opposed to Tomson and colleagues, where a non-user comparator group was selected (8). Non-users had epilepsy but were not treated, and this comparator group most likely included subjects with a very mild disease, for example only those with sporadic seizures. Despite the authors' adjustments for PS, added to the models as a continuous variable, a richer set of variables and the implementation of a high-dimensional PS would have provided a more robust adjustment, further reducing the likelihood of confounding by indication on the observed estimates (29). However, a recent study comprising 38,661 offspring of mothers with epilepsy, 42.6% of whom were exposed to AED, found that prenatal valproate exposure was associated with an increased risk of psychiatric disorders, primarily NDD (aHR for the combined endpoint: 1.80 [95% CI, 1.60-2.03]), whereas prenatal exposure to lamotrigine and oxcarbazepine was not associated with an increased risk of psychiatric disorders (30). The study also found that prenatal exposure to carbamazepine was associated with the risk of tic disorder (aHR, 1.76; 95%CI, 1.07-2.89). In contrast, prenatal exposure to topiramate was associated with ADHD (aHR, 2.38; 95% CI, 1.40-4.06), and levetiracetam exposure was associated with both anxiety (aHR 2.17; 95% CI, 1.26-3.72) and ADHD (aHR 1.78; 95% CI, 1.03-3.07), although the analysis of levetiracetam were limited due to a short follow-up period (average, 4.4 years). These findings, while underscoring the caution against the use of valproate in pregnancy, also raised concerns about risks of specific psychiatric disorders associated with levetiracetam (30). Nevertheless, in the current study, we conducted a sensitivity analysis comparing valproate to lamotrigine (sensitivity analysis 5^{A}) and levetiracetam (sensitivity analysis 5^{B}), separately. The results were consistent with the main analysis, indicating similar associations between offspring exposure to these drugs and the main outcome investigated, enhancing the validity and interpretability of the study findings.

According to Yang et al., additional sensitivity analyses using inactive comparators or the use of a negative control by assessing the risk of NDD or ASD in former valproate users (ie, 1 year-3 months prior to conception, thus outside the spermatogenesis window of inseminating sperm) could have provided evidence that the observed outcome was the result of the underlying indication rather than valproate (7). Although the current study did not estimate the effect based on ASD events, epilepsy was the most common indication for either valproate or lamotrigine/levetiracetam in all study countries. As a result of this, large differences in effect estimation are not expected but cannot be ruled out.

In the present PASS, a follow-up up to 12 years of age was considered for Denmark and Sweden (up to 10 years of age for Norway), and some NDD, especially autism disorder, may not be readily diagnosed in childhood (31). Thus, the likelihood of detecting such NDD diagnosis increases with the entry in school (32). Although data on offspring starting school were not present in the included data sources, and thus results could not be adjusted

for this characteristic, we found a pattern of higher incidence of NDD, including ASD rates, at ages when children begin formal schooling. Even if the model was adjusted for year of conception, an unbalanced year of conception in the 2 paternal exposure groups may have influenced the likelihood of being detected with NDD, including ASD, in the lamotrigine/levetiracetam group due to the shorter three-year follow-up in this group. However, this does not apply to Norway, as the year of conception and length of follow-up are comparable, due to the later index date (in 2010 in Norway, as compared to 1997 in Denmark and 2007 in Sweden). Indeed, the mean age of an ASD diagnosis is around 4-5 years old, and in the lamotrigine/levetiracetam group, roughly 71% had at least 4 years of follow-up versus 82% in the valproate group, considering the 3 countries. Similarly, regarding NDD outcome, we observed in this study 3 age peaks for detection of NDD (1-2 years, 5-6 years, and 7-8 years); in the lamotrigine/levetiracetam group, 34% had at least 8 years of follow-up versus 50% in the valproate group. Hence, offspring of the valproate group appeared to have a higher probability of being diagnosed with NDD or ASD.

With the aim to explore the genetic role in the development of NDD, including ASD, an analysis was performed in each study country to describe risk factors and the frequency of NDD, including ASD, in paternally-matched but exposure-discordant siblings (exploratory analysis 6). However, no conclusion was possible to draw since the small sample sizes (Denmark N=21; Sweden N=29; Norway N=2) precluded the observation of the outcome of interest or the calculation of its effect on NDD, including ASD.

As reported by Thomas, the majority of mothers with epilepsy treated with valproate have genetic generalized epilepsy types, which raises the question of whether women with generalized epilepsy are at higher risk of NDD in their offspring than those with focal epilepsy, difficult to disentangle considering that valproate is the primary drug for idiopathic generalized epilepsy (33). It is unclear, though, which definition the author used of "genetic generalized epilepsy" and whether the same author was referring to "idiopathic generalized epilepsy," a type of epilepsy known to have a genetic basis. Yet, it would be of interest to learn whether this hypothesis can be applied to fathers as well, considering that for male patients with idiopathic generalized epilepsy, valproate is the treatment of choice. However, the findings published so far related to the paternal exposure to valproate and the risk of NDD or ASD in their offspring, or lack thereof, need to be further investigated.

Although the effects of maternal exposure to AEDs on CM outcomes have been extensively examined, only a few studies have been able to include data related to drug ingestion by fathers prior to conception. A study using a composite of valproic acid, phenytoin, and phenobarbital found no association between paternal exposure and safety outcomes related to CM (ie, spontaneous abortion, preterm birth, perinatal mortality, small gestational age, and birth defects) (5). In line with the present findings, Tomson and colleagues (8) found no risk for major CM in Sweden (adjusted OR 0.9, 95% CI: 0.7, 1.2).

The authors observed 4.8% of major CM diagnosed in offspring paternally exposed to valproate versus 4.9% in offspring paternally unexposed. In the present study, where a more specific definition of major CM was used, we observed that 5.6% of offspring paternally exposed to valproate were diagnosed with major CM versus 5.9% of those paternally exposed to lamotrigine or levetiracetam in Sweden. The effect of paternal exposure to valproate on offspring CM was evaluated in our study using logistic models, and the coefficient observed was lower than the null and not significant both in the meta-analysis of the crude and adjusted OR in the Danish population. Besides, in a Danish nationwide cohort study, Yang and colleagues found that the use of valproate in the 3-month period prior to conception was not associated with an increased risk of CM, while lamotrigine exposure in the same time period was associated with a higher risk of CM (7).

These results from the only available real-world sources with paternal linkage, are the first to find an increased risk of NDD in offspring from fathers exposed to valproate, compared to those from fathers exposed to lamotrigine or levetiracetam and they have several limitations; hence more studies are warranted to confirm these findings.

4.4 Generalizability

This section supersedes section 11.4 from the final study report v1.1. Data sources are based on live births with medical record linkage to mother and father available in multiple registry databases recording longitudinal medical data in Denmark, Sweden, and Norway for NDD including ASD cohort; and live births, stillbirths, and spontaneous abortions during gestation with medical record linkage to mother and father available within such registries, for Norway and Denmark for CM. In this study, minimal inclusion and exclusion criteria were used with the goal of minimizing potential selection bias and capturing a comprehensive sample that could best represent nationwide real practice in the selected countries.

The included data sources are representative of the country's total population and patient lifetime data, and they have been demonstrably used for research to reveal the real-world patterns. This study has used offspring data with linkage data to both parents. A high rate of paternal linkage data is available in those registries, 97.5% for Denmark, 97% for Norway, and 90% for Sweden (see section 9.5 in the final study report v1.1).

An adequate number of offspring was reached for each study cohort in all study countries to reach the precision of 5% of significance and 80% of power (see section 9.5 of Protocol V6.0). Further, the follow-up of the study was up to the age of 12 years for the offspring in Denmark and Sweden, and up to the age of 10 years in Norway, enabling the identification of the safety outcomes of interest during the infancy and childhood period.

Finally, it needs to be considered that, although differences from specific-country characteristics of databases, the healthcare system, and the diagnosis and screening of outcomes of interest, the estimates obtained from the meta-analysis may be generalizable for the risk of NDD including ASD in children of the study countries. Regarding the CM, high heterogeneity and risk estimates in opposite directions in the 2 countries would make the results difficult to generalize.

4.5 Additional discussion

This section supersedes section 11.5 from the final study report v1.1.

4.5.1 Descriptive analysis for the primary outcome for Denmark, Sweden, and Norway

This section supersedes section 11.5.1 from the final study report v1.1.

The total number of offspring selected in the Primary outcome cohort, considering all 3 countries, was 14,998 (including 5,034 from Denmark, 6,664 from Sweden, and 3,300 from Norway).

Offspring characteristics

Overall, offspring characteristics from the descriptive cohort were similar in all 3 countries, with an expected distribution of the gestational age, ratio of males to females, and the offspring weight (34,35). Although offspring with epilepsy were excluded from the Primary outcome cohort for comparative analysis, a higher proportion of this condition was observed in offspring paternally exposed to valproate than in those exposed to lamotrigine or levetiracetam. This might be due to the fact that valproate is the treatment of choice (or first-line drug) for male patients with idiopathic generalized epilepsy, a type of epilepsy known to have a genetic basis and that, as such, can be found in several members of the same family. On the other hand, lamotrigine and levetiracetam are used for a wide range of conditions, including focal epilepsy (36).

The diagnosis of NDD, including ASD, was higher in offspring exposed to valproate than in those exposed to lamotrigine or levetiracetam consistently across the 3 countries (Denmark: 6.6% vs. 3.7%; Sweden: 5.4% vs. 3.5%; and Norway: 4.1% vs. 2.4%). A similar trend was observed when ASD was considered as a first NDD diagnosis or when all ASD diagnoses were considered (ie, not only as a first diagnosis) in both Sweden (2.2% vs. 0.9%, respectively, for valproate vs. lamotrigine/levetiracetam) and Norway (1.2% vs. 0.4%, respectively, for valproate vs. lamotrigine/levetiracetam), but not in Denmark (1.6% vs. 1.8%, respectively, for valproate vs. lamotrigine/levetiracetam). The median age in years at the first ASD diagnosis (6.1, 6.3, 3.6 vs. 7.5, 4.5, 5.6 [respectively for Denmark, Sweden, and Norway and for valproate vs. lamotrigine/levetiracetam groups]) is in line with the global mean age at ASD diagnosis (from 38 to 120 months) (37). Several factors may influence the age at diagnosis, including, but not limited to, the type and severity of ASD diagnosis, gender, ethnicity, calendar year of diagnosis (as detection methods have improved overtime), etc. This, however, was not within the scope of the present study; therefore, we cannot provide a conclusive explanation considering that these are crude data that have not been adjusted for other variables.

Maternal characteristics

With regard to maternal characteristics, maternal age distribution was similar in all countries (median [IQR] of 30. [27.0-34.0] years for Denmark, 31.0 [27.0-35.0] years for Sweden, and 31.0 [27.0-34.0] for Norway, respectively) and aligned with previous studies (35). The number of pregnancies in more recent years was lower than in earlier years, and can reflect more cautious behavior and a general European trend of declining birth rates (38). The most frequent maternal comorbidities diagnosed prior to childbirth in Denmark, Sweden, and Norway were neurotic disorders (6.8%, 11.8%, and 13.4% respectively), affective disorder (4.0%, 9.9%, and 9.5%, respectively), and gestational diabetes (3.7%, 3.0%, and 6.3%, respectively).

Smoking during pregnancy was observed among 16.1% mothers in Denmark, 6.4% in Sweden, and 5.2% in Norway. However, large differences in the proportion of missing information on smoking particularly before pregnancy (masked numbers in Denmark, 5.1% in Sweden, and 13.4% in Norway), and during pregnancy (4.0% in Denmark, 3.0% in Sweden, and 10.9% in Norway) were observed, which impairs direct comparisons between countries. The lowest proportion of missing information was observed in Sweden, since recording of smoking is a standard procedure during maternal clinic visits. The observed differences in prevalence of smoking percentage might also be influenced by different recording and data collection in the 3 countries, as outlined in section 9 in the final study report v1.1.

In Denmark, Sweden, and Norway, similar proportions of the offspring's mothers were found within a polypharmacy index during pregnancy between 1 and 4 (48.5%, 47.0%, and 46.6%, respectively). The prevalence of medications associated with neuropsychiatric adverse events during pregnancy was high in all 3 countries: 44.2% in Denmark, 45.2% in Sweden, and 43.0% in Norway. This result may be explained by the

fact that the list of medications for this category is lengthy and includes common medications such as ibuprofen and paracetamol. In contrast, maternal exposure to AED during pregnancy was very low (masked values in Denmark, 2.7% in Sweden, 2.8% in Norway). As expected, only a very small proportion of offspring would be both paternally and maternally exposed to AEDs, and this was confirmed in the data.

Paternal characteristics

Regarding paternal characteristics, the median (IQR) age of fathers at childbirth was similar in all countries (32.0 [29.0-36.0] years for Denmark, 34.0 [30.0-38.0] years for Sweden, and 33.0 [30.0-37.0] for Norway). The most common paternal comorbidities diagnosed prior to the childbirth in Denmark, Sweden, and Norway were neurotic disorders (9.2%, 21.9%, and 13.3%, respectively), affective disorder (excluding bipolar affective disorder and mania) (9.2%, 22.7%, and 18.4%, respectively), and bipolar affective disorders (5.5% and 22.9%, and 23.9%, respectively). The proportions of fathers with a polypharmacy index between 1 and 4 were similar in all countries (43.3% for Denmark, 40.9% for Sweden, and 42.6% for Norway). Likewise, the prevalence of paternal concomitant medications associated with neuropsychiatric adverse events prior to LMP2 was high in all countries (53.2% in Denmark, 57.9% in Sweden, and 62.3% in Norway). Fathers exposed to either lamotrigine or levetiracetam generally presented a higher proportion of clinical comorbidities (ie, paternal psychiatric disorders) in all 3 countries. For instance, among fathers exposed to valproate, 6.3% from Denmark, 13.5% from Sweden, and 7.5% from Norway presented neurotic disorders and 3.7% from Denmark, 11.0% from Sweden, and 7.8% from Norway presented affective disorder excluding bipolar disorder and mania. Among fathers exposed to either lamotrigine or levetiracetam, 11.3% from Denmark, 27.4% from Sweden, and 15.6% from Norway presented neurotic disorders, and 13.0% from Denmark, 30.3% from Sweden, and 22.6% from Norway presented affective disorder excluding bipolar disorder and mania. Except for bipolar affective disorder (more frequent in Norway), all mental health diagnoses were more frequent in Sweden than in Denmark and Norway; however, this does not necessarily illustrate a higher true prevalence, but rather potential differences in coding and clinical practice.

The K-means algorithm, analyzing DDD trajectories in fathers exposed to AEDs 3 months prior to conception (before LMP2), identified 2 different clusters: A (constant high exposure to AEDs) and B (constant low exposure) in both Denmark and Norway, and 3 different clusters: A, B, and C in Sweden (constant high exposure [A], low-to-high exposure [B], and high-to-low exposure [C]). Overall, fathers were treated quite similarly in the exposure groups, although in Norway a lower proportion of fathers in the valproate group was in cluster A (70.0%) as compared to lamotrigine/levetiracetam (76.4%), and a higher proportion of fathers in the valproate group was in cluster B (30.0%) as compared to lamotrigine/levetiracetam (23.6%).

Frequency of the outcome of NDD including ASD

From the total of 2,031 offspring from the Primary outcome cohort for descriptive Analysis in Denmark, 2,451 offspring from the Primary outcome cohort for descriptive analysis in Sweden, and 1,471 offspring from Primary outcome cohort for descriptive analysis in Norway, the overall cumulative incidence proportions (95% CI) of NDD including ASD for the total group (valproate + lamotrigine/levetiracetam) were 4.9% (3.9, 5.8), 4.2% (3.4, 5.0), and 2.9% (2.0, 3.7) respectively which are aligned with previous studies investigating prevalence of NDD in general population (39,40). For instance, a meta-analysis found the prevalence (95% CI) of intellectual disability national level of high income countries of 5.8% (5.5, 7.0) (40). However, the overall cumulative incidence proportion appears to be higher in offspring paternally exposed to valproate than in those paternally

exposed to lamotrigine/levetiracetam, across the 3 study countries, though these are unadjusted data that should be interpreted with caution.

The crude incidence rates for the first diagnosis of NDD, including ASD, in the follow-up period (0-12 years in Denmark and Sweden, and 0-10 years in Norway) in the cohort for descriptive analysis were higher in the valproate group than in lamotrigine/levetiracetam group: n=55, incidence rate: 6.6, (95% CI: 4.9, 8.3) per 1,000 PY vs n=44, incidence rate: 3.7 (95% CI: 2.6, 4.7) per 1,000 PY in Denmark; n=52, incidence rate: 5.4 (95% CI; 3.9, 6.8) per 1,000 PY vs n=52 incidence rate: 3.5 (95% CI: 2.6, 4.4) per 1,000 PY in Sweden; n=17, incidence rate: 8.3 (95% CI: 4.8, 13.2) per 1,000 PY vs n=25 incidence rate: 4.9 (95% CI: 3.2, 7.2) per 1,000 PY in Norway. For Denmark, the total patient-years of follow-up were 15,605.72 (7,691.63 for valproate and 7,914.08 for lamotrigine/levetiracetam group), and the mean follow-up in years per patient was 9.2 for the valproate group and 6.6 for the lamotrigine/levetiracetam group. For Sweden, the total patient-years of follow-up were 13,975.92 (6,483.28 for valproate and 7,492.64 for lamotrigine/levetiracetam group), and the mean follow-up in years per patient was 6.7 for the valproate group and 5.0 for the lamotrigine/levetiracetam group. For Norway, the total patient-years of follow-up were 7,164.42 (2,055.84 for valproate and 5,108.58 for lamotrigine/levetiracetam group), and the mean follow-up in years per patient was 5.0 for the valproate group and 4.8 for the lamotrigine/levetiracetam group. Also here, a trend toward higher incidence rates were observed in the valproate group versus the lamotrigine/levetiracetam group, which are unadjusted and therefore should be interpreted with caution.

The crude incidence proportion and rates of NDD, including ASD, appeared higher in males compared to females in all 3 countries, which is consistent with the known epidemiology of the diseases (40–42). In addition, males were diagnosed earlier (based on 5th and 10th percentiles of time to NDD distribution from Kaplan-Meier estimates). This can be explained by the fact that males display hyperactivity symptoms and are more likely to be diagnosed at younger age, which could trigger earlier investigations and diagnosis (41).

The overall median age in years at the first diagnosis of NDD including ASD in offspring of fathers from valproate group was 6.6 (IQR 4.7, 7.9) in Denmark, 6.2 (IQR 4.1, 8.7) in Sweden, and 5.1 (IQR 3.4, 7.3) in Norway for the valproate paternal exposure group. The corresponding numbers for the lamotrigine/levetiracetam group were 6.1 (IQR 3.9, 8.3) in Denmark, 5.2 (IQR 3.4, 8.2) in Sweden, and 4.3 (3.6, 6.6) in Norway. Also, offspring in the lamotrigine/levetiracetam group were conceived in the later period of the study compared to those in the valproate group in all countries, particularly in Denmark and Sweden. This is aligned with previous research that showed a declining trend for valproate use during pregnancy in the Nordic countries in more recent years (43). This slight difference in the rate of NDD between exposure groups likely reflects longer follow-up time in the valproate group (more offspring conceived in the early years of study period), and subsequently can also partly explain the higher risk of observing NDD in older children. Likewise, previous literature has shown that a child's birth-year may impact the first diagnosis of NDD (44). We hypothesize that improvements in the awareness, screening and diagnosis of NDD including ASD in more recent years, may explain the earlier diagnosis in children from lamotrigine/levetiracetam group (45,46). Other explanation could be more severe form of NDD in the lamotrigine/levetiracetam.

Risk factors and potential confounders

In the current study, potential risk factors and confounders were initially selected based on the literature and clinical expert opinion. These characteristics were related to the offspring, father, and mother, and their assessment was needed to decide which would be considered in the multivariable analysis. The distributions

of potential risk factors and confounders for the association between NDD including ASD and paternal exposure group were examined for those offspring within the Primary outcome cohort for comparative analysis.

As per the protocol definition, confounders are all those variables associated with both the exposure and the outcome of interest but that are not intermediate factors on the causal path between exposure and outcome; a variable is considered a risk factor if it is associated with the outcome independently of the paternal exposure and of the magnitude of the association.

Characteristics associated with the exposure

Maternal characteristics associated with the exposure were the mother's age in Denmark, affective disorder in Denmark and Norway, and maternal polypharmacy index prior to LMP2 and during pregnancy in Denmark and Sweden. Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 were associated with the exposure in Denmark and Sweden, and during pregnancy in Denmark and Norway. The following characteristics were associated with the exposure in Sweden: mother's alcohol abuse prior to LMP2, smoking prior to LMP2, and the maternal polypharmacy index during pregnancy. Smoking during pregnancy was associated to the exposure in both Sweden and Norway.

Similar to what was observed for fathers, regarding the above-mentioned maternal characteristics, mothers of offspring from the valproate exposure group generally presented a lower proportion of comorbidities, a lower polypharmacy index, a lower proportion of concomitant medications, and a slightly lower age. In Sweden and Norway, the proportion of alcohol, substance abuse, and smoking prior to LMP2 and during pregnancy was higher among mothers of offspring from the valproate exposure group.

Paternal characteristics associated with the exposure to valproate or lamotrigine/levetiracetam were the same in all study countries and comprised affective disorder excluding bipolar affective disorder and mania, bipolar affective disorder, neurotic disorder, paternal polypharmacy index, concomitant medications associated with valproate-indicated psychiatric conditions, concomitant medications associated with neuropsychiatric adverse events, father's age. Year of offspring conception was associated with the exposure to valproate or lamotrigine/levetiracetam in Denmark and Sweden only.

Fathers from the valproate group presented a lower proportion of comorbidities, a lower polypharmacy index, less frequently concomitant medications, and a slightly lower age than fathers from the comparator group. In Denmark and Sweden, they also had earlier years of offspring conception than fathers from the comparator group.

Characteristics associated with the primary outcome

Gender of the offspring was a risk factor for NDD, including ASD, with male offspring having a higher likelihood of the outcome than female offspring.

Mother's age and concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 were linked to the primary study outcome and thus considered a risk factor for NDD, including ASD, in Denmark and Norway. In Denmark and Sweden, maternal affective disorder was also a risk factor for NDD, including ASD. Moreover, only in Denmark were certain factors found associated with the outcome, namely smoking during pregnancy, maternal polypharmacy index prior to LMP2 and during pregnancy, concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy, maternal schizophrenia, schizotypal and delusional disorders (marginally significant), and substance abuse prior to

LMP2; in Norway, substance abuse during pregnancy also was found associated with the risk of NDD, including ASD.

Regarding paternal characteristics, the year of offspring conception was associated with NDD, including ASD, in all the study countries, and thus considered a risk factor, with more recent years of conception presenting a lower odds of the study's primary outcome. This association likely reflects the difference in the length of the follow-up between the valproate (longer) and lamotrigine/levetiracetam groups (shorter) in Denmark and Sweden, as observed and already discussed throughout the report. Of note, the lower risk of NDD or the lower probability of being detected or diagnosed with NDD may be due to the shorter follow-up time in the lamotrigine/levetiracetam, time which was not long enough to detect enough signs of the disease. It is therefore plausible that the offspring conceived in the latest years did not reach the age required for the diagnosis of NDD to be coded.

In addition, only in Sweden, the paternal polypharmacy index was associated with NDD, including ASD, with 2.5-fold higher odds in offspring of fathers with an index of 5-10.

Overall, in the current study, the a priori selected confounders and risk factors can be contextualized by previous literature findings listed below:

- Multiple epidemiological studies suggest a relationship between advanced paternal age at conception and adverse neurodevelopmental outcomes in offspring (47,48). This has been particularly noted regarding increased risk for autism, and it was identified as a confounder in our study.
- Children of parents diagnosed with mood disorders including bipolar affective disorder and mania have been shown to present with a higher risk of neurodevelopmental outcomes than those who do not present with these medical conditions. These mood disorders were identified as confounders in our study.
- Maternal epilepsy and maternal exposure to AEDs were considered strong risk factors and were used as exclusion criteria for the comparative, sensitivity, and exploratory analyses. In this report, we can observe that the number of exclusions due to these criteria was low (Denmark: N=64; Sweden N=63; Norway N=47) and did not affect the sample size or the generalizability of results.
- Maternal exposure to drugs other than AEDs - the plausibility of polypharmacy as a confounding variable or risk factor is based on evidence that polypharmacy is associated with harms, including adverse drug effects, drug-to-drug interaction, hospitalization, and mortality. Furthermore, there is evidence that psychoactive drugs of other therapeutic class may often be prescribed in combination with AEDs and may be a risk factor for NDD (such as antidepressants [6]). In line with these data, maternal polypharmacy index prior to LMP2 in Denmark and Sweden, concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 in all study countries, and during pregnancy in Denmark and Norway were included as covariates in the multivariate adjusted model. Likewise, concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 was considered a risk factor in Denmark and Norway, and in Denmark also during pregnancy.

4.5.2 Descriptive analysis for the secondary outcome for Denmark and Norway

This section supersedes section 11.5.2 from the final study report v1.1.

The secondary analysis for CM was conducted in Denmark and Norway. The total number of offspring selected in the Secondary outcome cohort was 7,092 (3,777 in Denmark and 3,315 in Norway). A sensitivity analysis regarding this outcome was conducted in Sweden in a population containing live births only.

Offspring characteristics

Most offspring within the Secondary outcome cohort were born at term (90.4% both in Denmark and Norway) and with an adequate weight (95.5% and 95.7% were weighting ≥2,500 g in Denmark and Norway, respectively). A slightly higher proportion of the offspring were males (51.8% in Denmark and 51.9% in Norway).

Maternal characteristics

With regards to maternal characteristics for the Secondary outcome cohort, the median (IQR) maternal age distribution in years was 30 (27-34) years both in Denmark and Norway. The most frequent maternal comorbidities diagnosed prior to childbirth were gestational diabetes (4.7%) and obesity (2.1%) in Denmark and diabetes (1.8%), gestational diabetes (1.8%), and epilepsy in Norway (1.7%). Overall, 17.1% out of 3,722 mothers in Denmark and 6.6% out of 3,315 mothers in Norway had a record of smoking during pregnancy. Overall, maternal exposure to AEDs was very low (less than or equal to 1.5% for any individual AED) both before LMP2 and during pregnancy in Denmark and Norway. Maternal exposure to medications with teratogenic activity or fetal toxicity prior to LMP2 and during pregnancy was 31.0% and 32.1% in Denmark and 29.4% and 30.5% in Norway. As offspring maternally exposed (3 months prior to conception and/or during pregnancy) to drugs with known teratogenic activity/fetal toxicity are at risk of developing the outcomes of interest for reasons other than valproate, ie, due to intake of other drugs associated with the CM (49), these offspring were excluded from the comparative, sensitivity and exploratory objective analyses. However, they were not excluded from the descriptive analyses, and this could explain the higher cumulative incidence rate of CM in both groups.

Paternal characteristics

Regarding paternal characteristics, the median (IQR) age of fathers at childbirth was similar in both countries (33.0 [29.0, 37.0] years for Denmark, and 33.0 [30.0, 38.0] for Norway). The proportion of fathers exposed to valproate was similar in both countries (19.3% in Denmark and 18.9% in Norway). Paternal exposure to medications with teratogenic activity or fetal toxicity prior to LMP2 was 63.9% in Denmark and 61.4% in Norway. Offspring from those exposed fathers were excluded from the comparative, sensitivity ad exploratory analyses. However, they were not excluded from the descriptive analyses, and this could explain the higher cumulative incidence rate of CM in both groups.

Frequency of the outcome of CM

For Denmark, within the Secondary outcome cohort for descriptive analysis, the frequency of CM was 12.5%, major CM was 4.2% while the frequency of minor malformations was 9.2%. For Norway, the corresponding numbers were 14.7% for CM, 7.9% for major CM and 8.7% for minor malformations. In Denmark, in the group paternally exposed to valproate, of those offspring in whom CM was reported (n=51; 9.3%), the majority had diagnosis of minor CM (6.7%), and 3.5% had a diagnosis of major CM. From 156 (14.1%) offspring with CM in

the lamotrigine/levetiracetam paternally exposed group, the majority (10.5%) had a diagnosis of minor CM, and 4.5% had a diagnosis of major CM. In Norway, in those paternally exposed to valproate, there was a CM report in 63 offspring (15.1%), 7.0% had a diagnosis of a major CM and 9.4% had a minor CM. In the lamotrigine/levetiracetam paternally exposed group, from 154 (14.5%) offspring in whom a CM was reported, 8.3% had diagnosis of a major CM and 8.4% had a minor CM. It should be noted, however, that major and minor CM categories were not mutually exclusive.

In our study, major malformations were identified by first identifying overall malformations and excluding minor malformations, ie, non-identification of minor malformations could lead to an overestimation of major malformations. The prevalence of major CM in pregnancies has been estimated at 3.7% of pregnancies among live births (up to 1 year of age) or stillbirths (50), and between 3.9% in 1997 to 5.3% in 2017 in a Danish study (51), and 2.1% in Norway (2006-2007) (52).

Regarding the incidence proportion for the first recorded diagnosis CM with overall study follow-up, the estimate associated with paternal exposure to valproate appeared higher in Norway (15.1% [95% CI: 11.7, 18.6]) than in Denmark (9.3% [95% CI: 6.9, 11.7]). Conversely, however, the incidence proportion associated with paternal exposure to lamotrigine or levetiracetam was similar (14.1% [95% CI: 12.1, 16.2] in Denmark and 14.5% [95% CI: 12.4, 16.7] in Norway), as was the overall incidence proportion of CM by country (12.5% [95% CI: 10.9, 14.1] in Denmark and 14.7 [95% CI: 12.9, 16.5] in Norway). These results may reflect the increasing trends in the detection of and registration of CM in later years, partially explaining the higher overall incidence proportion of CMs by country detected among levetiracetam and lamotrigine-exposed children, as these were exposed on average later in the period of the study. Also, a Danish population-based study found that offspring of fathers exposed to AEDs during the 3 months prior to conception had a higher risk of CM (7). Besides, the authors found that the association was higher for the father exposed to lamotrigine when compared to those exposed to valproic acid. However, more detailed analysis showed that this association was possibly attributed to the underlying indication rather than the effect of AEDs (7).

Risk factors and confounders

No risk factors or confounders were identified for the CM outcome, as none of the variables examined were significantly associated with either the exposure or the outcome in Denmark and Norway.

Some epidemiological studies suggest a relationship between advanced paternal age at conception and CM in offspring (53–55), however this was not shown to be the case in our study. Also, maternal age does not appear to be a risk factor for CM, even if it is supported by several publications (56,57). This might be a result of more frequent testing in older women during early pregnancy for fetal abnormalities, as recommended by some Nordic guidelines (58).

4.5.3 Exploratory analysis discussion

This section supersedes section 11.5.3 from the final study report v1.1.

Several exploratory analyses were performed to further investigate the study objectives in specific circumstances (Please see section 7 in the final study report). Overall, in each country a very low sample size was extracted for each exploratory analysis, specially for the Secondary outcome cohort.

The putative risk factors and frequencies of the outcomes of interest were described in the population of offspring born to fathers exposed to polytherapy of valproate or lamotrigine/levetiracetam and other AEDs, at the time of conception. For this exploratory analysis, 335 (91 in the valproate and 244 in lamotrigine/levetiracetam group) offspring were identified in Denmark, 414 (92 in valproate and 322 in lamotrigine/levetiracetam) in Sweden, and 204 (45 in valproate and 159 in lamotrigine/levetiracetam) in Norway for the Primary outcome cohort. In either monotherapy or polytherapy group, the most common indication for therapy with valproate or lamotrigine/levetiracetam was epilepsy. In Denmark, many of the offspring, maternal, and paternal demographic and clinical characteristics were masked, following the masking rules defined this country, limiting a comparison with the main analyses. As expected, the 2 cohorts differed for some characteristics, and consistently across the 3 study countries, a likely consequence of the reduced sample size and the different selected populations. In general, fewer risk factors or confounders were identified in the polytherapy group. As expected, the proportion of NDD, including ASD, was higher in the offspring of fathers exposed to valproate or to lamotrigine/levetiracetam with other AEDs in polytherapy when compared to the main analysis results. However, in Denmark, the cumulative proportion of NDD including ASD was similar in the offspring paternally exposed to valproate polytherapy compared to valproate monotherapy in the main analysis (5.5% vs 5.4%, respectively), though higher in the offspring paternally exposed to lamotrigine/levetiracetam polytherapy compared to lamotrigine/levetiracetam monotherapy. However, the group of fathers in the valproate polytherapy group was very small.

For the analysis of polytherapy in the Secondary outcome cohort (CM), 23 (none in valproate and 23 in lamotrigine/levetiracetam) offspring were identified in Denmark, and 35 (3 in valproate and 32 in lamotrigine/levetiracetam group) in Norway. Due to the small sample size, no conclusion on the putative risk factors or confounders could be drawn.

Risk factors and frequencies of the outcomes of interest were also described in paternal valproate exposure-discordant siblings (at least one offspring with paternal valproate exposure and one offspring without valproate exposure [ie, at least one offspring with paternal valproate exposure and one offspring exposed to lamotrigine/levetiracetam]). For this analysis, 21 (11 on valproate and 10 on lamotrigine or levetiracetam) offspring were identified in Denmark, 29 (15 on valproate and 14 on lamotrigine or levetiracetam) in Sweden, and 2 (1 on valproate and 1 on lamotrigine or levetiracetam) in Norway for the Primary outcome cohort. Overall, the follow-up length was longer in the valproate group than in the lamotrigine/levetiracetam group. However, no other conclusion could be drawn since none of the offspring's, father's, or mother's characteristics were considered risk factors or confounders due to the small sample size and lack of observed characteristics, such as maternal and paternal comorbidities.

In the Secondary outcome cohort, no events were observed for Denmark and only one for Norway (in lamotrigine/levetiracetam group), in siblings and their offspring who were paternally and maternally matched exposure-discordant discordant (valproate vs. lamotrigine/levetiracetam monotherapy) at conception. No

conclusion could be drawn because most paternal, maternal, and offspring characteristics were not observed due to the small sample size.

5. Other information

This section supersedes section 12 from the final study report v1.1.

None.

6. Conclusions

This section supersedes section 13 from the final study report v1.1.

This real-world retrospective study provides the first data on NDD and CM in offspring paternally exposed to valproate during 3-month preconception, compared to those exposed to lamotrigine/levetiracetam. The pooled HR indicated a moderate risk (HR 1.50, 95% CI: 1.09, 2.07) of NDD including ASD in offspring paternally exposed to valproate compared to those paternally exposed to lamotrigine/levetiracetam.

The pooled crude risk of CM suggested no higher risk in offspring paternally exposed to valproate when compared to those exposed to lamotrigine/levetiracetam. Results were based on crude estimates which were potentially biased and also affected by considerable heterogeneity, thus these findings should be interpreted with caution.

Overall, this retrospective observational study has several limitations, including the difference in follow-up duration between the 2 groups, especially in Denmark, and the different time period of exposure.

7. References

This section supersedes section 14 from the final study report v1.1.

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8. Appendix

This section supersedes section 15 from the final study report v1.1.

8.1 Norway

This section supersedes section 15.3 from the final study report v1.1.

8.1.1 Description of the offspring, maternal and paternal characteristics in the Primary outcome cohort

This section supersedes section 15.3.1.1 from the final study report v1.1.

Characteristics of the offspring, mothers and fathers from the Primary outcome cohort are reported from Table 46 to Table 48. Among the 3,300 offspring from the Primary outcome cohort, 51.9% were male, 1.1% were diagnosed with epilepsy, and 0.8% were exposed to AEDs during the period they were followed-up (Table 46). Please note that all these offspring were excluded from the comparative analyses, therefore distribution of these characteristics might differ in those analyses (see Figure 1).

Regarding maternal characteristics of this group, the median (IQR) age of mothers at childbirth was 31.0 (27.0-34.0) years. The most frequent maternal comorbidities diagnosed prior to childbirth were neurotic disorder (13.0%), affective disorder (8.6%), gestational diabetes (7.1%), diabetes (1.9%), and epilepsy (1.7%). Majority of the mothers were non-smokers prior to LMP2 (72.3%) and during pregnancy (82.6%); however, missing values were observed for 13.2% and 10.8% of mothers, respectively (Table 47).

Maternal exposure to AEDs prior to LMP2 and during pregnancy was low, and the proportion of use of each AED (including valproate, lamotrigine and levetiracetam) was lower than 1%, except for the category of 'Other antiepileptics' (1.6%); these mothers were excluded from the comparative analysis. In total, 44.9% of mothers had at least one prescription of concomitant medications during pregnancy associated with neuropsychiatric adverse events, while prior to LMP2 this percentage was 68.1% (Table 48).

Regarding paternal characteristics of this group, the median (IQR) age of fathers at childbirth was 34.0 (30.0-38.0) years. The most frequent paternal comorbidities diagnosed prior to childbirth were affective disorder excluding bipolar affective disorder and mania (13.6%), neurotic disorder (13.3%), and bipolar affective disorder (11.7%). With regard to paternal exposure to AEDs, 12.5% of fathers were exposed to valproate in monotherapy, and 32.1% were exposed to lamotrigine/levetiracetam in monotherapy in the 3 months lookback period from LMP2, the remaining ones were exposed to other AEDs. Only 2.0% of conceptions occurred in 2019; this small proportion is due to study period ending in December 2019, which resulted in the inclusion only of those conceptions that occurred in the first months of the year, and which resulted in a childbirth in the same year (Table 49).

Table 46 Description of the offspring characteristics in the Primary outcome cohort in Norway (N=3,300)

NDD - offspring characteristics		
Number of pregnancies	**3300**	
	N	**%**
Gestational age (weeks)		
<28 (extremely preterm)	9	0.27
28-31 (very preterm)	19	0.58
32-36 (moderate to late preterm)	144	4.36
37-41 (at term)	2994	90.73
≥42 (post-term)	134	4.06
Missing	0	0.00
Birth weight (g)		
<1000 (extremely low)	16	0.48
1000-1499 (very low)	11	0.33
1500-2499 (low)	106	3.21
≥2500	3167	95.97
Missing	0	0.00
Gender [a]		
Male	1711	51.85
Female	1589	48.15
Missing	0	0.00
Comorbidities [b]		
Congenital CMV	0	0.00
Congenital rubella	0	0.00
Epilepsy	36	1.09
Fetal alcohol syndrome	0	0.00
Fragile X syndrome	0	0.00
Lejeune/cri du chat syndrome	0	0.00
Tuberous sclerosis	2	0.06
Medication use [b]		
Exposure to AEDs	26	0.79

AED: Antiepileptic drugs; CMV: Cytomegalovirus; NDD: Neurodevelopmental disorders
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) between index and exit date

Table 47 Description of the maternal characteristics in the Primary outcome cohort in Norway (N=3,300)

NDD - offspring characteristics		
Number of pregnancies	**3300**	
	N	**%**
Mother's age [a]		
≤20 years	48	1.45
21-25	474	14.36
26-30	1096	33.21
31-35	1084	32.85
36-40	483	14.64
>40	115	3.48
Mean (SD)	30.77 (5.12)	
Median (25^{th} - 75^{th} percentile)	31.00 (27.00, 34.00)	
Min, max	17.00, 47.00	
Missing	0	0.00
Comorbidities		
Affective disorder [b]	283	8.58
Diabetes [b]	64	1.94
Epilepsy [b]	55	1.67
Neurotic disorder [b]	428	12.97
Schizophrenia, schizotypal and delusional disorders [b]	3	0.09
Obesity [c]	34	1.03
CMV [d]	0	0.00
Gestational diabetes [d]	233	7.06
Rubella [d]	0	0.00
Lifestyle characteristics		
Alcohol abuse prior to LMP2 [c]	12	0.36
Alcohol abuse during pregnancy [d]	5	0.15
Substance abuse prior to LMP2 [c]	21	0.64
Substance abuse during pregnancy [d]	20	0.61
Smoking prior to LMP2 [c]		
Yes	477	14.45
No	2387	72.33
Missing	436	13.21
Smoking during pregnancy [d]		
Yes	218	6.61
No	2725	82.58
Missing	357	10.82
Medication use		
Exposure to AEDs prior to LMP2 [e]		
Valproate	2	0.06
Lamotrigine	27	0.82

NDD - offspring characteristics		
Number of pregnancies	**3300**	
	N	**%**
Levetiracetam	2	0.06
Barbiturates and derivatives	0	0.00
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [f]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	8	0.24
Carboxamide derivatives	9	0.27
Fatty acid derivatives	2	0.06
Other antiepileptics	51	1.55
Exposure to AEDs during pregnancy [d]		
Valproate	0	0.00
Lamotrigine	26	0.79
Levetiracetam	3	0.09
Barbiturates and derivatives	1	0.03
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [f]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	4	0.12
Carboxamide derivatives	8	0.24
Fatty acid derivatives	0	0.00
Other antiepileptics	48	1.45
Maternal polypharmacy index prior to LMP2 [e]		
0	2097	63.55
1-4	1152	34.91
5-10	50	1.52
>10	1	0.03
Mean (SD)	0.66 (1.15)	
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 1.00)	
Min, max	0.00, 12.00	
Maternal polypharmacy index during pregnancy [d]		
0	1632	49.45
1-4	1574	47.70
5-10	94	2.85
>10	0	0.00
Mean (SD)	0.98 (1.33)	
Median (25^{th} - 75^{th} percentile)	1.00 (0.00, 1.00)	
Min, max	0.00, 10.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [c] - mothers with at least one prescription	335	10.15

NDD - offspring characteristics		
Number of pregnancies	**3300**	
	N	**%**
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	174	5.27
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [c] -mothers with at least one prescription	2246	68.06
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [d] - mothers with at least one prescription	1480	44.85

AED: Antiepileptic drugs; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; SD: Standard deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.
a) at index (childbirth)
b) all available data prior to index date
c) 12 months lookback from LMP2
d) during pregnancy (from LMP2 until index date)
e) 3 months lookback from LMP2
f) Oxazolidine derivatives were not sold in Norway during the study period

Table 48 Description of the paternal characteristics in the Primary outcome cohort in Norway (N=3,300)

NDD - paternal characteristics		
Number of pregnancies	**3300**	
	N	**%**
Father's age [a]		
≤20 years	9	0.27
21-25	201	6.09
26-30	707	21.42
31-35	1072	32.48
36-40	738	22.36
>40	573	17.36
Mean (SD)	34.56 (6.57)	
Median (25^{th} - 75^{th} percentile)	34.00 (30.00, 38.00)	
Min, max	18.00, 67.00	
Missing	0	0.00
Year of offspring conception [b]		
2009	251	7.61
2010	376	11.39
2011	318	9.64
2012	355	10.76
2013	323	9.79
2014	350	10.61
2015	357	10.82

NDD - paternal characteristics		
Number of pregnancies	**3300**	
	N	**%**
2016	322	9.76
2017	296	8.97
2018	286	8.67
2019	66	2.00
Comorbidities [c]		
Affective disorder excluding bipolar affective disorder and mania	447	13.55
Bipolar affective disorder	386	11.70
Mania	15	0.45
Neurotic disorder	439	13.30
Schizophrenia, schizotypal and delusional disorders	49	1.48
Lifestyle characteristics		
Substance abuse [e]	74	2.24
Medication use		
Exposure to AEDs [f]		
Valproate [g]	622	18.85
Lamotrigine [g]	1097	33.24
Levetiracetam [g]	343	10.39
Barbiturates and derivatives [g]	19	0.58
Hydantoin derivatives [g]	21	0.64
Oxazolidine derivatives [d,g]	0	0.00
Succinimide derivatives [g]	5	0.15
Benzodiazepine derivatives [g]	147	4.45
Carboxamide derivatives [g]	518	15.70
Fatty acid derivatives [g]	622	18.85
Other antiepileptics [g]	2333	70.70
Valproate in monotherapy	413	12.52
Lamotrigine in monotherapy	896	27.15
Levetiracetam in monotherapy	162	4.91
Lamotrigine/levetiracetam in monotherapy	1058	32.06
Paternal polypharmacy index [f]		
0	1572	47.64
1-4	1569	47.55
5-10	153	4.64
>10	6	0.18
Mean (SD)	1.17 (1.62)	
Median (25^{th} - 75^{th} percentile)	1.00 (0.00, 2.00)	
Min, max	0.00, 14.00	

NDD - paternal characteristics		
Number of pregnancies	**3300**	
	N	**%**
Concomitant medications associated with valproate-indicated psychiatric conditions [e] - fathers with at least one prescription	1490	45.15
Concomitant medications associated with neuropsychiatric adverse events [e] - fathers with at least one prescription	2320	70.30
Fathers exposed to AEDs polytherapy prior to LMP2 [f]	454	13.76
Fathers exposed to valproate in combination with other AEDs prior to LMP2 [f]	205	6.21
Fathers switching to/from an AED other than valproate, lamotrigine, levetiracetam prior to LMP2 [f]	242	7.33

AED: antiepileptic drugs; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: neurodevelopmental disorders; SD: Standard Deviation
Legend: Number of offspring represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over the total number of offspring.

a) at index (childbirth)
b) at mother's LMP2
c) all available data prior to index date
d) Oxazolidine derivatives were not sold in Norway during the study period
e) 12 months lookback from LMP2
f) 3 months lookback from LMP2
g) in mono- or polytherapy

8.1.2 Description of the offspring, maternal and paternal characteristics in the secondary outcome cohort

This section supersedes section 15.3.1.2 from the final study report v1.1.

Characteristics of the offspring, mothers and fathers from the Secondary outcome cohort are reported from Table 49 to Table 51.

Among the 3,315 offspring in the Secondary outcome cohort, 51.9% were male, 90.3%, were born at term, 95.7% were weighing ≥2500 g. The comorbidities of congenital herpes simplex and congenital varicella were present in <5 offspring, while the rest were absent (Table 49).

Regarding maternal characteristics of mothers from the Secondary outcome cohort, the median (IQR) age of mothers at childbirth was 30.0 (27.0, 34.0) years. The most frequent maternal comorbidities prior to childbirth were diabetes (1.8%) and gestational diabetes (1.8%). Smoking status prior to LMP2 was 14.5% and during pregnancy 6.6%. However, missing data for smoking status prior to LMP2 and during pregnancy were 13.3% and 10.9%, respectively. Exposure to other antiepileptics 3 months prior to LMP2 and during pregnancy was observed among 1.5% and 1.4% of mothers, respectively (Table 50).

Regarding characteristics of fathers from the Secondary outcome cohort, the median (IQR) age of fathers at childbirth was 33.0 (30.0, 38.0) years. With regards to exposure to any AEDs, 18.8% of fathers were exposed

to valproate in monotherapy and 33.1% were exposed to lamotrigine/levetiracetam in monotherapy in the 3 months lookback period from LMP2, while the remaining fathers were exposed to other antiepileptics. Considering the Secondary outcome cohort for descriptive analyses, 61.4% of fathers were exposed to teratogenic activity/fetal toxicity prior to LMP2 (Table 51).

Table 49 Description of the offspring characteristics for the Secondary outcome cohort in Norway (N=4,676)

CM - offspring characteristics		
Number of pregnancies	**3315**	
	N	**%**
Gestational age (weeks)		
<28 (extremely preterm)	16	0.48
28-31 (very preterm)	21	0.63
32-36 (moderate to late preterm)	149	4.49
37-41 (at term)	2995	90.35
≥42 (post-term)	134	4.04
Missing	0	0.00
Birth weight (g)		
<1000 (extremely low)	22	0.66
1000-1499 (very low)	14	0.42
1500-2499 (low)	107	3.23
≥2500	3171	95.66
Missing	1	0.03
Gender		
Male	1720	51.89
Female	1594	48.08
Missing	1	0.03
Comorbidities [a]		
Congenital CMV	0	0.00
Congenital Herpes Simplex	1	0.03
Congenital rubella	0	0.00
Congenital toxoplasmosis	0	0.00
Congenital varicella	1	0.03
Fetal alcohol syndrome	0	0.00

CM: Congenital Malformations; CMV: Cytomegalovirus
Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. 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) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark, birthdate of live offspring in Sweden) and exit date

Table 50 Description of the maternal characteristics for the Secondary outcome cohort in Norway (N=4,676)

CM - maternal characteristics		
Number of pregnancies	**3315**	
	N	**%**
Mother's age at index date [a]		
≤20 years	62	1.87
21-25	537	16.20
26-30	1155	34.84
31-35	1028	31.01
36-40	444	13.39
>40	89	2.68
Mean (SD)	30.27 (5.12)	
Median (25^{th} - 75^{th} percentile)	30.00 (27.00, 34.00)	
Min, max	17.00, 46.00	
Missing	0	0.00
Comorbidities		
Diabetes [b]	60	1.81
Epilepsy [b]	55	1.66
Obesity [c]	34	1.03
CMV [d]	0	0.00
Folate deficiency [d]	0	0.00
Gestational diabetes [d]	61	1.84
Herpes simplex virus [d]	2	0.06
Rubella [d]	0	0.00
Toxoplasmosis [d]	0	0.00
Varicella [d]	4	0.12
Lifestyle characteristics		
Alcohol abuse prior to LMP2 [c]	12	0.36
Alcohol abuse during pregnancy [d]	5	0.15
Substance abuse prior to LMP2 [c]	21	0.63
Substance abuse during pregnancy [d]	15	0.45
Smoking prior to LMP2 [c]		
Yes	480	14.48
No	2395	72.25
Missing	440	13.27
Smoking during pregnancy [d]		
Yes	218	6.58
No	2735	82.50
Missing	362	10.92

CM - maternal characteristics		
Number of pregnancies	**3315**	
	N	**%**
Medication use		
Exposure to AEDs prior to LMP2 [a]		
Valproate	2	0.06
Lamotrigine	27	0.81
Levetiracetam	2	0.06
Barbiturates and derivatives	0	0.00
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [e]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	8	0.24
Carboxamide derivatives	9	0.27
Fatty acid derivatives	2	0.06
Other antiepileptics	51	1.54
Exposure to AEDs during pregnancy [d]		
Valproate	0	0.00
Lamotrigine	26	0.78
Levetiracetam	2	0.06
Barbiturates and derivatives	1	0.03
Hydantoin derivatives	0	0.00
Oxazolidine derivatives [e]	0	0.00
Succinimide derivatives	0	0.00
Benzodiazepine derivatives	1	0.03
Carboxamide derivatives	7	0.21
Fatty acid derivatives	0	0.00
Other antiepileptics	46	1.39
Maternal exposure to teratogenic activity/fetal toxicity prior to LMP2 [f] - mothers with at least one prescription	973	29.35
Maternal exposure to teratogenic activity/fetal toxicity during pregnancy [d] - mothers with at least one prescription	1011	30.50

AED: antiepileptic drugs; CM: Congenital Malformations; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; SD: Standard deviation

Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. 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 (12th week of gestation in Norway, 22nd week of gestation in Denmark, birthdate of live offspring in Sweden)
b) all available data prior to index date
c) 12-months lookback from LMP2
d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
e) Oxazolidine derivatives were not sold in Norway during the study period
f) 3-months lookback from LMP2

Table 51 Description of the paternal characteristics for the Secondary outcome cohort in Norway (N=4,676)

CM - paternal characteristics		
Number of pregnancies	**3315**	
	N	**%**
Father's age [a]		
≤20 years	16	0.48
21-25	234	7.06
26-30	782	23.59
31-35	1071	32.31
36-40	699	21.09
>40	513	15.48
Mean (SD)	34.05 (6.57)	
Median (25^{th} - 75^{th} percentile)	33.00 (30.00, 38.00)	
Min, max	17.00, 66.00	
Missing	0	0.00
Year of child conception [b]		
2009	252	7.60
2010	378	11.40
2011	321	9.68
2012	358	10.80
2013	324	9.77
2014	350	10.56
2015	355	10.71
2016	323	9.74
2017	299	9.02
2018	288	8.69
2019	67	2.02
Medication use		
Exposure to AEDs		
Valproate [d]	625	18.85
Lamotrigine [d]	1098	33.12
Levetiracetam [d]	345	10.41
Barbiturates and derivatives [d]	19	0.57
Hydantoin derivatives [d]	21	0.63
Oxazolidine derivatives [d,e]	0	0.00
Succinimide derivatives [d]	5	0.15
Benzodiazepine derivatives [d]	147	4.43
Carboxamide derivatives [d]	522	15.75
Fatty acid derivatives [d]	625	18.85
Other antiepileptics [d]	2343	70.68
Valproate in monotherapy	416	12.55
Lamotrigine in monotherapy	897	27.06

CM - paternal characteristics		
Number of pregnancies	**3315**	
	N	**%**
Levetiracetam in monotherapy	163	4.92
Lamotrigine/levetiracetam in monotherapy	1060	31.98
Fathers exposed to AEDs polytherapy prior to LMP2 [c]	457	13.79
Fathers exposed to valproate in combination with other AEDs prior to LMP2 [c]	205	6.18
Fathers switching to/from an AED other than valproate, lamotrigine, levetiracetam prior to LMP2 [c]	243	7.33
Paternal exposure to teratogenic activity/fetal toxicity prior to LMP2 [c,f]	2035	61.39

AED: antiepileptic drugs; CM: Congenital Malformations; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; SD: Standard deviation

Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once. 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 (12th week of gestation in Norway, 22nd week of gestation in Denmark, birthdate of live offspring in Sweden)
b) at mother's LMP2
c) 3-months lookback from LMP2
d) in mono- or polytherapy
e) Oxazolidine derivatives were not sold in Norway during the study period
f) Please note, that the list of teratogens include 'All other AEDs'

8.1.3 Cumulative incidence proportion of NDD by gender

This section supersedes section 15.3.2 from the final study report v1.1.

Table 52 Cumulative incidence proportion (risk) of NDD by paternal exposure group for male offspring; primary outcome

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	205	562	465	97	767
0-1 years	n	1	0	0	0	1
	n/N*100	0.49 (-0.47, 1.44)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.13 (-0.12, 0.39)
	N	189	501	419	82	690
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	166	446	374	72	612
2-3 years	n	0	2	2	0	2
	n/N*100	0.00 (0.00, 0.00)	0.45 (-0.17, 1.07)	0.53 (-0.20, 1.27)	0.00 (0.00, 0.00)	0.33 (-0.13, 0.78)
	N	144	388	327	61	532
3-4 years	n	1	6	5	1	7
	n/N*100	0.69 (-0.66, 2.05)	1.55 (0.32, 2.77)	1.53 (0.20, 2.86)	1.64 (-1.55, 4.83)	1.32 (0.35, 2.28)
	N	122	322	275	47	444
4-5 years	n	2	2	1	1	4
	n/N*100	1.64 (-0.61, 3.89)	0.62 (-0.24, 1.48)	0.36 (-0.35, 1.08)	2.13 (-2.00, 6.25)	0.90 (0.02, 1.78)
	N	105	266	230	36	371
5-6 years	n	1	1	0	1	2
	n/N*100	0.95 (-0.91, 2.81)	0.38 (-0.36, 1.11)	0.00 (0.00, 0.00)	2.78 (-2.59, 8.15)	0.54 (-0.21, 1.28)
	N	83	193	169	24	276

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
6-7 years	n	2	5	5	0	7
	n/N*100	2.41 (-0.89, 5.71)	2.59 (0.35, 4.83)	2.96 (0.40, 5.51)	0.00 (0.00, 0.00)	2.54 (0.68, 4.39)
	N	59	130	118	12	189
7-8 years	n	2	1	1	0	3
	n/N*100	3.39 (-1.23, 8.01)	0.77 (-0.73, 2.27)	0.85 (-0.81, 2.50)	0.00 (0.00, 0.00)	1.59 (-0.19, 3.37)
	N	36	92	82	10	128
8-9 years	n	0	2	2	0	2
	n/N*100	0.00 (0.00, 0.00)	2.17 (-0.81, 5.15)	2.44 (-0.90, 5.78)	0.00 (0.00, 0.00)	1.56 (-0.59, 3.71)
	N	12	43	37	6	55
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	205	562	465	97	767
Overall (0-10 years)	n	9	19	16	3	28
	n/N*100	4.39 (1.59, 7.19)	3.38 (1.89, 4.88)	3.44 (1.78, 5.10)	3.09 (-0.35, 6.54)	3.65 (2.32, 4.98)

NDD: neurodevelopmental disorders
Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which were determined based on the results of the univariate analyses. As an example, this table presents incidence proportions stratified by gender. Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) were presented.

Table 53 Cumulative incidence proportion (risk) of NDD by paternal exposure group for female offspring; primary outcome

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	N	208	496	431	65	704
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	192	447	389	58	639
1-2 years	n	1	0	0	0	1
	n/N*100	0.52 (-0.50, 1.54)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.16 (-0.15, 0.46)
	N	176	404	352	52	580
2-3 years	n	2	2	2	0	4
	n/N*100	1.14 (-0.43, 2.70)	0.50 (-0.19, 1.18)	0.57 (-0.22, 1.35)	0.00 (0.00, 0.00)	0.69 (0.02, 1.36)
	N	150	345	299	46	495
3-4 years	n	1	0	0	0	1
	n/N*100	0.67 (-0.64, 1.97)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.20 (-0.19, 0.60)
	N	127	283	250	33	410
4-5 years	n	0	3	2	1	3
	n/N*100	0.00 (0.00, 0.00)	1.06 (-0.13, 2.25)	0.80 (-0.30, 1.90)	3.03 (-2.82, 8.88)	0.73 (-0.09, 1.56)
	N	98	234	208	26	332
5-6 years	n	1	0	0	0	1
	n/N*100	1.02 (-0.97, 3.01)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.30 (-0.29, 0.89)
	N	77	188	171	17	265
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	56	147	134	13	203

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
7-8 years	n	2	0	0	0	2
	n/N*100	3.57 (-1.29, 8.43)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.00 (0.00, 0.00)	0.99 (-0.37, 2.34)
	N	34	103	97	6	137
8-9 years	n	1	1	1	0	2
	n/N*100	2.94 (-2.74, 8.62)	0.97 (-0.92, 2.86)	1.03 (-0.98, 3.04)	0.00 (0.00, 0.00)	1.46 (-0.55, 3.47)
	N	15	39	38	1	54
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	208	496	431	65	704
Overall (0-10 years)	n	8	6	5	1	14
	n/N*100	3.85 (1.23, 6.46)	1.21 (0.25, 2.17)	1.16 (0.15, 2.17)	1.54 (-1.45, 4.53)	1.99 (0.96, 3.02)

NDD: neurodevelopmental disorders
Incidence proportions may be stratified according to relevant strong risk factors (such as age or gender) which were determined based on the results of the univariate analyses. As an example, this table presents incidence proportions stratified by gender. Number of offspring at risk at the beginning of each year of follow-up (N), number of offspring with a new event during the year (n) and proportion (n/N×100) with the 95% confidence interval (CI) were presented.

8.1.4 Cumulative incidence rate and time to NDD diagnosis by gender

This section supersedes section 15.3.3 from the final study report v1.1.

Table 54 Cumulative incidence rate of NDD by paternal exposure group for males; primary outcome

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
0-1 years	PY	195.42	533.01	443.27	89.74	728.43
	n	1	0	0	0	1
	n/PY*1000	5.12 (0.13, 28.51)	0.00 (-, 6.92)	0.00 (-, 8.32)	0.00 (-, 41.11)	1.37 (0.03, 7.65)
0-2 years	PY	371.21	1004.93	837.96	166.97	1376.14
	n	1	0	0	0	1
	n/PY*1000	2.69 (0.07, 15.01)	0.00 (-, 3.67)	0.00 (-, 4.40)	0.00 (-, 22.09)	0.73 (0.02, 4.05)
0-3 years	PY	526.51	1421.06	1188.1	232.96	1947.57
	n	1	2	2	0	3
	n/PY*1000	1.9 (0.05, 10.58)	1.41 (0.17, 5.08)	1.68 (0.20, 6.08)	0.00 (-, 15.83)	1.54 (0.32, 4.50)
0-4 years	PY	660.11	1774.21	1486.58	287.63	2434.32
	n	2	8	7	1	10
	n/PY*1000	3.03 (0.37, 10.94)	4.51 (1.95, 8.88)	4.71 (1.89, 9.70)	3.48 (0.09, 19.37)	4.11 (1.97, 7.55)
0-5 years	PY	774.38	2067.23	1738.68	328.56	2841.61
	n	4	10	8	2	14
	n/PY*1000	5.17 (1.41, 13.23)	4.84 (2.32, 8.90)	4.60 (1.99, 9.07)	6.09 (0.74, 21.99)	4.93 (2.69, 8.27)
0-6 years	PY	869.44	2293.11	1933.86	359.24	3162.55
	n	5	11	8	3	16
	n/PY*1000	5.75 (1.87, 13.42)	4.80 (2.39, 8.58)	4.14 (1.79, 8.15)	8.35 (1.72, 24.41)	5.06 (2.89, 8.22)
	PY	940.9	2455.65	2076.98	378.67	3396.55

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
0-7 years	n	7	16	13	3	23
	n/PY*1000	7.44 (2.99, 15.33)	6.52 (3.72, 10.58)	6.26 (3.33, 10.70)	7.92 (1.63, 23.15)	6.77 (4.29, 10.16)
	PY	986.20	2564.34	2174.39	389.95	3550.54
0-8 years	n	9	17	14	3	26
	n/PY*1000	9.13 (4.17, 17.32)	6.63 (3.86, 10.61)	6.44 (3.52, 10.80)	7.69 (1.59, 22.48)	7.32 (4.78, 10.73)
	PY	1012	2635.66	2236.99	398.67	3647.66
0-9 years	n	9	19	16	3	28
	n/PY*1000	8.89 (4.07, 16.88)	7.21 (4.34, 11.26)	7.15 (4.09, 11.62)	7.53 (1.55, 21.99)	7.68 (5.10, 11.09)
	PY	1020.09	2656.92	2255.33	401.59	3677.01
0-10 years	n	9	19	16	3	28
	n/PY*1000	8.82 (4.03, 16.75)	7.15 (4.31, 11.17)	7.09 (4.06, 11.52)	7.47 (1.54, 21.83)	7.61 (5.06, 11.01)

NDD: Neurodevelopmental Disorders; PY: Person-Years
Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which were determined based on the results of the univariate analyses. As an example, this table presents incidence rates stratified by gender. Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) were presented. It was not always possible to estimate the lower bound of the 95% CI for the corresponding incidence rate

Table 55 Cumulative incidence rate of NDD by paternal exposure group for females; primary outcome

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	PY	200.51	469.16	407.67	61.49	669.67
0-1 years	n	0	0	0	0	0
	n/PY*1000	0.00 (-, 18.40)	0.00 (-, 7.86)	0.00 (-, 9.05)	0.00 (-, 59.99)	0.00 (-, 5.51)
	PY	383.16	896.3	779.96	116.35	1279.46
0-2 years	n	1	0	0	0	1
	n/PY*1000	2.61 (0.07, 14.54)	0.00 (-, 4.12)	0.00 (-, 4.73)	0.00 (-, 31.71)	0.78 (0.02, 4.35)
	PY	548.78	1275.65	1111.53	164.12	1824.43
0-3 years	n	3	2	2	0	5
	n/PY*1000	5.47 (1.13, 15.98)	1.57 (0.19, 5.66)	1.80 (0.22, 6.50)	0.00 (-, 22.48)	2.74 (0.89, 6.40)
	PY	691.30	1593.54	1388.42	205.12	2284.85
0-4 years	n	4	2	2	0	6
	n/PY*1000	5.79 (1.58, 14.81)	1.26 (0.15, 4.53)	1.44 (0.17, 5.20)	0.00 (-, 17.98)	2.63 (0.96, 5.72)
	PY	805.56	1853.58	1618.54	235.04	2659.13
0-5 years	n	4	5	4	1	9
	n/PY*1000	4.97 (1.35, 12.71)	2.70 (0.88, 6.30)	2.47 (0.67, 6.33)	4.25 (0.11, 23.71)	3.38 (1.55, 6.42)
	PY	892.42	2063.72	1806.86	256.85	2956.13
0-6 years	n	5	5	4	1	10
	n/PY*1000	5.60 (1.82, 13.07)	2.42 (0.79, 5.65)	2.21 (0.60, 5.67)	3.89 (0.10, 21.69)	3.38 (1.62, 6.22)
	PY	960.11	2234.01	1962.5	271.51	3194.12
0-7 years	n	5	5	4	1	10
	n/PY*1000	5.21 (1.69, 12.15)	2.24 (0.73, 5.22)	2.04 (0.56, 5.22)	3.68 (0.09, 20.52)	3.13 (1.50, 5.76)
	PY	1003.93	2361.46	2080.38	281.08	3365.39
0-8 years	n	7	5	4	1	12

		Paternal exposure group				
NDD		**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Follow-up period						
	n/PY*1000	6.97 (2.80, 14.37)	2.12 (0.69, 4.94)	1.92 (0.52, 4.92)	3.56 (0.09, 19.82)	3.57 (1.84, 6.23)
	PY	1028.70	2431.59	2147.38	284.21	3460.29
0-9 years	n	8	6	5	1	14
	n/PY*1000	7.78 (3.36, 15.32)	2.47 (0.91, 5.37)	2.33 (0.76, 5.43)	3.52 (0.09, 19.60)	4.05 (2.21, 6.79)
	PY	1035.75	2451.66	2167.04	284.62	3487.42
0-10 years	n	8	6	5	1	14
	n/PY*1000	7.72 (3.33, 15.22)	2.45 (0.90, 5.33)	2.31 (0.75, 5.38)	3.51 (0.09, 19.58)	4.01 (2.19, 6.74)

NDD: Neurodevelopmental Disorders; PY: Person-Years
Legend: Cumulative incidence rates may be stratified according to relevant strong risk factors (such as age or gender) which were determined based on the results of the univariate analyses. As an example, this table presents incidence rates stratified by gender. Person-years at risk during the age period (PY), number of new events during the age period (n) and rate (n/PY×1000) were presented. It was not always possible to estimate the lower bound of the 95% CI for the corresponding incidence rate

Table 56 Time to NDD by paternal exposure group stratified by offspring gender Primary outcome cohort in Norway

	Paternal exposure group (Male offspring)				
NDD	**Valproate**	**Lamotrigine /levetiracetam**	**Lamotrigine**	**Levetiracetam**	**Total (valproate + lamotrigine /levetiracetam)**
Number of events	9	19	16	3	28
Number of censor	196	543	449	94	739
Survival time					
5th percentile	79.00 (53.10, -)	83.73 (52.83, -)	83.7 3 (48.23, -)	64.47 (52.83, -)	80.77 (53.10, -)
10th percentile	93.70 (79.00, -)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
25th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
	Paternal exposure group (Female offspring)				
Number of events	8	6	5	1	14
Number o f censor	200	490	426	64	690
Survival time					
5th percentile	89.53 (32.97, -)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
10th percentile	99.23 (89.53, -)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
25th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
median	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)
75th percentile	-(-,-)	-(-,-)	-(-,-)	-(-,-)	-(-,-)

NDD: Neurodevelopmental disorders
Legend: Due to low number of events the median time-to-event could not be calculated. Over the study period, the frequency of events was lower than 10% in the cohort, therefore only the 5th percentile of the time to diagnosis could be estimated, and it was not always possible to estimate the upper bound of the 95% CI for the corresponding time-to-event

8.1.5 Variables estimate from propensity score

This section supersedes section 15.3.4 from the final study report v1.1.

Table 57 Variable importance metric from random forest propensity score model; Primary outcome cohort in Norway

NDD	Variable importance
Variable (or interaction) [a]	
Offspring risk factors/confounders	
Gender [b]	-0.01
Maternal risk factors/confounders	
Mother's age [b] (categorical)	-0.02
Affective disorder [d]	-0.01
Diabetes [d]	0.01
Gestational diabetes [e]	0.00
Neurotic disorder [d]	0.02
Schizophrenia, schizotypal and delusional disorders [d]	0.02
Obesity [f]	0.02
Alcohol abuse prior to LMP2 [f]	0.02
Alcohol abuse during pregnancy [e]	0.03
Substance abuse prior to LMP2 [f]	0.02
Substance abuse during pregnancy [e]	0.06
Smoking during pregnancy [e]	0.05
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.01
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	-0.03

NDD	Variable importance
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] -mothers with at least one prescription	-0.01
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]	0.04
Neurotic disorder [d]	-0.03
Schizophrenia, schizotypal and delusional disorders [d]	0.05
Substance abuse [f]	0.04
Year of offspring conception [i]	-0.01

LMP2: Last menstrual period date plus 2 weeks; NDD: neurodevelopmental disorders
Legend: Importance metric is represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.

a) Candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. All two-way interactions were considered
b) at index (childbirth)
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) at mother's LMP2

Table 58 Variable estimates from logistic regression informed by random forest propensity score model; Primary outcome cohort in Norway

NDD	Estimate		
Variable (or interaction) [a]	**OR**	**95% CI**	**P-value**
Offspring risk factors/confounders			
Gender [b]			
Male	Reference	-	-
Female	1.08	0.83, 1.41	0.5718
Maternal risk factors/confounders			
Mother's age [b] (categorical)			
≤20 years	1.12	0.40, 3.16	0.8295
21-25	0.97	0.64, 1.46	0.8768
26-30	Reference	-	-
31-35	0.98	0.71, 1.34	0.8818
36-40	0.77	0.49, 1.20	0.2480
>40	0.42	0.17, 1.05	0.0626
Affective disorder [d]	0.62	0.34, 1.14	0.1273
Diabetes [d]	0.65	0.21, 2.04	0.4646
Neurotic disorder [d]	1.13	0.73, 1.74	0.5899
Obesity [f]	1.12	0.30, 4.18	0.8654
Smoking during pregnancy [e]			
No	Reference	-	-
Yes	1.94	1.09, 3.46	0.0246
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [f] - mothers with at least one prescription	0.73	0.40, 1.32	0.2912
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [e] - mothers with at least one prescription	0.27	0.09, 0.82	0.0211
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [f] -mothers with at least one prescription	1.10	0.81, 1.47	0.5448
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [e] - mothers with at least one prescription	0.96	0.73, 1.28	0.7966

NDD	Estimate		
Variable (or interaction) [a]	**OR**	**95% CI**	**P-value**
Paternal risk factors/confounders			
Affective disorder [d,g]	0.37	0.22, 0.61	<.0001
Bipolar affective disorder [d]	0.53	0.36, 0.79	0.0017
Neurotic disorder [d]	0.44	0.25, 0.78	0.0050
Schizophrenia, schizotypal and delusional disorders [d]	0.89	0.27, 2.93	0.8417
Substance abuse [f]	0.71	0.20, 2.55	0.5986
Year of offspring conception [i,j]			
2009-2013	Reference	-	-
2014-2019	0.97	0.74, 1.27	0.8339

NDD: neurodevelopmental disorders; CI: Confidence Interval; LMP2: Last menstrual period date plus 2 weeks; OR: odds ratio
Legend: Odds ratios (OR), 95% confidence intervals (CI) and p-values are represented for risk factors and confounders included in the propensity score (PS) model. All variables potentially included in the PS model are listed here, however some of the variables might not be included in the final set of variables.

a) candidate covariates were considered to enter the PS model if associated with the study outcome based on univariate analyses. Additionally, two-way interactions were included in the PS model if identified as clinically meaningful
b) at index (childbirth)
d) all available data prior to index date
e) during pregnancy (from LMP2 until index date)
f) 12 months lookback from LMP2
g) excluding bipolar affective disorder and mania
h) 3-months lookback from LMP2
i) at mother's LMP2
j) calendar years were grouped in each country according to the length of the study period

Table 59 Balance of risk factors/confounders after PS weighting (PS scores obtained using logistic regression); primary outcome

NDD	Absolute standardized difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Offspring risk factors/confounders				
Gender [c]	0.02	Yes	1.01	Yes
Congenital CMV [d]	-	- [**]	-	- [***]
Congenital rubella [d]	-	- [**]	-	- [***]
Fetal alcohol syndrome [d]	-	- [**]	-	- [***]
Fragile X syndrome [d]	-	- [**]	-	- [***]
Lejeune/cri du chat syndrome [d]	-	- [**]	-	- [***]
Tuberous sclerosis [d]	-	- [**]	-	- [***]
Maternal risk factors/confounders				
Mother's age [c] (categorical)	0.00*	Yes	1.04	Yes
Affective disorder [e]	0.03	Yes	1.11	Yes
Diabetes [e]	0.04	Yes	0.73	Yes
Gestational diabetes [f]	0.07	Yes	0.77	Yes
Neurotic disorder [e]	0.07	Yes	1.16	Yes
Schizophrenia, schizotypal and delusional disorders [e]	-	- [**]	-	- [***]
Obesity [g]	0.03	Yes	0.70	Yes
CMV [g]	-	- [**]	-	- [***]
Rubella [g]	-	- [**]	-	- [***]
Alcohol abuse prior to LMP2 [g]	0.04	Yes	-	- [***]
Alcohol abuse during pregnancy [f]	-	- [**]	-	- [***]
Substance abuse prior to LMP2 [g]	-	- [**]	-	- [***]
Substance abuse during pregnancy [f]	-	- [**]	-	- [***]
Smoking prior to LMP2 [g]	0.05	Yes	1.13	Yes
Smoking during pregnancy [f]	0.04	Yes	1.16	Yes
Maternal polypharmacy index prior to LMP2 [i] (categorical)	0.00*	Yes	1.05	Yes

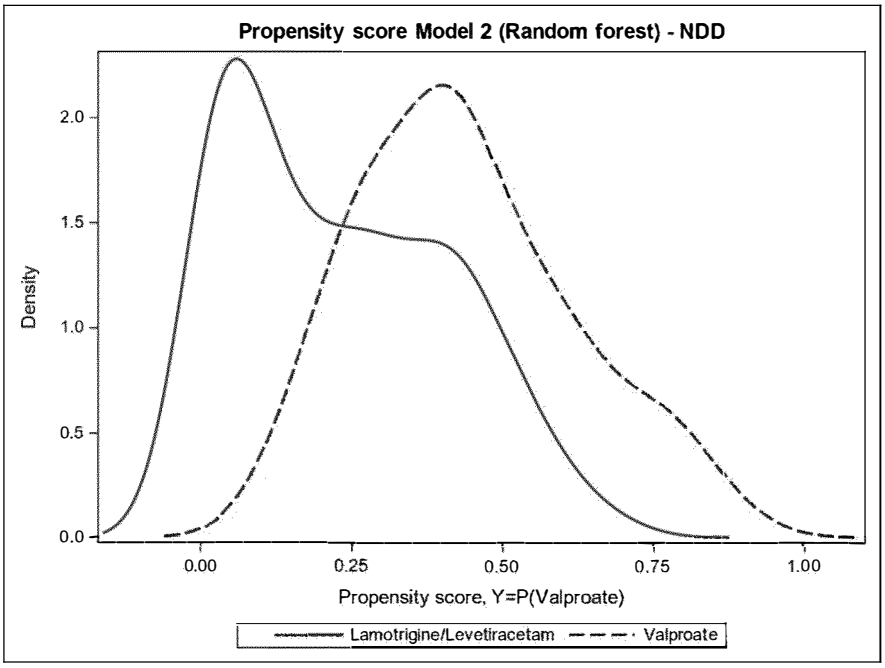
NDD	Absolute standardized difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]
Maternal polypharmacy index during pregnancy [f] (categorical)	0.00*	Yes	1.07	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [g] - mothers with at least one prescription	0.02	Yes	1.06	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [f] - mothers with at least one prescription	0.09	Yes	0.66	Yes
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [g] -mothers with at least one prescription	0.04	Yes	1.04	Yes
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [f] -mothers with at least one prescription	0.01	Yes	1.01	Yes
Paternal risk factors/confounders				
Affective disorder [e,h]	0.05	Yes	1.09	Yes
Bipolar affective disorder [e]	0.07	Yes	1.10	Yes
Mania [e]	0.12	No	-	- [***]
Neurotic disorder [e]	0.05	Yes	1.12	Yes
Schizophrenia, schizotypal and delusional disorders [e]	0.04	Yes	0.70	Yes
Substance abuse [g]	0.08	Yes	0.46	Yes
Paternal polypharmacy index [i] (categorical)	0.01*	Yes	0.98	Yes
Concomitant medications associated with valproate-indicated psychiatric conditions [g] – fathers with at least one prescription	0.16	No	0.86	Yes
Concomitant medications associated with neuropsychiatric adverse events [g] - fathers with at least one prescription	0.02	Yes	1.02	Yes
Father's age [c] (categorical)	0.01*	Yes	0.95	Yes
Year of offspring conception [j]	0.00*	Yes	1.00	Yes

NDD	Absolute standardized difference	Balanced achieved [a]	Variance ratio (valproate vs lamotrigine /levetiracetam)	Balanced achieved [b]

CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; NDD: neurodevelopmental disorders; PS: Propensity score

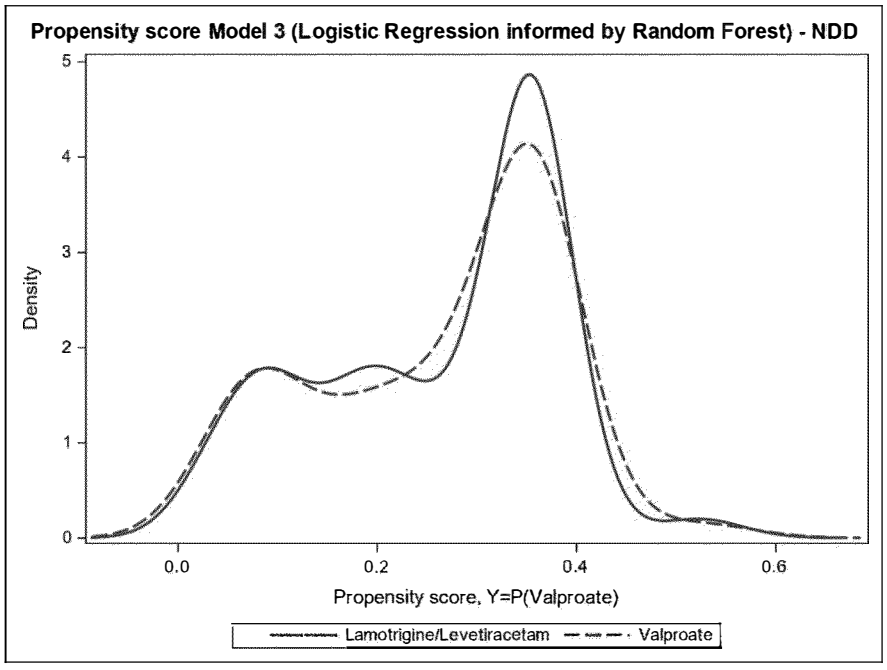
a) absolute standardized difference below 0.1
b) variance ratio between 0 and 2
c) at index (childbirth)
d) between index and exit date
e) all available data prior to index date
f) during pregnancy (from LMP2 until index date)
g) 12 months lookback from LMP2
h) excluding bipolar affective disorder and mania
i) 3 months lookback from LMP2
j) at mother's LMP2

* Mahalanobis distance is calculated for categorical variables with more than 2 levels.
** The standardized difference is not calculated if a binary variable has only 1 category level in the weighted patient data.
*** The variance ratio is not calculated if a variable has only 1 category level in one of valproate and comparator groups (the denominator of the variance ratio is 0).



NDD: Neurodevelopmental disorders; PS: Propensity score

Figure 7 Balance of PS Model 2- Random Forest; Primary outcome cohort in Norway.

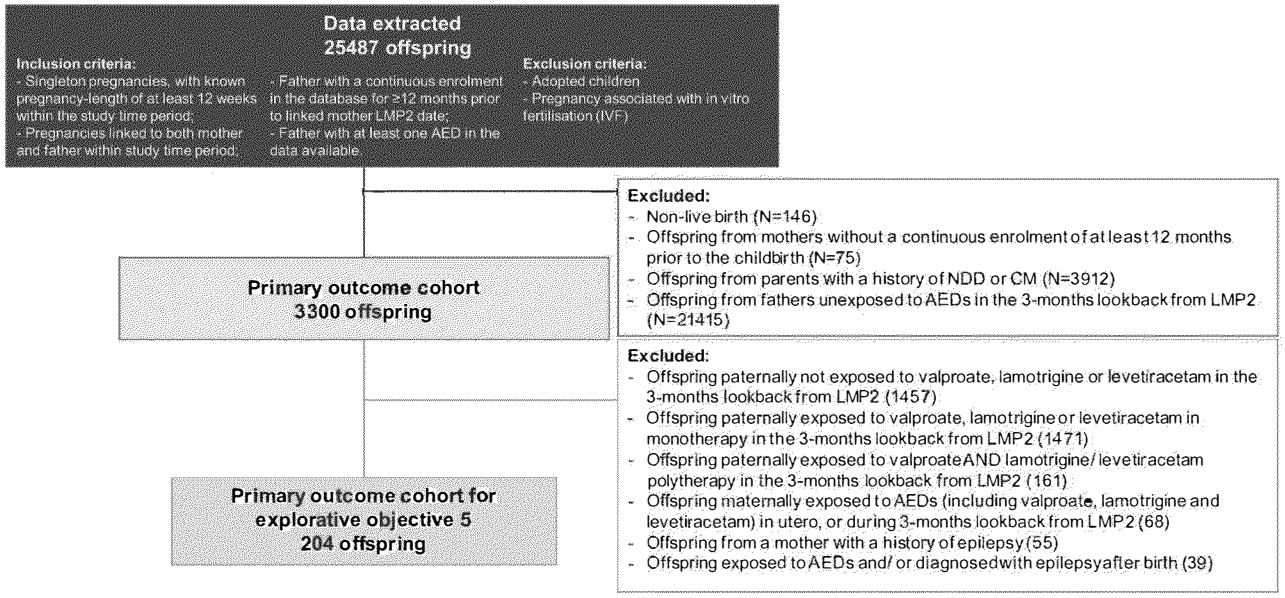


NDD: neurodevelopmental disorders; PS: Propensity score

Figure 8 Balance of PS Model 3 – Logistic Regression informed by Random Forest; Primary outcome cohort in Norway

8.1.6 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Explorative analysis 5)

This section supersedes section 15.3.5 from the final study report v1.1.



AED: antiepileptic drugs; CM: Congenital Malformation; NDD: neurodevelopmental disorders; LMP2: Last menstrual period date plus 2 weeks

Figure 9 Study population of Primary outcome cohort for Exploratory Analyses 5 in Norway

Table 60 Offspring demographic characteristics by paternal exposure group; primary outcome

NDD	Paternal exposure group: Valproate (polytherapy)		Paternal exposure group: Lamotrigine/ Levetiracetam (polytherapy)	
Number of pregnancies	**N=45**		**N=159**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	1	0.63
28-31 (very preterm)	0	0.00	3	1.89
32-36 (moderate to late preterm)	3	6.67	5	3.14
37-41 (at term)	41	91.11	147	92.45
≥42 (post-term)	1	2.22	3	1.89
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	2	1.26
1000-1499 (very low)	0	0.00	1	0.63
1500-2499 (low)	2	4.44	4	2.52
≥2500	43	95.56	152	95.60
Missing	0	0.00	0	0.00
Gender [a]				
Male	19	42.22	76	47.80
Female	26	57.78	83	52.20
Missing	0	0.00	0	0.00
Year of birth				
2010	7	15.56	20	12.58
2011	5	11.11	20	12.58
2012	7	15.56	24	15.09
2013	2	4.44	15	9.43
2014	4	8.89	15	9.43
2015	6	13.33	15	9.43
2016	4	8.89	12	7.55
2017	1	2.22	16	10.06
2018	7	15.56	12	7.55
2019	2	4.44	10	6.29
Total number of years of follow-up	222.55		856.15	
Mean follow-up year	4.95		5.38	

NDD: Neurodevelopmental disorders
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 Offspring clinical characteristics by paternal exposure group; primary outcome

NDD	Paternal exposure group: Valproate (polytherapy)		Lamotrigine/ levetiracetam (polytherapy)	
Number of pregnancies	N=45		N=159	
	N	%	N	%
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Epilepsy	0	0.00	0	0.00
Fetal alcohol syndrome	0	0.00	0	0.00
Fragile X syndrome	0	0.00	0	0.00
Lejeune/cri du chat syndrome	0	0.00	0	0.00
Tuberous sclerosis	0	0.00	1	0.63
Medication use				
Exposure to AEDs [a]	0	0.00	0	0.00
Outcomes				
ASD (ever, not only as 1st NDD diagnosis)	1	2.22	2	1.26
ASD (as 1st NDD diagnosis)	1	2.22	1	0.63
NDD including ASD	3	6.67	6	3.77
Age at the first diagnosis (years)				
ASD (ever, not only as 1st NDD diagnosis) [b,c]				
0-1	0	0.00	0	0.00
2-3	1	100.00	0	0.00
4-5	0	0.00	1	50.00
6-7	0	0.00	0	0.00
8-9	0	0.00	1	50.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	1	100.00	2	100.00
NDD including ASD [b,c]				
0-1	1	33.33	0	0.00
2-3	1	33.33	1	16.67
4-5	0	0.00	3	50.00
6-7	1	33.33	1	16.67
8-9	0	0.00	1	16.67
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	3	100.00	6	100.00

AED: Antiepileptic drug; ASD: Autism Spectrum Disorder; CMV: Cytomegalovirus; NDD: Neurodevelopmental disorders;
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) between index (childbirth) and exit date
b) Categories may be adapted according to the data.

c) Denominator for the percentage is the number of offspring with the outcome.

Table 62 Maternal demographic characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD	**Valproate (polytherapy)**		**Lamotrigine/ levetiracetam (polytherapy)**	
Number of pregnancies	**N=45**		**N=159**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	4	8.89	1	0.63
21-25	6	13.33	25	15.72
26-30	15	33.33	60	37.74
31-35	11	24.44	51	32.08
36-40	6	13.33	19	11.95
>40	3	6.67	3	1.89
Mean (SD)	30.07 (6.09)		30.31 (4.81)	
Median (25^{th} - 75^{th} percentile)	30.00 (26.00, 34.00)		30.00 (27.00, 34.00)	
Min, max	18.00, 43.00		20.00, 44.00	
Missing	0	0.00	0	0.00

Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; 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 63 Maternal clinical characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD	**Valproate (polytherapy)**		**Lamotrigine/levetiracetam (polytherapy)**	
Number of pregnancies	**N=45**		**N=159**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder [a]	3	6.67	10	6.29
Diabetes [a]	0	0.00	2	1.26
Epilepsy [a]	0	0.00	0	0.00
Neurotic disorder [a]	6	13.33	10	6.29
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Obesity [b]	1	2.22	1	0.63
CMV [c]	0	0.00	0	0.00
Gestational diabetes [c]	2	4.44	10	6.29
Rubella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	1	0.63
Smoking prior to LMP2 [b]				
Yes	3	6.67	17	10.69
No	34	75.56	110	69.18
Missing	8	17.78	32	20.13
Smoking during pregnancy [c]				
Yes	0	0.00	8	5.03
No	38	84.44	124	77.99
Missing	7	15.56	27	16.98
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00

NDD	Paternal exposure group			
	Valproate (polytherapy)		Lamotrigine/levetiracetam (polytherapy)	
Number of pregnancies	N=45		N=159	
	N	%	N	%
Exposure to AED during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K means cluster prior to LMP2 [d]				
Unexposed	45	100.00	159	100.00
K means cluster during pregnancy [c]				
Unexposed	45	100.00	159	100.00
Maternal polypharmacy index prior to LMP2 [d]				
0	33	73.33	111	69.81
1-4	12	26.67	48	30.19
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.44 (0.94)		0.49 (0.88)	
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 1.00)		0.00 (0.00, 1.00)	
Min, max	0.00, 4.00		0.00, 4.00	
Maternal polypharmacy index during pregnancy [c]				
0	23	51.11	80	50.31
1-4	21	46.67	73	45.91
5-10	1	2.22	6	3.77
>10	0	0.00	0	0.00
Mean (SD)	0.82 (1.15)		0.94 (1.27)	
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 1.00)		0.00 (0.00, 2.00)	
Min, max	0.00, 6.00		0.00, 6.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	3	6.67	10	6.29

NDD Number of pregnancies	Paternal exposure group Valproate (polytherapy) N=45		Lamotrigine/levetiracetam (polytherapy) N=159	
	N	%	N	%
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	2	4.44	4	2.52
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] -mothers with at least one prescription	25	55.56	107	67.30
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	22	48.89	73	45.91

AED: Antiepileptic drugs; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; NDD: Neurodevelopmental disorders; 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) 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 64 Paternal demographic characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD	**Valproate (polytherapy)**		**Lamotrigine/levetiracetam (polytherapy)**	
Number of pregnancies	**N=45**		**N=159**	
	N	**%**	**N**	**%**
Father's age [a]				
≤20 years	1	2.22	0	0.00
21-25	1	2.22	14	8.81
26-30	11	24.44	42	26.42
31-35	13	28.89	57	35.85
36-40	10	22.22	25	15.72
>40	9	20.00	21	13.21
Mean (SD)	33.84 (5.85)		33.47 (6.23)	
Median (25^{th} - 75^{th} percentile)	34.00 (30.00, 37.00)		33.00 (30.00, 37.00)	
Min, max	19.00, 45.00		21.00, 57.00	
Missing	-		-	
Year of offspring conception [b]				
2009	6	13.33	15	9.43
2010	5	11.11	20	12.58
2011	7	15.56	22	13.84
2012	3	6.67	18	11.32
2013	3	6.67	16	10.06
2014	5	11.11	13	8.18
2015	5	11.11	15	9.43
2016	2	4.44	10	6.29
2017	6	13.33	17	10.69
2018	3	6.67	11	6.92
2019	0	0.00	2	1.26

LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; 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)

b) at mother's LMP2

Table 65 Paternal clinical characteristics by paternal exposure group; primary outcome

NDD	Paternal exposure group: Valproate (polytherapy) N=45		Lamotrigine/levetiracetam (polytherapy) N=159	
Number of pregnancies	N	%	N	%
Comorbidities				
Affective disorder excluding bipolar affective disorder and mania [a]	5	11.11	9	5.66
Bipolar affective disorder [a]	1	2.22	6	3.77
Mania [a]	0	0.00	0	0.00
Neurotic disorder [a]	2	4.44	14	8.81
Schizophrenia, schizotypal and delusional disorders [a]	1	2.22	1	0.63
Lifestyle characteristics				
Substance abuse [c]	1	2.22	1	0.63
Medication use				
Exposure to AEDs[d]				
Fatty acid derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Barbiturates derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Fatty acid derivatives and other antiepileptics	11	24.44	0	0.00
Carboxamide derivatives and other antiepileptics	0	0.00	73	45.91
Fatty acid derivatives and Carboxamide derivatives	21	46.67	0	0.00
Benzodiazepine derivatives and other antiepileptics	0	0.00	8	5.03
Benzodiazepine derivatives and Fatty acid derivatives	2	4.44	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives	0	0.00	0	0.00
Succinimide derivatives and other antiepileptics	0	0.00	1	0.63
Succinimide derivatives and Fatty acid derivatives	2	4.44	0	0.00
Carboxamide derivatives and Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives and Fatty acid derivatives	0	0.00	0	0.00
Hydantoin derivatives and Carboxamide derivatives	0	0.00	0	0.00
Hydantoin derivatives and other antiepileptics	0	0.00	3	1.89
Hydantoin derivatives and Succinimide derivatives	0	0.00	0	0.00

NDD / Number of pregnancies	Paternal exposure group: Valproate (polytherapy) N=45		Lamotrigine/levetiracetam (polytherapy) N=159	
	N	%	N	%
Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Fatty acid derivatives	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives	0	0.00	0	0.00
Barbiturates derivatives and Benzodiazepine derivatives	0	0.00	0	0.00
Barbiturates derivatives and Hydantoin derivatives	0	0.00	0	0.00
Carboxamide derivatives and Barbiturates derivatives and Hydantoin derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Carboxamide derivatives and Fatty acid derivatives and other antiepileptics	5	11.11	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	1	0.63
Benzodiazepine derivatives and Succinimide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Hydantoin derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	0	0.00
Hydantoin derivatives and Carboxamide derivatives and Fatty acid derivatives	1	2.22	0	0.00
Barbiturates derivatives and Carboxamide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Fatty acid derivatives and Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	1	0.63
Hydantoin derivatives and Succinimide derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
AED indication				
Epilepsy	37	82.22	133	83.65
Bipolar affective disorder and mania	1	2.22	6	3.77
Other/unknown	7	15.56	20	12.58
K means cluster [d]				
Group A	38	84.44	140	88.05
Group B	7	15.56	19	11.95
Paternal polypharmacy index [d]				
0	26	57.78	108	67.92
1-4	17	37.78	48	30.19
5-10	2	4.44	3	1.89
>10	0	0.00	0	0.00
Mean (SD)	0.87 (1.44)		0.67 (1.35)	

NDD Number of pregnancies	Paternal exposure group Valproate (polytherapy) N=45		Lamotrigine/levetiracetam (polytherapy) N=159	
	N	%	N	%
Median (25th - 75th percentile)	0.00 (0.00, 1.00)		0.00 (0.00, 1.00)	
Min, max	0.00, 7.00		0.00, 9.00	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	33	73.33	82	51.57
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription	28	62.22	89	55.97

AED: Antiepileptic drugs; LMP2: Last menstrual period date plus 2 weeks; NDD: Neurodevelopmental disorders; 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) all available data prior to index date (childbirth)

b) at mother's LMP2

c) 12-months lookback from LMP2

d) 3-months lookback from LMP2

e) Valproate or lamotrigine/levetiracetam in combination with other AED(s). Each combination found in the data will be listed here.

Table 66 Association between potential offspring risk factors/confounders for NDD by paternal exposure group; primary outcome

	Paternal exposure group				Comparison
NDD **Number of pregnancies**	**Valproate (polytherapy)** **N=45**		**Lamotrigine/ levetiracetam (polytherapy)** **N=159**		**Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)** **-**
	N	**%**	**N**	**%**	
Offspring risk factors/confounders					
Gender [a]					
Male	19	42.22	76	47.80	-
Female	26	57.78	83	52.20	-
Missing	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.44 (0.5079)
Congenital CMV [b]	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	-
Fetal alcohol syndrome [b]	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	1	0.63	1.00 (1.0000)*

CMV: Cytomegalovirus; NDD: Neurodevelopmental disorders
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 analyzed was less than 5 Fischer's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) between index and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 67 Association between potential maternal risk factors/confounders for NDD by paternal exposure group; primary outcome

	Paternal exposure group				Comparison
NDD **Number of pregnancies**	**Valproate (polytherapy)**		**Lamotrigine/ Levetiracetam (polytherapy)**		**Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)**
	N=45		**N=159**		-
	N	**%**	**N**	**%**	
Maternal risk factors/confounders					
Mother's age [a] (categorical)					
≤20 years	4	8.89	1	0.63	-
21-25	6	13.33	25	15.72	-
26-30	15	33.33	60	37.74	-
31-35	11	24.44	51	32.08	-
36-40	6	13.33	19	11.95	-
>40	3	6.67	3	1.89	-
Test statistics	-	-	-	-	13.53 (0.0189)
Mother's age [a] (continuous)					
Mean (SD)	30.07 (6.09)		30.31 (4.81)		-0.25 (0.8071)
Median (25^{th} - 75^{th} percentile)	30.00 (26.00, 34.00)		30.00 (27.00, 34.00)		-
Min, max	18.00, 43.00		20.00, 44.00		-
Missing	0	0.00	0	0.00	-
Affective disorder [b]	3	6.67	10	6.29	1.00 (1.0000)*
Diabetes [b]	0	0.00	2	1.26	1.00 (1.0000)*
Gestational diabetes [c]	2	4.44	10	6.29	1.00 (1.0000)*
Neurotic disorder [b]	6	13.33	10	6.29	2.41 (0.1207)
Schizophrenia, schizotypal and delusional disorders [b]	0	0.00	0	0.00	-
Obesity [d]	1	2.22	1	0.63	0.39 (0.3934)*
CMV [c]	0	0.00	0	0.00	-
Rubella [c]	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [d]	0	0.00	0	0.00	-
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [d]	0	0.00	0	0.00	-
Substance abuse during pregnancy [c]	0	0.00	1	0.63	1.00 (1.0000)*
Smoking prior to LMP2 [d]					
Yes	3	6.67	17	10.69	-
No	34	75.56	110	69.18	-
Missing	8	17.78	32	20.13	-
Test statistics without 'Missing' category	-	-	-	-	0.56 (0.5695)*

	Paternal exposure group				Comparison
NDD **Number of pregnancies**	**Valproate (polytherapy)**		**Lamotrigine/ Levetiracetam (polytherapy)**		**Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)**
	N=45		**N=159**		-
	N	**%**	**N**	**%**	
Smoking during pregnancy [c]					
Yes	0	0.00	8	5.03	-
No	38	84.44	124	77.99	-
Missing	7	15.56	27	16.98	-
Test statistics without 'Missing' category	-	-	-	-	0.20 (0.2013)*
Maternal polypharmacy index prior to LMP2 [e](categorical)					
0	33	73.33	111	69.81	-
1-4	12	26.67	48	30.19	-
5-10	0	0.00	0	0.00	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.21 (0.6471)
Maternal polypharmacy index prior to LMP2 [e] (continuous)					
Mean (SD)	0.44 (0.94)		0.49 (0.88)		4468.50 (0.6087)*
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 1.00)		0.00 (0.00, 1.00)		-
Min, max	0.00, 4.00		0.00, 4.00		-
Maternal polypharmacy index during pregnancy [c](categorical)					
0	23	51.11	80	50.31	-
1-4	21	46.67	73	45.91	-
5-10	1	2.22	6	3.77	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	0.25 (0.8804)
Maternal polypharmacy index during pregnancy[c] (continuous)					
Mean (SD)	0.82 (1.15)		0.94 (1.27)		4507.00 (0.7448)*
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 1.00)		0.00 (0.00, 2.00)		-
Min, max	0.00, 6.00		0.00, 6.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	3	6.67	10	6.29	1.00 (1.0000)*

NDD Number of pregnancies	Paternal exposure group Valproate (polytherapy) N=45		Lamotrigine/ Levetiracetam (polytherapy) N=159		Comparison Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy) -
	N	%	N	%	
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	2	4.44	4	2.52	0.61 (0.6152)*
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription	25	55.56	107	67.30	2.12 (0.1457)
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	22	48.89	73	45.91	0.12 (0.7238)

CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; 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 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 analyzed 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 68 Association between potential paternal risk factors/confounders for NDD by paternal exposure group; primary outcome

	Paternal exposure group				Comparison
NDD	**Valproate (polytherapy)**		**Lamotrigine/ Levetiracetam (polytherapy)**		**Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)**
Number of pregnancies	**N=45**		**N=159**		**-**
Paternal risk factors/confounders					
Affective disorder excluding bipolar affective disorder and mania [a]	5	11.11	9	5.66	1.63 (0.2017)
Bipolar affective disorder [a]	1	2.22	6	3.77	1.00 (1.0000)*
Mania [a]	0	0.00	0	0.00	-
Neurotic disorder [a]	2	4.44	14	8.81	0.53 (0.5312)*
Schizophrenia, schizotypal and delusional disorders [a]	1	2.22	1	0.63	0.39 (0.3934)*
Substance abuse [c]	1	2.22	1	0.63	0.39 (0.3934)*
Paternal polypharmacy index [d] (categorical)					
0	26	57.78	108	67.92	-
1-4	17	37.78	48	30.19	-
5-10	2	4.44	3	1.89	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	2.12 (0.3465)
Paternal polypharmacy index [d] (continuous)					
Mean (SD)	0.87 (1.44)		0.67 (1.35)		4978.50 (0.2149)*
Median (25th - 75th percentile)	0.00 (0.00, 1.00)		0.00 (0.00, 1.00)		-
Min, max	0.00, 7.00		0.00, 9.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] - fathers with at least one prescription	33	73.33	82	51.57	6.75 (0.0094)
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription	28	62.22	89	55.97	0.56 (0.4544)
Father's age [e] (categorical)					
≤20 years	1	2.22	0	0.00	-
21-25	1	2.22	14	8.81	-
26-30	11	24.44	42	26.42	-
31-35	13	28.89	57	35.85	-
36-40	10	22.22	25	15.72	-
>40	9	20.00	21	13.21	-

	Paternal exposure group				Comparison
NDD	**Valproate (polytherapy)**		**Lamotrigine/ Levetiracetam (polytherapy)**		**Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)**
Number of pregnancies	**N=45**		**N=159**		-
Test statistics	-	-	-	-	8.11 (0.1502)
Father's age [e] (continuous)					
Mean (SD)	33.84 (5.85)		33.47 (6.23)		4921.00 (0.3775)*
Median (25th - 75th percentile)	34.00 (30.00, 37.00)		33.00 (30.00, 37.00)		-
Min, max	19.00, 45.00		21.00, 57.00		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [f,g]					
2009-2013	24	53.33	91	57.23	-
2014-2019	21	46.67	68	42.77	-
Test statistics	-	-	-	-	0.22 (0.6415)

LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; 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 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 analyzed 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

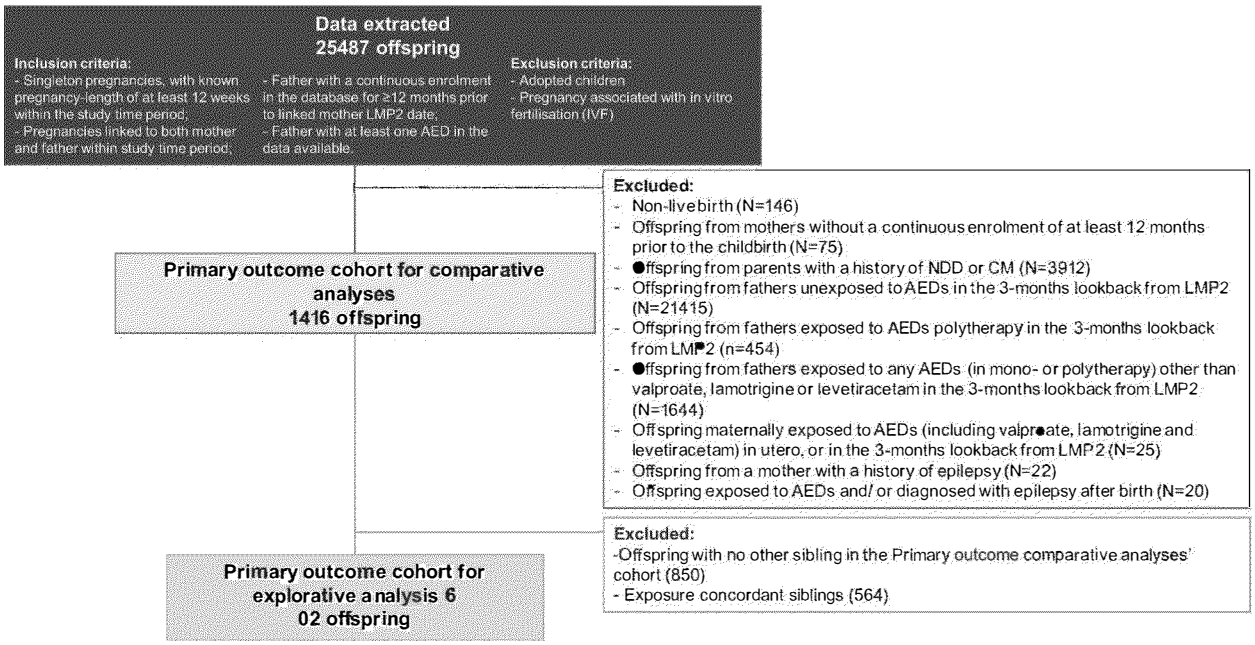
e) at index

f) at mother's LMP2

g) calendar years will be grouped in each country according to the length of the study period

8.1.7 Exposure to valproate or lamotrigine/levetiracetam in paternally and maternally matched siblings (Explorative analysis 6)

This section supersedes section 15.3.6 from the final study report v1.1.



AED: antiepileptic drugs; CM: Congenital Malformation; LMP2: Last menstrual period date plus 2 weeks; NDD: neurodevelopmental disorders

Figure 10. Study population of Primary outcome cohort for Exploratory Analyses 6 in Norway

Table 69 Offspring demographic characteristics by paternal exposure group; primary outcome

NDD	Paternal exposure group: Valproate		Paternal exposure group: Lamotrigine/ Levetiracetam (composite)	
Number of pregnancies	N=1		N=1	
	N	%	N	%
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	0	0.00
28-31 (very preterm)	0	0.00	0	0.00
32-36 (moderate to late preterm)	0	0.00	0	0.00
37-41 (at term)	1	100.00	1	100.00
≥42 (post-term)	0	0.00	0	0.00
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	0	0.00
1000-1499 (very low)	0	0.00	0	0.00
1500-2499 (low)	0	0.00	0	0.00
≥2500	1	100.00	1	100.00
Missing	0	0.00	0	0.00
Gender [a]				
Male	0	0.00	0	0.00
Female	1	100.00	1	100.00
Missing	0	0.00	0	0.00
Year of birth				
2010	0	0.00	0	0.00
2011	0	0.00	0	0.00
2012	0	0.00	0	0.00
2013	0	0.00	0	0.00
2014	0	0.00	0	0.00
2015	1	100.00	0	0.00
2016	0	0.00	0	0.00
2017	0	0.00	0	0.00
2018	0	0.00	1	100.00
2019	0	0.00	0	0.00
Total number of years of follow-up	4.90		1.92	
Mean follow-up year	4.90		1.92	

NDD: neurodevelopmental disorders
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 70 Offspring clinical characteristics by paternal exposure group; primary outcome

NDD	Paternal exposure group: Valproate N=1		Lamotrigine/ levetiracetam (composite) N=1	
Number of pregnancies	**N**	**%**	**N**	**%**
Comorbidities				
Congenital CMV [a]	0	0.00	0	0.00
Congenital rubella [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00
Fetal alcohol syndrome [a]	0	0.00	0	0.00
Fragile X syndrome [a]	0	0.00	0	0.00
Lejeune/cri du chat syndrome [a]	0	0.00	0	0.00
Tuberous sclerosis [a]	0	0.00	0	0.00
Medication use				
Exposure to AEDs [a]	0	0.00	0	0.00
Outcomes				
ASD (ever, not only as 1st diagnosis)	0	0.00	0	0.00
NDD including ASD	0	0.00	0	0.00
Age at the first diagnosis (years)				
ASD (ever, not only as 1st diagnosis) [b,c]				
0-1	0	0.00	0	0.00
2-3	0	0.00	0	0.00
4-5	0	0.00	0	0.00
6-7	0	0.00	0	0.00
8-9	0	0.00	0	0.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	0	0.00	0	0.00
NDD including ASD [b,c]				
0-1	0	0.00	0	0.00
2-3	0	0.00	0	0.00
4-5	0	0.00	0	0.00
6-7	0	0.00	0	0.00
8-9	0	0.00	0	0.00
10-11	0	0.00	0	0.00
Total (offspring with the outcome)	0	0.00	0	0.00

AED: Antiepileptic drugs; ASD: Autism Spectrum Disorder; CMV: Cytomegalovirus; NDD: Neurodevelopmental disorders
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) between index (childbirth) and exit date
b) Categories may be adapted according to the data.
c) Denominator for the percentage is the number of offspring with the outcome.

Table 71 Maternal demographic characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD	**Valproate**		**Lamotrigine/levetiracetam (composite)**	
Number of pregnancies	**N=1**		**N=1**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	0	0.00	0	0.00
21-25	0	0.00	0	0.00
26-30	1	100.00	0	0.00
31-35	0	0.00	1	100.00
36-40	0	0.00	0	0.00
>40	0	0.00	0	0.00
Mean (SD)	30.00 (.)		33.00 (.)	
Median (25^{th} - 75^{th} percentile)	30.00 (30.00, 30.00)		33.00 (33.00, 33.00)	
Min, max	30.00, 30.00		33.00, 33.00	
Missing	0	0.00	0	0.00

Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; 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 72 Maternal clinical characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD	**Valproate**		**Lamotrigine/ levetiracetam (composite)**	
Number of pregnancies	**N=1**		**N=1**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder [a]	0	0.00	0	0.00
Diabetes [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00
Neurotic disorder [a]	0	0.00	0	0.00
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Obesity [b]	0	0.00	0	0.00
CMV [c]	0	0.00	0	0.00
Gestational diabetes [c]	0	0.00	0	0.00
Rubella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	0	0.00
Smoking prior to LMP2 [b]				
No	1	100.00	1	100.00
Smoking during pregnancy [c]				
No	1	100.00	1	100.00
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
Exposure to AED during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00

NDD	Paternal exposure group			
	Valproate		Lamotrigine/ levetiracetam (composite)	
Number of pregnancies	N=1		N=1	
	N	%	N	%
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K means cluster prior to LMP2 [d]				
Unexposed	1	100.00	1	100.00
K means cluster during pregnancy [c]				
Unexposed	1	100.00	1	100.00
Maternal polypharmacy index prior to LMP2 [d]				
0	1	100.00	1	100.00
1-4	0	0.00	0	0.00
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.00 (.)		0.00 (.)	
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 0.00)		0.00 (0.00, 0.00)	
Min, max	0.00, 0.00		0.00, 0.00	
Maternal polypharmacy index during pregnancy [c]				
0	1	100.00	1	100.00
1-4	0	0.00	0	0.00
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.00 (.)		0.00 (.)	
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 0.00)		0.00 (0.00, 0.00)	
Min, max	0.00, 0.00		0.00, 0.00	
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [b] - mothers with at least one prescription	0	0.00	0	0.00
Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy [c] - mothers with at least 1 prescription	0	0.00	0	0.00
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [b] - mothers with at least one prescription	1	100.00	1	100.00

NDD	Paternal exposure group			
	Valproate		Lamotrigine/ levetiracetam (composite)	
Number of pregnancies	N=1		N=1	
	N	%	N	%
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	0	0.00	0	0.00

AED: Antiepileptic drugs; CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; 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) 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 73 Paternal demographic characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD	**Valproate**		**Lamotrigine/levetiracetam (composite)**	
Number of pregnancies	**N=1**		**N=1**	
	N	**%**	**N**	**%**
Father's age [a]				
≤20 years	0	0.00	0	0.00
21-25	0	0.00	0	0.00
26-30	0	0.00	0	0.00
31-35	1	100.00	1	100.00
36-40	0	0.00	0	0.00
>40	0	0.00	0	0.00
Mean (SD)	31.00 (.)		34.00 (.)	
Median (25^{th} - 75^{th} percentile)	31.00 (31.00, 31.00)		34.00 (34.00, 34.00)	
Min, max	31.00, 31.00		34.00, 34.00	
Missing	-		-	
Year of offspring conception [b]				
2009	0	0.00	0	0.00
2010	0	0.00	0	0.00
2011	0	0.00	0	0.00
2012	0	0.00	0	0.00
2013	0	0.00	0	0.00
2014	1	100.00	0	0.00
2015	0	0.00	0	0.00
2016	0	0.00	0	0.00
2017	0	0.00	1	100.00
2018	0	0.00	0	0.00
2019	0	0.00	0	0.00

LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; 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)

b) at mother's LMP2

Table 74 Paternal clinical characteristics by paternal exposure group; primary outcome

	Paternal exposure group			
NDD	**Valproate**		**Lamotrigine/levetiracetam (composite)**	
Number of pregnancies	**N=1**		**N=1**	
	N	**%**	**N**	**%**
Comorbidities				
Affective disorder excluding bipolar affective disorder and mania [a]	0	0.00	0	0.00
Bipolar affective disorder [a]	0	0.00	0	0.00
Mania [a]	0	0.00	0	0.00
Neurotic disorder [a]	0	0.00	1	100.00
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00
Lifestyle characteristics				
Substance abuse [c]	0	0.00	0	0.00
Medication use				
AED indication				
Epilepsy	0	0.00	0	0.00
Bipolar affective disorder and mania	0	0.00	0	0.00
Other/unknown	1	100.00	1	100.00
K means cluster [d]				
Group A	1	100.00	0	0.00
Group B	0	0.00	1	100.00
Paternal polypharmacy index [d]				
0	1	100.00	0	0.00
1-4	0	0.00	1	100.00
5-10	0	0.00	0	0.00
>10	0	0.00	0	0.00
Mean (SD)	0.00 (.)		2.00 (.)	
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 0.00)		2.00 (2.00, 2.00)	
Min, max	0.00, 0.00		2.00, 2.00	
Concomitant medications associated with valproate-indicated psychiatric conditions [c] – fathers with at least one prescription	1	100.00	1	100.00
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription	1	100.00	1	100.00

AED: Antiepileptic drugs; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; 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) all available data prior to index date (childbirth)

c) 12-months lookback from LMP2

d) 3-months lookback from LMP2

Table 75 Association between potential offspring risk factors/confounders for NDD by paternal exposure group; primary outcome

	Paternal exposure group				Comparison
NDD	**Valproate**		**Lamotrigine/levetiracetam (composite)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=1**		**N=1**		**-**
	N	**%**	**N**	**%**	
Offspring risk factors/confounders					
Male	0	0.00	0	0.00	-
Female	1	100.00	1	100.00	-
Missing	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-
Congenital CMV [b]	0	0.00	0	0.00	-
Congenital rubella [b]	0	0.00	0	0.00	-
Fetal alcohol syndrome [b]	0	0.00	0	0.00	-
Fragile X syndrome [b]	0	0.00	0	0.00	-
Lejeune/cri du chat syndrome [b]	0	0.00	0	0.00	-
Tuberous sclerosis [b]	0	0.00	0	0.00	-

CMV: Cytomegalovirus; NDD: Neurodevelopmental disorders
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 analyzed was less than 5 Fischer's Exact test was used. Differences between continuous variables were tested using two-sample t-tests, or Mann-Whitney test in case the distribution of the variable was not normal.
a) at index (childbirth)
b) between index and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 76 Association between potential maternal risk factors/confounders for NDD by paternal exposure group; primary outcome

	Paternal exposure group				Comparison
NDD	**Valproate**		**Lamotrigine/levetiracetam (composite)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=1**		**N=1**		-
	N	**%**	**N**	**%**	
Maternal risk factors/confounders					
Mother's age [a] (categorical)					
≤20 years	0	0.00	0	0.00	-
21-25	0	0.00	0	0.00	-
26-30	1	100.00	0	0.00	-
31-35	0	0.00	1	100.00	-
36-40	0	0.00	0	0.00	-
>40	0	0.00	0	0.00	-
Test statistics	-	-	-	-	1.00 (1.0000)*
Mother's age [a] (continuous)					
Mean (SD)	30.00 (.)		33.00 (.)		-
Median (25^{th} - 75^{th} percentile)	30 (30.00, 30.00)		33 (33.00, 33.00)		-
Min, max	30.00, 30.00		33.00, 33.00		-
Missing	0	0.00	0	0.00	-
Affective disorder [b]	0	0.00	0	0.00	-
Diabetes [b]	0	0.00	0	0.00	-
Gestational diabetes [c]	0	0.00	0	0.00	-
Neurotic disorder [b]	0	0.00	0	0.00	-
Schizophrenia, schizotypal and delusional disorders [b]	0	0.00	0	0.00	-
Obesity [d]	0	0.00	0	0.00	-
CMV [c]	0	0.00	0	0.00	-
Rubella [c]	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [d]	0	0.00	0	0.00	-
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [d]	0	0.00	0	0.00	-
Substance abuse during pregnancy [c]	0	0.00	0	0.00	-
Smoking prior to LMP2 [d]					
Yes	0	0.00	0	0.00	-
No	1	100.00	1	100.00	-
Missing	0	0.00	0	0.00	-
Test statistics without 'Missing' category	-	-	-	-	-

	Paternal exposure group				Comparison
NDD	**Valproate**		**Lamotrigine/levetiracetam (composite)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=1**		**N=1**		**-**
	N	**%**	**N**	**%**	
Smoking during pregnancy [c]					
Yes	0	0.00	0	0.00	-
No	1	100.00	1	100.00	-
Missing	0	0.00	0	0.00	-
Test statistics without 'Missing' category	-	-	-	-	-
Maternal polypharmacy index prior to LMP2 [e](categorical)					
0	1	100.00	1	100.00	-
1-4	0	0.00	0	0.00	-
5-10	0	0.00	0	0.00	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-
Maternal polypharmacy index prior to LMP2 [e] (continuous)					
Mean (SD)	0.00 (.)		0.00 (.)		-
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 0.00)		0.00 (0.00, 0.00)		-
Min, max	0.00, 0.00		0.00, 0.00		-
Maternal polypharmacy index during pregnancy [c](categorical)					
0	1	100.00	1	100.00	-
1-4	0	0.00	0	0.00	-
5-10	0	0.00	0	0.00	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-
Maternal polypharmacy index during pregnancy [c] (continuous)					
Mean (SD)	0.00 (.)		0.00 (.)		-
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 0.00)		0.00 (0.00, 0.00)		-
Min, max	0.00, 0.00		0.00, 0.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 [d] - mothers with at least one prescription	0	0.00	0	0.00	-
Concomitant medications associated with valproate-indicated psychiatric conditions	0	0.00	0	0.00	

	Paternal exposure group				Comparison
NDD	**Valproate**		**Lamotrigine/levetiracetam (composite)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=1**		**N=1**		**-**
	N	**%**	**N**	**%**	
during pregnancy [c] - mothers with at least 1 prescription					
Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 [d] - mothers with at least one prescription	1	100.00	1	100.00	
Concomitant medications associated with neuropsychiatric adverse events during pregnancy [c] - mothers with at least one prescription	0	0.00	0	0.00	
		0.00		0.00	
		0.00		0.00	

CMV: Cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; 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 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 analyzed 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

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

Table 77 Association between potential paternal risk factors/confounders for NDD by paternal exposure group; primary outcome

	Paternal exposure group				Comparison
NDD	**Valproate**		**Lamotrigine/levetiracetam (composite)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=1**		**N=1**		**-**
	N	**%**	**N**	**%**	
Paternal risk factors/confounders					
Affective disorder [a,b]	0	0.00	0	0.00	-
Bipolar affective disorder [a]	0	0.00	0	0.00	-
Mania [a]	0	0.00	0	0.00	-
Neurotic disorder [a]	0	0.00	1	100.00	2.00 (0.1573)
Schizophrenia, schizotypal and delusional disorders [a]	0	0.00	0	0.00	-
Substance abuse [c]	0	0.00	0	0.00	-
Paternal polypharmacy index [d] (categorical)					
0	1	100.00	0	0.00	-
1-4	0	0.00	1	100.00	-
5-10	0	0.00	0	0.00	-
>10	0	0.00	0	0.00	-
Test statistics	-	-	-	-	2.00 (0.1573)
Paternal polypharmacy index [d] (continuous)					
Mean (SD)	0.00 (.)		2.00 (.)		-
Median (25^{th} - 75^{th} percentile)	0.00 (0.00, 0.00)		2.00 (2.00, 2.00)		-
Min, max	0.00, 0.00		2.00, 2.00		-
Concomitant medications associated with valproate-indicated psychiatric conditions [c] – fathers with at least one prescription	1	100.00	1	100.00	-
Concomitant medications associated with neuropsychiatric adverse events [c] - fathers with at least one prescription	1	100.00	1	100.00	-
Father's age [e] (categorical)					
≤20 years	0	0.00	0	0.00	-
21-25	0	0.00	0	0.00	-
26-30	0	0.00	0	0.00	-
31-35	1	100.00	1	100.00	-
36-40	0	0.00	0	0.00	-
>40	0	0.00	0	0.00	-
Test statistics	-	-	-	-	-

	Paternal exposure group				Comparison
NDD	**Valproate**		**Lamotrigine/levetiracetam (composite)**		**Valproate vs Lamotrigine /levetiracetam**
Number of pregnancies	**N=1**		**N=1**		**-**
	N	**%**	**N**	**%**	
Father's age [e] (continuous)					
Mean (SD)	31.00 (.)		34.00 (.)		-
Median (25th - 75th percentile)	31.00 (31.00, 31.00)		34.00 (34.00, 34.00)		-
Min, max	31.00, 31.00		34.00, 34.00		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [f,g]					
2009-2013	0	0.00	0	0.00	-
2014-2019	1	100.00	1	100.00	-
Test statistics	-	-	-	-	-

LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; NDD: Neurodevelopmental disorders; SD: Standard deviation

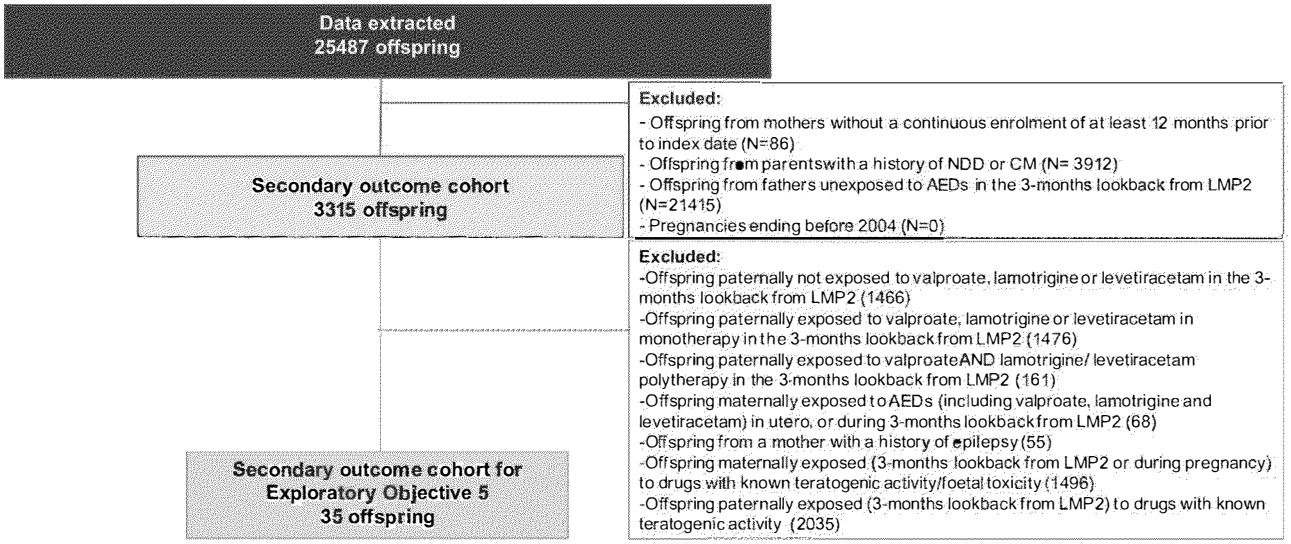
Legend: Number of pregnancies represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages were calculated over 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 analyzed 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)
b) excluding bipolar affective disorder and mania
c) 12-months lookback from LMP2
d) 3-months lookback from LMP2
e) at index
f) at mother's LMP2
g) calendar years will be grouped in each country according to the length of the study period

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

8.1.8 Exposure to valproate or lamotrigine/levetiracetam in polytherapy (Explorative analysis 5 CM)

This section supersedes section 15.3.7 from the final study report v1.1.



An offspring may be present in more than one exclusion criterion

CM: Congenital Malformation; NDD: neurodevelopmental disorders; AED: antiepileptic drugs; LMP2: Last menstrual period date plus 2 weeks

Figure 11 Study population of Secondary outcome cohort for Exploratory Analyses 5 in Norway

Table 78 Offspring demographic characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM	**Valproate (polytherapy)**		**Lamotrigine/ Levetiracetam (polytherapy)**	
Number of pregnancies	**N=3**		**N=32**	
	N	**%**	**N**	**%**
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	1	3.13
28-31 (very preterm)	0	0.00	1	3.13
32-36 (moderate to late preterm)	0	0.00	1	3.13
37-41 (at term)	3	100.00	29	90.63
≥42 (post-term)	0	0.00	0	0.00
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	1	3.13
1000-1499 (very low)	0	0.00	1	3.13
1500-2499 (low)	0	0.00	0	0.00
≥2500	3	100.00	30	93.75
Missing	0	0.00	0	0.00
Gender [a]				
Male	2	66.67	16	50.00
Female	1	33.33	16	50.00
Missing	0	0.00	0	0.00
Year of birth				
2010	0	0.00	4	12.50
2011	0	0.00	2	6.25
2012	2	66.67	3	9.38
2013	0	0.00	3	9.38
2014	0	0.00	4	12.50
2015	1	33.33	5	15.63
2016	0	0.00	3	9.38
2017	0	0.00	4	12.50
2018	0	0.00	3	9.38
2019	0	0.00	1	3.13

CM: Congenital Malformations
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 79 Offspring clinical characteristics paternal exposure group; secondary outcome

	Paternal exposure group			
CM **Number of pregnancies**	**Valproate (polytherapy)** **N=3**		**Lamotrigine/ Levetiracetam (polytherapy)** **N=32**	
	N	**%**	**N**	**%**
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital Herpes Simplex	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00
Congenital varicella	0	0.00	0	0.00
Fetal alcohol syndrome	0	0.00	0	0.00
Outcomes				
CM	0	0.00	1	3.13
Major CM (at any time)	0	0.00	1	3.13
Minor CM (at any time)	0	0.00	1	3.13
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]				
Stillbirth	0	0.00	0	0.00
Spontaneous abortion	0	0.00	0	0.00
Intrauterine growth retardation	0	0.00	1	100.00
Perinatal mortality	0	0.00	0	0.00

CM: Congenital Malformations; CMV: cytomegalovirus
Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
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) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date
b) Denominator for the percentage is the number of offspring with CM.

Table 80 Maternal demographic characteristics by paternal exposure group; secondary outcome

CM Number of pregnancies	Paternal exposure group Valproate (polytherapy) N=3		 Lamotrigine/ Levetiracetam (polytherapy) N=32	
	N	%	N	%
Mother's age [a]				
≤20 years	0	0.00	1	3.13
21-25	1	33.33	6	18.75
26-30	2	66.67	11	34.38
31-35	0	0.00	13	40.63
36-40	0	0.00	1	3.13
>40	0	0.00	0	0.00
Mean (SD)	25.67 (4.51)		29.09 (4.55)	
Median (25^{th} - 75^{th} percentile)	26.00 (21.00, 30.00)		28.50 (26.00, 33.00)	
Min, max	21.00, 30.00		19.00, 37.00	
Missing	0	0.00	0	0.00

CM: Congenital Malformations; SD: Standard Deviation; Min: Minimum; Max: Maximum
Legend: Number of pregnancies represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics 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 81 Maternal clinical characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM	**Valproate (polytherapy)**		**Lamotrigine/levetiracetam (polytherapy)**	
Number of pregnancies	**N=3**		**N=32**	
	N	**%**	**N**	**%**
Comorbidities				
Diabetes [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00
Obesity [b]	0	0.00	0	0.00
CMV [c]	0	0.00	0	0.00
Folate deficiency [c]	0	0.00	0	0.00
Gestational diabetes [c]	0	0.00	1	3.13
Herpes simplex virus [c]	0	0.00	0	0.00
Rubella [c]	0	0.00	0	0.00
Toxoplasmosis [c]	0	0.00	0	0.00
Varicella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	0	0.00
Smoking prior to LMP2 [b]				
Yes	0	0.00	0	0.00
No	3	100.00	23	71.88
Missing	0	0.00	9	28.13
Smoking during pregnancy [c]				
Yes	0	0.00	1	3.13
No	3	100.00	25	78.13
Missing	0	0.00	6	18.75
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00

CM Number of pregnancies	Paternal exposure group Valproate (polytherapy) N=3		Lamotrigine/levetiracetam (polytherapy) N=32	
	N	%	N	%
Other antiepileptics	0	0.00	0	0.00
Exposure to AEDs during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K means cluster prior to LMP2 [d]				
Unexposed	3	100.00	32	100.00
K means cluster during pregnancy [c]				
Unexposed	3	100.00	32	100.00
Maternal exposure to teratogenic activity/fetal toxicity prior to LMP2 [d] - mothers with at least one prescription	0	0.00	0	0.00
Maternal exposure to teratogenic activity/fetal toxicity during pregnancy [c] - mothers with at least one prescription	0	0.00	0	0.00

AED: Antiepileptic Drug; CM: Congenital Malformations; CMV: cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks
Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
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) all available data prior to index date (12th week of gestation in Norway, 22nd week of gestation in Denmark)
b) 12-months lookback from LMP2
c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
d) 3-months lookback from LMP2
e) Oxazolidine derivatives were not sold in Norway during the study period

Table 82 Paternal demographic characteristics by paternal exposure group; secondary outcome

CM Number of pregnancies	Paternal exposure group Valproate (polytherapy) N=3		Lamotrigine/levetiracetam (polytherapy) N=32	
	N	%	N	%
Father's age [a]				
≤20 years	0	0.00	0	0.00
21-25	1	33.33	2	6.25
26-30	1	33.33	11	34.38
31-35	1	33.33	13	40.63
36-40	0	0.00	3	9.38
>40	0	0.00	3	9.38
Mean (SD)	28.00 (3.61)		32.09 (5.47)	
Median (25^{th} - 75^{th} percentile)	27.00 (25.00, 32.00)		32.00 (28.00, 34.50)	
Min, max	25.00, 32.00		24.00, 50.00	
Year of offspring conception [b]				
2009	0	0.00	3	9.38
2010	0	0.00	3	9.38
2011	2	66.67	2	6.25
2012	0	0.00	3	9.38
2013	0	0.00	4	12.50
2014	1	33.33	5	15.63
2015	0	0.00	3	9.38
2016	0	0.00	5	15.63
2017	0	0.00	3	9.38
2018	0	0.00	1	3.13
2019	0	0.00	0	0.00

CM: Congenital Malformations, LMP2: Last menstrual period date plus 2 weeks; SD: Standard Deviation, Min: Minimum, Max: Maximum

Legend: Number of pregnancies represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics 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 83 Paternal clinical characteristics by paternal exposure group; secondary outcome

CM Number of pregnancies	Paternal exposure group Valproate (polytherapy) N=3		Lamotrigine/levetiracetam (polytherapy) N=32	
	N	%	N	%
Medication use				
Exposure to AEDs [a, b]				
Fatty acid derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Barbiturates derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	18	56.25
Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Carboxamide derivatives and other antiepileptics	0	0.00	13	40.63
Fatty acid derivatives and Carboxamide derivatives	2	66.67	0	0.00
Benzodiazepine derivatives and other antiepileptics	0	0.00	1	3.13
Benzodiazepine derivatives and Fatty acid derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives	0	0.00	0	0.00
Succinimide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Hydantoin derivatives and Carboxamide derivatives	0	0.00	0	0.00
Hydantoin derivatives and other antiepileptics	0	0.00	0	0.00
Hydantoin derivatives and Succinimide derivatives	0	0.00	0	0.00
Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00
Barbiturates derivatives and Fatty acid derivatives	0	0.00	0	0.00
Barbiturates derivatives and Carboxamide derivatives	0	0.00	0	0.00
Barbiturates derivatives and Benzodiazepine derivatives	0	0.00	0	0.00
Benzodiazepine derivatives and Fatty acid derivatives and other antiepileptics	0	0.00	0	0.00
Carboxamide derivatives and Fatty acid derivatives and other antiepileptics	1	33.33	0	0.00
Benzodiazepine derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	0	0.00
Benzodiazepine derivatives and Succinimide derivatives and Fatty acid derivatives	0	0.00	0	0.00
Fatty acid derivatives and Barbiturates derivatives and other antiepileptics	0	0.00	0	0.00

CM Number of pregnancies	Paternal exposure group Valproate (polytherapy) N=3		Lamotrigine/levetiracetam (polytherapy) N=32	
	N	%	N	%
Barbiturates derivatives and Carboxamide derivatives and other antiepileptics	0	0.00	0	0.00
AED indication				
Epilepsy	3	100.00	29	90.63
Bipolar affective disorder and mania	0	0.00	0	0.00
Other/unknown	0	0.00	3	9.38
K means cluster [a]				
Group A	3	100.00	26	81.25
Group B	0	0.00	6	18.75
Paternal exposure to teratogenic activity/fetal toxicity [a]	0	0.00	0	0.00

AED: Antiepileptic Drug, CM: Congenital Malformations; LMP2: Last menstrual period date plus 2 weeks
Cluster A: constant moderate exposure, Cluster B: moderate to low exposure
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) 3-months lookback from LMP2
b) Valproate or lamotrigine/levetiracetam in combination with other AED(s). Each combination found in the data will be listed here.

Table 84 Association between potential offspring risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				Comparison
CM	**Valproate (polytherapy)**		**Lamotrigine/levetiracetam (polytherapy)**		**Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)**
Number of pregnancies	**N=3**		**N=32**		**-**
	N	**%**	**N**	**%**	
Offspring risk factors/confounders[a]					
Congenital CMV	0	0.00	0	0.00	-
Congenital Herpes Simplex	0	0.00	0	0.00	-
Congenital rubella	0	0.00	0	0.00	-
Congenital toxoplasmosis	0	0.00	0	0.00	-
Congenital varicella	0	0.00	0	0.00	-
Fetal alcohol syndrome	0	0.00	0	0.00	-

CM: Congenital Malformations; CMV: Cytomegalovirus
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 analyzed 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) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date
* A non-parametric test was used in this comparison. Fisher's exact test was used for categorical variables. For continuous variables, the Mann-Whitney U test was performed.

Table 85 Association between potential maternal risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				Comparison
CM	**Valproate (polytherapy)**		**Lamotrigine/levetiracetam (polytherapy)**		**Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)**
Number of pregnancies	**N=3**		**N=32**		**-**
	N	**%**	**N**	**%**	
Maternal risk factors/confounders					
Mother´s age [a](categorical)					
≤20 years	0	0.00	1	3.13	-
21-25	1	33.33	6	18.75	-
26-30	2	66.67	11	34.38	-
31-35	0	0.00	13	40.63	-
36-40	0	0.00	1	3.13	-
>40	0	0.00	0	0.00	-
Test statistics	-	-	-	-	2.47 (0.6504)
Mother´s age [a](continuous)					
Mean (SD)	25.67 (4.51)		29.09 (4.55)		-1.26 (0.3170)
Median (25^{th} - 75^{th} percentile)	26.00 (21.00, 30.00)		28.50 (26.00, 33.00)		-
Min, max	21.00, 30.00		19.00, 37.00		-
Missing	0	0.00	0	0.00	-
Diabetes [b]	0	0.00	0	0.00	-
Obesity [c]	0	0.00	0	0.00	-
Alcohol abuse prior to LMP2 [c]	0	0.00	0	0.00	-
Alcohol abuse during pregnancy [d]	0	0.00	0	0.00	-
Substance abuse prior to LMP2 [c]	0	0.00	0	0.00	-
Substance abuse during pregnancy [d]	0	0.00	0	0.00	-
Smoking prior to LMP2 [c]					
No	3	100.00	23	71.88	-
Yes	0	0.00	0	0.00	-
Missing	0	0.00	9	28.13	-
Test statistics without 'Missing' category	-	-	-	-	-
Smoking during pregnancy [d]					
No	3	100.00	25	78.13	-
Yes	0	0.00	1	3.13	-
Missing	0	0.00	6	18.75	-
Test statistics without 'Missing' category	-	-	-	-	1.00 (1.0000)*
CMV [d]	0	0.00	0	0.00	-

	Paternal exposure group				Comparison
CM	**Valproate (polytherapy)**		**Lamotrigine/levetiracetam (polytherapy)**		**Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)**
Number of pregnancies	**N=3**		**N=32**		**-**
	N	**%**	**N**	**%**	
Folate deficiency [d]	0	0.00	0	0.00	-
Gestational diabetes [d]	0	0.00	1	3.13	1.00 (1.0000)*
Herpes simplex virus [d]	0	0.00	0	0.00	-
Rubella [d]	0	0.00	0	0.00	-
Toxoplasmosis [d]	0	0.00	0	0.00	-
Varicella [d]	0	0.00	0	0.00	-

CM: Congenital Malformations; CMV: cytomegalovirus; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; 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 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 analyzed 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 (12th week of gestation in Norway, 22nd week of gestation in Denmark)

b) all available data prior to index date

c) 12-months lookback from LMP2

d) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)

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

Table 86 Association between potential paternal risk factors/confounders for CM by paternal exposure group; secondary outcome

	Paternal exposure group				Comparison
CM	Valproate (polytherapy)		Lamotrigine/levetiracetam (polytherapy)		Valproate (polytherapy) vs Lamotrigine /levetiracetam (polytherapy)
Number of pregnancies	N=3		N=32		-
	N	%	N	%	
Paternal risk factors/confounders					
Father´s age [a](categorical)					
≤20 years	0	0.00	0	0.00	-
21-25	1	33.33	2	6.25	-
26-30	1	33.33	11	34.38	-
31-35	1	33.33	13	40.63	-
36-40	0	0.00	3	9.38	-
>40	0	0.00	3	9.38	-
Test statistics	-	-	-	-	2.95 (0.5667)
Father´s age [a] (continuous)					
Mean (SD)	28.00 (3.61)		32.09 (5.47)		-1.78 (0.1741)
Median (25^{th} - 75^{th} percentile)	27.00 (25.00, 32.00)		32.00 (28.00, 34.50)		-
Min, max	25.00, 32.00		24.00, 50.00		-
Missing	0	0.00	0	0.00	-
Year of offspring conception [b,c]					
2009-2013	2	66.67	15	46.88	-
2014-2019	1	33.33	17	53.13	-
Test statistics	-	-	-	-	0.43 (0.5119)

CM: Congenital Malformations; SD: Standard Deviation; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum

Legend: Number of pregnancies represent the total number of offspring with linked mother and father. The same mother/father can appear more than once. In that case, their characteristics were described in relationship to the exposure window for each individual offspring. Percentages 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 analyzed 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 (12^{th} week of gestation in Norway, 22^{nd} week of gestation in Denmark)

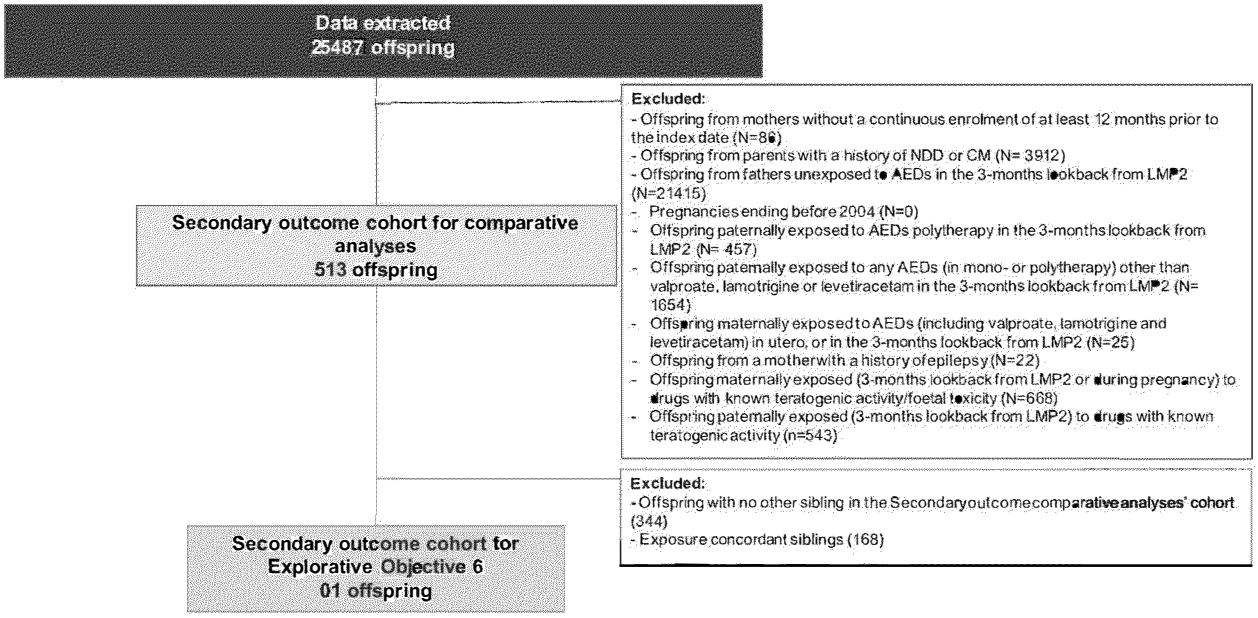
b) at mother's LMP2

c) calendar years will be grouped in each country according to the length of the study period

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

8.1.9 Exposure to valproate or lamotrigine/levetiracetam in paternally and maternally matched siblings (Exploratory analysis 6 CM)

This section supersedes section 15.3.8 from the final study report v1.1.



AED: antiepileptic drugs; CM: Congenital Malformation; NDD: neurodevelopmental disorders; LMP2: Last menstrual period date plus 2 weeks

Figure 12 Study population of Secondary outcome cohort for Exploratory Analyses 6 in Norway

Table 87 Offspring demographic characteristics by paternal exposure group; secondary outcome

CM Number of pregnancies	Paternal exposure group: Valproate N=0		Lamotrigine/levetiracetam N=1	
	N	%	N	%
Gestational age (weeks)				
<28 (extremely preterm)	0	0.00	0	0.00
28-31 (very preterm)	0	0.00	0	0.00
32-36 (moderate to late preterm)	0	0.00	0	0.00
37-41 (at term)	0	0.00	1	100.00
≥42 (post-term)	0	0.00	0	0.00
Missing	0	0.00	0	0.00
Birth weight (g)				
<1000 (extremely low)	0	0.00	0	0.00
1000-1499 (very low)	0	0.00	0	0.00
1500-2499 (low)	0	0.00	0	0.00
≥2500	0	0.00	1	100.00
Missing	0	0.00	0	0.00
Gender [a]				
Male	0	0.00	0	0.00
Female	0	0.00	1	100.00
Missing	0	0.00	0	0.00
Year of birth				
2010	0	0.00	0	0.00
2011	0	0.00	0	0.00
2012	0	0.00	1	100.00
2013	0	0.00	0	0.00
2014	0	0.00	0	0.00
2015	0	0.00	0	0.00
2016	0	0.00	0	0.00
2017	0	0.00	0	0.00
2018	0	0.00	0	0.00
2019	0	0.00	0	0.00

CM: Congenital malformations.
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 88 Offspring clinical characteristics paternal exposure group; secondary outcome

CM	Paternal exposure group			
	Valproate		Lamotrigine/ levetiracetam (composite)	
Number of pregnancies	N=0		N=1	
	N	%	N	%
Comorbidities [a]				
Congenital CMV	0	0.00	0	0.00
Congenital Herpes Simplex	0	0.00	0	0.00
Congenital rubella	0	0.00	0	0.00
Congenital toxoplasmosis	0	0.00	0	0.00
Congenital varicella	0	0.00	0	0.00
Fetal alcohol syndrome	0	0.00	0	0.00
Outcomes				
CM	0	0.00	0	0.00
Major CM (at any time)	0	0.00	0	0.00
Minor CM (at any time)	0	0.00	0	0.00
Frequency of adverse pregnancy outcomes associated to a diagnosis of CM [b]				
Stillbirth	0	0.00	0	0.00
Spontaneous abortion [c]	0	0.00	0	0.00
Intrauterine growth retardation	0	0.00	0	0.00
Perinatal mortality	0	0.00	0	0.00

CMV: Cytomegalovirus; CM: Congenital malformations.
Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
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) between index (12th week of gestation in Norway, 22nd week of gestation in Denmark) and exit date
b) Denominator for the percentage is the number of offspring with CM.
c) Information on spontaneous abortion is not available in Denmark.

Table 89 Maternal demographic characteristics by paternal exposure group; secondary outcome

	Paternal exposure group			
CM	**Valproate**		**Lamotrigine/levetiracetam**	
Number of pregnancies	**N=0**		**N=1**	
	N	**%**	**N**	**%**
Mother's age [a]				
≤20 years	0	0.00	0	0.00
21-25	0	0.00	1	100.00
26-30	0	0.00	0	0.00
31-35	0	0.00	0	0.00
36-40	0	0.00	0	0.00
>40	0	0.00	0	0.00
Mean (SD)	-		25.00 (.)	
Median (25^{th} - 75^{th} percentile)	-		25.00 (25.00, 25.00)	
Min, max	-		25.00, 25.00	
Missing	0	0.00	0	0.00

CM: Congenital malformations; SD: Standard deviation; Min: Minimum; Max: Maximum.
Legend: Number of pregnancies represent the total number of offspring with linked mother and father. The same mother/father can appear more than once.
In that case, their characteristics 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 90 Maternal clinical characteristics by paternal exposure group; secondary outcome

CM	Paternal exposure group: Valproate N=0		Lamotrigine/levetiracetam (composite) N=1	
Number of pregnancies	**N**	**%**	**N**	**%**
Comorbidities				
Diabetes [a]	0	0.00	0	0.00
Epilepsy [a]	0	0.00	0	0.00
Obesity [b]	0	0.00	0	0.00
CMV [c]	0	0.00	0	0.00
Folate deficiency [c]	0	0.00	0	0.00
Gestational diabetes [c]	0	0.00	0	0.00
Herpes simplex virus [c]	0	0.00	0	0.00
Rubella [c]	0	0.00	0	0.00
Toxoplasmosis [c]	0	0.00	0	0.00
Varicella [c]	0	0.00	0	0.00
Lifestyle characteristics				
Alcohol abuse prior to LMP2 [b]	0	0.00	0	0.00
Alcohol abuse during pregnancy [c]	0	0.00	0	0.00
Substance abuse prior to LMP2 [b]	0	0.00	0	0.00
Substance abuse during pregnancy [c]	0	0.00	0	0.00
Smoking prior to LMP2 [b]	0	0.00	0	0.00
Yes	0	0.00	0	0.00
No	0	0.00	1	100.00
Missing	0	0.00	0	0.00
Smoking during pregnancy [c]	0	0.00	0	0.00
Yes	0	0.00	0	0.00
No	0	0.00	1	100.00
Missing	0	0.00	0	0.00
Medication use				
Exposure to AEDs prior to LMP2 [d]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00

CM	Paternal exposure group: Valproate		Lamotrigine/levetiracetam (composite)	
Number of pregnancies	N=0		N=1	
	N	%	N	%
Other antiepileptics	0	0.00	0	0.00
Exposure to AEDs during pregnancy [c]				
Valproate	0	0.00	0	0.00
Lamotrigine	0	0.00	0	0.00
Levetiracetam	0	0.00	0	0.00
Barbiturates and derivatives	0	0.00	0	0.00
Hydantoin derivatives	0	0.00	0	0.00
Oxazolidine derivatives [e]	0	0.00	0	0.00
Succinimide derivatives	0	0.00	0	0.00
Benzodiazepine derivatives	0	0.00	0	0.00
Carboxamide derivatives	0	0.00	0	0.00
Fatty acid derivatives	0	0.00	0	0.00
Other antiepileptics	0	0.00	0	0.00
K means cluster prior to LMP2 [d]				
Unexposed	0	0.00	1	100.00
K means cluster during pregnancy [c]				
Unexposed	0	0.00	1	100.00
Maternal exposure to teratogenic activity/fetal toxicity prior to LMP2 [d] - mothers with at least one prescription	0	0.00	0	0.00
Maternal exposure to teratogenic activity/fetal toxicity during pregnancy [c] - mothers with at least one prescription	0	0.00	0	0.00

AED: Antiepileptic Drug; CM: Congenital malformations; CMV: Cytomegalovirus; LMP2: as Menstrual period date plus 2 weeks
Legend: Number of pregnancies represent the total number of live and non-live offspring with linked mother and father. The same mother/father can appear more than once.
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) all available data prior to index date (12th week of gestation in Norway, 22nd week of gestation in Denmark)
b) 12-months lookback from LMP2
c) during pregnancy (from LMP2 until the earliest of: the first record of a diagnosis of major CM (or if absent the first record of any CM diagnosis), and the date of end of pregnancy)
d) 3-months lookback from LMP2
e) Oxazolidine derivatives were not sold in Norway during the study period

Table 91 Paternal demographic characteristics by paternal exposure group; secondary outcome

CM	Paternal exposure group: Valproate		Lamotrigine/levetiracetam	
Number of pregnancies	N=0		N=1	
	N	%	N	%
Father's age [a]				
≤20 years	0	0.00	0	0.00
21-25	0	0.00	0	0.00
26-30	0	0.00	1	100.00
31-35	0	0.00	0	0.00
36-40	0	0.00	0	0.00
>40	0	0.00	0	0.00
Mean (SD)	-		30.00 (.)	
Median (25^{th} - 75^{th} percentile)	-		30.00 (30.00, 30.00)	
Min, max	-		30.00, 30.00	
Year of offspring conception [b]				
2009	0	0.00	0	0.00
2010	0	0.00	0	0.00
2011	0	0.00	0	0.00
2012	0	0.00	1	100.00
2013	0	0.00	0	0.00
2014	0	0.00	0	0.00
2015	0	0.00	0	0.00
2016	0	0.00	0	0.00
2017	0	0.00	0	0.00
2018	0	0.00	0	0.00
2019	0	0.00	0	0.00

CM: Congenital malformations; LMP2: Last menstrual period date plus 2 weeks; Min: Minimum; Max: Maximum; 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)
b) at mother's LMP2

Table 92 Paternal clinical characteristics by paternal exposure group; secondary outcome

CM	Paternal exposure group			
	Valproate		Lamotrigine/levetiracetam (composite)	
Number of pregnancies	N=0		N=1	
	N	%	N	%
Medication use				
AED indication				
Epilepsy	0	0.00	1	100.00
Bipolar affective disorder and mania	0	0.00	0	0.00
Other/unknown	0	0.00	0	0.00
K means cluster [a]				
Group A	0	0.00	1	100.00
Paternal exposure to teratogenic activity/fetal toxicity [a]	0	0.00	0	0.00

AED: Antiepileptic drug; CM: Congenital malformations; LMP2: Last menstrual period date plus 2 weeks
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) 3-months lookback from LMP2
Cluster A: Constant moderate exposure; Cluster B: Moderate to low exposure.

8.2 Denmark

8.2.1 Rectified Tables (Final Report v1.1)

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

Analyses	Population considered	HR (95% CI) estimates		HR (95% CI) estimates by cluster of exposure	
		Crude*	Adjusted***	Cluster A	Cluster B
Main analysis N sample = 1950	Please check section 9.3	0.94 (0.60, 1.46)	1.34 (0.79, 2.25)	1.38 (0.69, 2.74)	1.30 (0.60, 2.83)
Sensitivity analysis 1 N sample = 2049	Extended risk window of paternal valproate exposure (6 months)	0.86 (0.56, 1.32)	1.13 (0.68, 1.89)	1.51 (0.79, 2.87)	0.80 (0.35, 1.84)
Sensitivity analysis 3 N sample = 1931	Exclusion of offspring with low birth weight or born prior to 8th months	0.93 (0.59, 1.46)	1.36 (0.82, 2.27)	1.50 (0.80, 2.84)	1.19 (0.53, 2.69)
Sensitivity analysis 5A N sample = 1837	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	0.98 (0.62, 1.54)	1.51 (0.90, 2.53)	1.57 (0.81, 3.04)	1.42 (0.63, 3.20)
Sensitivity analysis 5B N sample = 906	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	**	0.59 (0.18, 1.95)	0.70 (0.16, 3.06)	0.43 (0.06, 3.30)
Sensitivity analysis 6 N sample = 1950	Comparison of PS-weighted model with covariate adjustment model	-	1.22 (0.77, 1.92)	-	-
Sensitivity analysis 7 N sample = 1987	Effect of paternal exposure to valproate on NDD in offspring exposed and unexposed to AEDs after birth, and/or diagnosed with epilepsy	1.03 (0.68, 1.57)*	1.41 (0.84, 2.38)	1.42 (0.75, 2.67)	1.38 (0.59, 3.22)
Sensitivity analysis 11 N sample = 1950	Narrow definition of NDD	0.98 (0.61, 1.55)	1.59 (0.89, 2.86)	1.60 (0.75, 3.41)	1.55 (0.64, 3.78)

AED: antiepileptic drugs; CI: Confidence Interval; HR: Hazard ratio; LMP2: Last menstrual period date plus 2 weeks; NDD: neurodevelopmental disorders; PS: Propensity score; 5A analysis comparing valproate and lamotrigine; 5B analysis comparing valproate and levetiracetam

* For sensitivity analysis 7 the "crude" hazard ratio was adjusted for offspring epilepsy and offspring exposure AED.

** Due to the sample size, the estimated HR was not interpretable (>100,000). Crude and adjusted models do not always use the same population leading to differences in the sample size and number of events in the models.

***** The logistic regression PS models used in sensitivity analysis include variables following described:**

Sensitivity analysis 1: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Mother's age", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", "Maternal polypharmacy index prior to LMP2", mothers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal**

risk factors/confounders: "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception". " In sensitivity analysis 1 the HR were further adjusted for "Maternal affective disorder"

Sensitivity analysis 3: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", "Maternal polypharmacy index prior to LMP2", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Year of offspring conception at mother's LMP2"

Sensitivity analysis 5A: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Substance abuse during pregnancy", "Smoking during pregnancy", mothers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception"

Sensitivity analysis 5B: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Smoking during pregnancy", mothers with at least one prescription of "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2"

Sensitivity analysis 6: no PS weighting performed

Sensitivity analysis 7: Offspring risk factors/confounders: "Gender"; **Maternal risk factors/confounders:** "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", "Obesity", "Substance abuse during pregnancy", "Smoking during pregnancy", "Maternal polypharmacy index prior to LMP2", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Concomitant medications associated with neuropsychiatric adverse events during pregnancy"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Mania", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Year of offspring conception". In sensitivity analysis 7, the HR were further adjusted for offspring epilepsy and offspring exposure AED

Sensitivity analysis 11: Maternal risk factors/confounders: "Mother's Age", "Affective disorder", "Diabetes", "Gestational diabetes", "Neurotic disorder", "Obesity", "Smoking during pregnancy", mothers with at least one prescription of: "Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2", "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy", "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2"; **Paternal risk factors/confounders:** "Affective disorder", "Bipolar affective disorder", "Neurotic disorder", "Schizophrenia, schizotypal and delusional disorders", fathers with at least one prescription of: "Concomitant medications associated with neuropsychiatric adverse events prior to LMP2", "Year of offspring conception". In sensitivity analysis 11 the HR were further adjusted for "Maternal affective disorder" and "Concomitant medications associated with valproate-indicated psychiatric conditions during pregnancy"

Table 57 Summary of main analysis and sensitivity analyses for the Secondary outcome cohort in Denmark

Analyses*	Population considered	OR (95% CI) estimates		OR (95% CI) estimates by cluster of exposure	
		Crude	Adjusted*	Cluster A	Cluster B
Main analysis N sample = 648	Please check Section 9.3 in the final study report	0.62 (0.37, 1.04)	0.61 (0.36, 1.06)	0.68 (0.31, 1.48)	0.54 (0.26, 1.12)
Sensitivity analysis 4 N sample = 648	Handling of missing CM diagnosis	0.62 (0.37, 1.04)	0.61 (0.36, 1.06)	0.68 (0.31, 1.48)	0.54 (0.26, 1.12)
Sensitivity analysis 5[A] N sample = 581	Simple pairwise comparisons for the exposure groups: lamotrigine (monotherapy)	0.62 (0.36, 1.06)	0.61 (0.35, 1.07)	0.65 (0.29, 1.45)	0.54 (0.26, 1.16)
Sensitivity analysis 5[B] N sample = 326	Simple pairwise comparisons for the exposure groups: levetiracetam (monotherapy)	0.62 (0.27, 1.42)	0.64 (0.27, 1.52)		
Sensitivity analysis 9 N sample = 646	Narrow case definition for secondary outcome	0.61 (0.35, 1.06)	0.60 (0.34, 1.06)	0.69 (0.32, 1.49)	0.51 (0.24, 1.10)

CI: Confidence Interval; CM: Congenital malformations; LMP2: Last menstrual period plus 2 weeks; OR: Odds ratio; **5[A]** analysis comparing valproate and lamotrigine; **5[B]** analysis comparing valproate and levetiracetam; *: the number of this event was 0 and **OR** could not be estimated***: The logistic regression PS models used in sensitivity analysis include variables following described:**

Sensitivity analysis 1: not applicable.

Sensitivity analysis 4: Offspring risk factors/confounders: "Fetal alcohol syndrome"**; Maternal risk factors/confounders:** "Alcohol abuse prior to LMP2", "Alcohol abuse during pregnancy", "Substance abuse prior to LMP2", "Substance abuse during pregnancy", "Smoking during pregnancy", "Gestational diabetes"

Sensitivity analysis 5[A]: Offspring risk factors/confounders: "Fetal alcohol syndrome"; **Maternal risk factors/confounders:** "Alcohol abuse prior to LMP2", "Alcohol abuse during pregnancy", Substance abuse prior to LMP2", "Smoking during pregnancy"

Sensitivity analysis 5[B]: Offspring risk factors/confounders: "Congenital varicella" **Maternal risk factors/confounders:** "Diabetes", "Obesity", "Substance abuse during pregnancy", Varicella during pregnancy"

Sensitivity analysis 9: Offspring risk factors/confounders: "Fetal alcohol syndrome"; **Maternal risk factors/confounders:** "Alcohol abuse during pregnancy", "Substance abuse during pregnancy", "Smoking during pregnancy", "Gestational diabetes"

8.3 Missing values

8.3.1 Norway

Table 93. Missing data patterns; primary outcome in Norway

Group	Offspring risk factors / confounders[a]	Maternal risk factors/confounders[b]		Paternal risk factors/confounders[c]		
	None of the factors over 5% missingness	Smoking prior LMP2	Smoking during pregnancy	None of the factors over 5% missingness	Freq	Perc
Group 1					1218.00	86.02
Group 2		X	X		151.00	10.66
Group 3		X			40.00	2.82
Group 4			X		7.00	0.49

LMP2: Last menstrual period date plus 2 weeks
a) Gender, Congenital Cytomegalovirus (CMV), Congenital rubella, Fœtal alcohol syndrome, Fragile X syndrome, Lejeune/cri du chat syndrome, Tuberous sclerosis
b) Other maternal factors (none was over 5% missingness): Mother's age, Affective disorder, Diabetes, Gestational diabetes, Neurotic disorder, Schizophrenia, schizotypal and delusional disorders, Obesity, CMV, Rubella, Alcohol abuse prior to LMP2, Alcohol abuse during pregnancy, Substance abuse prior to LMP2, Substance abuse during pregnancy, Maternal polypharmacy index prior to LMP2, Maternal polypharmacy index during pregnancy, Concomitant medications associated with valproate-indicated psychiatric conditions prior to LMP2 - mothers with at least one prescription, Concomitant medications associated with valproate -indicated psychiatric conditions during pregnancy - mothers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events prior to LMP2 - mothers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events during pregnancy - mothers with at least one prescription
c) Bipolar affective disorder, Mania, Affective disorder excluding bipolar affective disorder and mania, neurotic disorder, Schizophrenia, schizotypal and delusional disorders, Substance abuse, Paternal polypharmacy index, Concomitant medications associated with valproate -indicated psychiatric conditions - fathers with at least one prescription, Concomitant medications associated with neuropsychiatric adverse events - fathers with at least one prescription, Father's age, Year of offspring conception
The 4 groups represent 4 subgroups of offspring with the following patterns:
Group 1. No risk factors or confounders missing
Group 2. Maternal smoking prior to LMP2 and during pregnancy missing
Group 3. Only maternal smoking prior to LMP2 missing
Group 4. Only maternal smoking during pregnancy missing

Table 94. Missing data patterns; secondary outcome in Norway

	Offspring risk factors/confounders[a]	Maternal risk factors/confounders[b]		Paternal risk factors/confounders[c]		
Group	None of the factors over 5% missingness	Smoking prior LMP2	Smoking during pregnancy	None of the factors over 5% missingness	Freq	Perc
Group 1					438.00	85.38
Group 2		X	X		58.00	11.31
Group 3		X			15.00	2.92
Group 4			X		2.00	0.39

LMP2: Last menstrual period date plus 2 weeks
a) Congenital Cytomegalovirus (CMV), Congenital Herpes Simplex, Congenital rubella, Congenital toxoplasmosis, Congenital varicella, Fetal alcohol syndrome
b) Other maternal factors (none was over 5% missingness): Mother's age, Diabetes, Obesity, Alcohol abuse prior to LMP2, Alcohol abuse during pregnancy, Substance abuse prior to LMP2, Substance abuse during pregnancy, CMV, Folate deficiency, Gestational diabetes, Herpes simplex virus, Rubella, Toxoplasmosis, Varicella
c) Father's age, Year of offspring conception
The 4 groups represent 4 subgroups of offspring with the following patterns:
Group 1. No risk factors or confounders missing
Group 2. Maternal smoking prior to LMP2 and during pregnancy missing
Group 3. Only maternal smoking prior to LMP2 missing
Group 4. Only maternal smoking during pregnancy missing
Secondary Outcome cohort for comparative analyses is used in the summary.