Systematic review

Risk of neurodevelopmental disorders associated with paternal use of valproate during spermatogenesis: a living meta-analysis—version 1

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ABSTRACT

Objective To evaluate the association of paternal use of valproate during spermatogenesis compared with paternal use of lamotrigine or levetiracetam on offspring risk of neurodevelopmental disorders (NDDs).

Methods Eligibility criteria: observational, peer-reviewed studies reporting neurodevelopmental outcomes of children exposed to paternal monotherapy use of valproate vs lamotrigine or levetiracetam during spermatogenesis.

Information sources: the databases PubMed, Embase, Cochrane Library and Web of Science were systematically searched from January 1995 to October 2025.

Synthesis of results and risk of bias: a random-effects model was used to estimate pooled HRs and 95% CI, with heterogeneity assessed using I^2 statistic for any NDD.

We present a meta-analysis of observational, peer-reviewed studies reporting neurodevelopmental outcomes of children exposed to paternal monotherapy use of valproate versus lamotrigine or levetiracetam during spermatogenesis. Given the major regulatory implications of paternal valproate safety, the recent emergence of new population-based data, and the expectation of further large studies, we designed this work as a living systematic review and meta-analysis that will be updated as new eligible evidence becomes available.

Results We identified three eligible studies based on data from (1) Norway and Sweden, (2) Norway and Taiwan and (3) Denmark. As two studies included Norwegian data, their results are referred to as 'Norway 1' and 'Norway 2' for clarity. In the meta-analysis of data from Denmark, Sweden and Norway 1, the pooled HR of offspring NDDs was 1.05 (95% CI 0.87 to 1.27; I^2=0.0%), and in meta-analysis of data from Denmark, Sweden and Norway 2, it was 1.03 (95% CI 0.85 to 1.24; I^2=0.0%).

In the meta-analysis including Taiwan, Denmark, Sweden and Norway 1, the pooled HR was 1.06 (95% CI 0.88 to 1.27; I^2=0.0%), and when including data from Taiwan, Denmark, Sweden and Norway 2, the pooled HR was 1.04 (95% CI 0.87 to 1.25; I^2=0.0%).

Conclusions In this living meta-analysis, we found no evidence that paternal exposure to valproate compared with lamotrigine/levetiracetam during spermatogenesis was associated with increased risk of NDDs in offspring.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Recent restrictions and precautionary measures related to the use of valproate in males are being implemented across Europe, due to concerns of reproductive risks.

WHAT THIS STUDY ADDS

⇒ In this living meta-analysis including data from Denmark, Norway, Sweden and Taiwan, there was no evidence of an association between paternal valproate use and risk of neurodevelopmental disorders when compared with paternal lamotrigine or levetiracetam use.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This meta-analysis of population-based studies from four countries calls for a consideration of the restrictions on the use of valproate in males of fertile age.

INTRODUCTION

In January 2024, the European Medicines Agency (EMA) recommended precautionary measures for the treatment of male patients with valproate due to potential risk of neurodevelopmental disorders (NDDs) in children born to men treated with valproate medicines.[1] According to these precautionary measures, "doctors should inform male patients who are taking valproate about the possible risk and discuss the need to consider effective contraception, for both the patient and their female partner. Valproate treatment of male patients should be reviewed regularly to consider whether it remains the most suitable treatment, particularly when the patient is planning to conceive a child".[1] These precautionary measures followed a post-authorisation safety study from Denmark, Norway and Sweden, prepared by the Contract Research Organization IQVIA on behalf of the Market Authorization Holders (MAHs).[2–5] In this study, paternal valproate exposure during spermatogenesis was found to be associated with an increased risk of NDDs in the offspring (pooled adjusted HR (aHR)=1.50 (95% CI 1.09 to 2.07)).[1–6] In addition to the EMA's precautionary measures, the UK

Medicines and Healthcare products Regulatory Agency (MHRA) has issued a warning against the use of valproate in males under 55 years of age due to concerns regarding male fertility and risk of NDDs in offspring.[7]

However, subsequent to these restrictions on valproate use in males, concerns have been raised that the scientific data do not convincingly substantiate the inference of a paternally mediated risk from valproate to children,[8 9] and register studies based on the same population databases as those used in the IQVIA analyses have been unable to replicate the findings.[10–13] In July 2025, the EMA's Pharmacovigilance Risk Assessment Committee (PRAC) therefore initiated a procedure to understand the difference in the findings across the studies and requested further information and analyses from the MAHs for valproate.[14] This has recently led to the formation of a consortium of MAHs for valproate, which will initiate the PaTernal exposure to vAlproate, further iNvestiGation on the risk of NeuroDevelopmental Disorders (NDD) and Major Congenital Malformation (MCM) in Offspring: A Non-Interventional Post-Authorization Safety Study (TANGO) to further investigate the association between paternal exposure to valproate and the risk of NDDs. This study is expected to be completed by the end of March 2028.[15]

To address conflicting views and findings and in the light of the potential harm with valproate withdrawal,[16] we present a meta-analysis of observational, peer-reviewed studies reporting neurodevelopmental outcomes of children exposed to paternal monotherapy use of valproate versus lamotrigine or levetiracetam during spermatogenesis, that is, the same exposure definitions initially included in the IQVIA study report.[2–6] Given the major regulatory implications of paternal valproate safety,[1 7] the recent emergence of new population-based data[10–13] and the expectation of further large studies (including the French EPIPHARE report[17] and the TANGO[15]), we designed this work as a living systematic review and meta-analysis[18] that will be updated as new eligible evidence becomes available.

METHODS

The databases PubMed, Cochrane Library, Embase and Web of Science were searched in October 2025 using the search terms: (paternal OR father) AND (spermiogenesis OR spermatogenesis OR pregnan* OR gestation* OR prenatal OR antenatal OR in utero OR fetus OR fetal OR infant OR newborn) AND (valproate OR 'valproic acid' OR lamotrigine OR levetiracetam) (Online supplemental figure 1).[19] We followed the extension of the Preferred Reporting Items for Systematic Reviews and Meta-Analyses 2020 statement for living systematic reviews[18] (https://www.prisma-statement.org/lsr). The aim was to identify human peer-reviewed observational studies reporting neurodevelopmental outcomes in children exposed to paternal monotherapy use of valproate during spermatogenesis compared with children exposed to paternal monotherapy use of lamotrigine or levetiracetam, that is, similar to the IQVIA study.[2–6]

Data extraction and statistical analysis

We extracted adjusted HRs (aHRs) or relative risks (aRRs), and their corresponding 95% CIs for any NDD as well as for individual disorders (ie, autism spectrum disorder (ASD), attention-deficit/hyperactivity disorder (ADHD), intellectual disability (ID) and disorders of psychological development) from primary studies. Pooled HRs with 95% CIs were then calculated, and between-study heterogeneity was assessed using the I^2 statistic. A random-effects model based on inverse-variance method with the Paule-Mandel estimator was applied using R-package 'metagen' in R (V.4.3.2)[20] to address potential between-country differences. An I^2 value exceeding 50% was interpreted as indicating substantial heterogeneity. A pooled risk estimate of NDDs in offspring exposed to paternal monotherapy use of valproate compared with lamotrigine or levetiracetam restricted to offspring of fathers with epilepsy was included as an additional analysis, as data were available from all included studies.

Additional analyses

In additional analyses, we estimated pooled estimates of NDDs in children of fathers who used valproate compared with children of fathers who used lamotrigine or levetiracetam allowing combination therapy during spermatogenesis.

At the time of preparation of the current meta-analysis, we became aware of a non-peer-reviewed French study reported online on 6 November 2025.[17] Although this study had not been published in a peer-reviewed journal and thus did not meet our inclusion criteria, we include its results in a sensitivity analysis to assess their impact on pooled estimates.

Certainty of evidence

We did not undertake a formal Grading of Recommendations Assessment, Development and Evaluation (GRADE) assessment because all included studies were registry-based nationwide cohort studies with highly similar designs, data sources and outcome definitions. Given methodological homogeneity and the narrow evidence base, a structured GRADE evaluation was not considered informative for distinguishing certainty levels across outcomes.

Living mode parameters

To establish a live online meta-analysis platform, we used the analytical resource MetaAnalysisOnline.com.[21] All analyses were conducted in March 2026.

This review is maintained in living mode. We plan to rerun the literature search in all databases at least every 6 months, and more frequently if we become aware of new large population-based studies through regulatory communications (eg, EMA or national medicines agencies), study registries or direct contact with investigators. Whenever at least one new eligible study is identified, we will repeat screening, data extraction and meta-analysis for all relevant outcomes. Updated pooled estimates will be generated in R and on MetaAnalysisOnline.com,[21] where all versions of the meta-analysis will be archived with time-stamped shareable links. We intend to maintain the review in living mode at least until completion and publication of major ongoing studies, including TANGO,[15] after which the need for further updates and potential retirement of the living mode will be re-evaluated.

This is version 1 of the living review; consequently, there are no changes in methods or eligibility criteria relative to the preceding version.

RESULTS

We identified three peer-reviewed studies describing neurodevelopmental outcomes in children after paternal use of valproate during spermatogenesis compared with paternal use of lamotrigine or levetiracetam (online supplemental figure 1). The studies were based on data from (**Study 1**) Norway and Sweden,[12] (**Study 2**) Norway and Taiwan[13] and (**Study 3**) Denmark.[11] Thus, two studies included overlapping Norwegian data; for clarity, results from Study 1[12] are referred to as 'Norway 1' and those from Study 2[13] as 'Norway 2'. Summary details and results of the

Table 1 Register-based studies of NDDs in offspring exposed to paternal monotherapy use of valproate during spermatogenesis

	Study 1 (Razaz *et al*[12])		Study 2 (Meng *et al*[13])		Study 3 (Christensen *et al*[11])
	Sweden	**Norway 1**	**Norway 2**	**Taiwan**	**Denmark**
Study period	2007–2022	2010–2019	2010–2021	2010–2021	1997–2018
Inclusion criteria (liveborn children)	All children born 2007–2020	All children born 2010–2018	Singleton children born 2010–2015	Singleton children born 2010–2015	Singleton children born 1997–2017
Births (n)	1 517 108	519 313	367 960	1 234 223	1 278 978
Sample size—after exclusions					
Paternal lamotrigine/ levetiracetam exposure, n	3093 (0.20%)	1109 (0.21%)	730 (0.20%)	96 (0.01%)	1401 (0.11%)
Paternal valproate exposure, n	1588 (0.10%)	463 (0.09%)	319 (0.09%)	564 (0.05%)	961 (0.08%)
Exposure definitions					
Exposure window (ie, period of spermatogenesis)	Prescriptions from LMP −120 days to LMP +14 days	Prescriptions from LMP −120 days to LMP +14 days	Prescriptions overlapping with LMP −76 days to LMP +14 days	Prescriptions overlapping with LMP −76 days to LMP +14 days	Prescriptions from LMP −120 days to LMP +14 days
Outcome definitions of NDD*					
Composite NDD endpoint	Any diagnosis of specific NDDs*	Any diagnosis of specific NDDs*	Any diagnosis of specific NDDs *	Any diagnosis of specific NDDs *	Any diagnosis of specific NDDs*
Follow-up period	From age 1 year until end of 2022	From age 1 year until end of 2019	From specific ages until end of 2021†	From specific ages until end of 2021†	From age 1 year until end of 2018
Follow-up age (min–max) years	1–15	1–10	1–12†	1–12†	1–22
Median (IQR) age at the end of follow-up					
Paternal lamotrigine/ levetiracetam exposure	6.9 (4.3–9.1)	4.0 (2.0–6.2)	8.8 (7.2–10.2)	8.1 (6.7–9.4)	6.5 (3.7–10.3)
Paternal valproate exposure	7.5 (4.5–10.3)	4.1 (2.0–6.1)	8.5 (7.2–10.2)	7.8 (6.3–9.3)	11.6 (6.4–16.0)
Number of children with NDD					
Paternal lamotrigine/ levetiracetam exposure, n	247	39	59	16	50
Paternal valproate exposure, n	159	21	24	127	67
Adjustment method	Cox regression with covariate adjustment	Cox regression with covariate adjustment	Pooled logistic regression with propensity score fine stratification weighting	Pooled logistic regression with propensity score fine stratification weighting	Cox regression with covariate adjustment

*Please see online supplemental table 1 for specific NDD International Classification of Disease, version 10 codes (ICD-10 codes).
†At least 6 years of follow-up from delivery.
LMP, last menstrual period; NDDs, neurodevelopmental disorders.

individual studies are presented in table 1, and in online supplemental table 1-6, and compared with key summary details from the IQVIA study in table 2.[2–4 6]

The designs of the studies are described in their respective publications,[11–13] but all were register-based cohort studies using data from national patient registers for capturing diagnoses of NDDs and epilepsy, and national prescription registries for the identification of paternal use of antiseizure medication during spermatogenesis.[11–13] To assess the impact of methodological differences between the two Norwegian studies,[12 13] and to facilitate direct comparison with the IQVIA study,[2–6] the data from these studies were included in separate analyses together with the Danish[11] and Swedish[12] data. In secondary analyses, data from Taiwan were included as well.

Analyses including data from Denmark, Norway and Sweden

Overall risk of neurodevelopmental disorders

In the meta-analysis of data from studies 1 and 3 (Sweden, Norway 1 and Denmark),[11 12] the pooled HR of any offspring NDD was 1.05 (95% CI 0.87 to 1.27; I^2=0.0%; figure 1A), and in the analysis of data from studies 1, 2 and 3 (Sweden, Norway 2 and Denmark), the pooled HR was 1.03 (95% CI 0.85 to 1.24; I^2=0.0%; figure 1B).

Risk of specific neurodevelopmental disorders

In the meta-analyses of specific NDDs, the pooled HR for offspring risk of ASD was 1.07 (95% CI 0.69 to 1.68; I^2=36.9%) in studies 1 and 3 (Sweden, Norway 1 and Denmark),[11 12] and 1.07 (95% CI 0.69 to 1.65; I^2=34.8%) in studies 1, 2 and 3 (Sweden, Norway 2 and Denmark; figure 2); for ADHD, the pooled HR was 0.90 (95% CI 0.70 to 1.17; I^2=6.8%), in studies 1 and 3 (Sweden, Norway 1 and Denmark), and 0.91 (95% CI 0.64 to 1.31; I^2=30.7%), in studies 1, 2 and 3 (Sweden, Norway 2 and Denmark; figure 2); for ID, the pooled HR was 1.36 (95% CI 0.82 to 2.28; I^2=0.0%), in studies 1 and 3 (Sweden and Denmark; figure 2), and for disorders of psychological development, the pooled HR was 1.21 (95% CI 0.82 to 1.77; I^2=0.0%) in studies 1 and 3 (Sweden, Norway 1 and Denmark; figure 2). ID and disorders of psychological development were further subclassified in Study 2 (Norway 2),[13] and did therefore not contribute to meta-analyses of the overall categories.

Analyses restricted to offspring of fathers with epilepsy

In analyses restricted to offspring of **fathers with epilepsy**, the pooled HR of any offspring NDD was 1.26 (95% CI 0.96 to 1.65; I^2=0.0%) in studies 1 and 3 (Sweden, Norway

Table 2 NDDs in offspring exposed to paternal use of valproate during spermatogenesis—the IQVIA study[2–4 6]

	IQVIA study[2–4 6]		
	Sweden	**Norway**	**Denmark**
Study period	2007–2019	2010–2019	1997–2018
Inclusion criteria (liveborn children)	Singleton children born 2007–2019	Singleton children born 2010–2019	Singleton children born 1997–2018
Births (n)	Not reported	Not reported	Not reported
Sample size—after exclusion*			
Paternal lamotrigine/levetiracetam exposure, n	1425	1018	1157
Paternal valproate exposure, n	930	398	793
Sample size—after exclusion and PSW§			
Paternal lamotrigine/levetiracetam exposure, n	1334	910	1118
Paternal valproate exposure, n	841	325	678
Exposure definitions			
Exposure window (ie, period of spermatogenesis)	Prescriptions overlapping with LMP −76 days to LMP +14 days	Prescriptions overlapping with LMP −76 days to LMP +14 days	Prescriptions overlapping with LMP −76 days to LMP +14 days
Outcome definitions of NDD			
Composite NDD endpoint	Any diagnosis of specific NDDs†	Any diagnosis of specific NDDs†	Any diagnosis of specific NDDs†
Follow-up period	From birth until the end of 2019‡	From birth until the end of 2019‡	From birth until the end of 2018‡
Follow-up age (min–max) years	0–12	0–10	0–12
Median (IQR) follow-up time/age at the end of follow-up			
Paternal lamotrigine/levetiracetam exposure	4.53 (2.16–7.71)	4.74 (2.50–7.17)	6.36 (3.42–10.05)
Paternal valproate exposure	6.59 (3.74–9.79)	4.96 (2.76–7.22)	11.48 (6.56–12.00)
Number of children with NDD			
Paternal lamotrigine/levetiracetam exposure, n	34	21	36
Paternal valproate exposure, n	47	13	38
Adjustment method	Adjusted propensity score-weighted Cox regression model	Adjusted propensity score-weighted Cox regression model	Adjusted propensity score-weighted Cox regression model

*Crude model: excluded from comparative cohort: pregnancies associated with in vitro fertilisation, multiple pregnancies, parents with congenital malformations or NDDs, parents with incomplete enrolment in the registries 12 months before pregnancy, offspring or mothers with epilepsy or treated with antiseizure medications (ASMs).
†Please see reference Colas *et al*[6] for specific NDD International Classification of Disease, version 10 codes (ICD-10 codes).
‡Follow-up stopped at 12 years of age in Denmark and Sweden and at 10 years in Norway.
§PSW and adjusted model. In addition to the criteria-based exclusions (*), observations with missing values on covariates and influential observations were excluded from the PS model and subsequently from the weighted Cox model.
NDDs, neurodevelopmental disorders; PS, propensity score; PSW, propensity score weighting.

1 and Denmark), and the pooled HR was 1.23 (95% CI 0.93 to 1.62; I^2=0.0%) in the analysis of data from studies 1, 2 and 3 (Sweden, Norway 2 and Denmark) (online supplemental figure 2 and online supplemental table 7).

Analyses including data from Denmark, Norway, Sweden and Taiwan

Overall risk of neurodevelopmental disorders

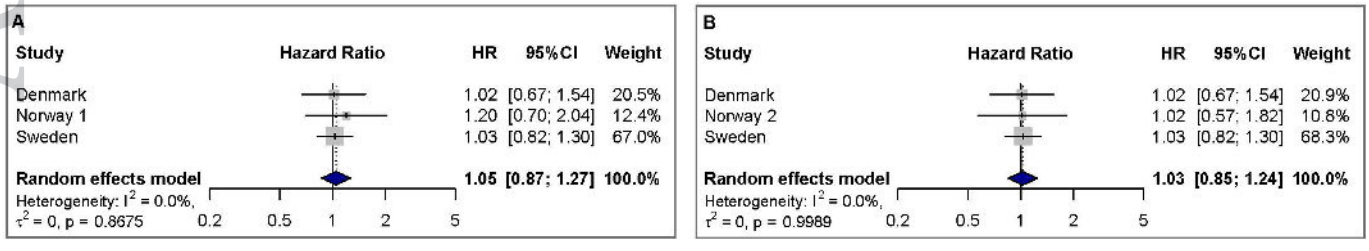

Figure 1 HRs of **neurodevelopmental disorders** (composite outcome) in children of fathers who used valproate in monotherapy compared with children of fathers who used lamotrigine or levetiracetam in monotherapy during spermatogenesis. Panel A: studies 1 and 3 (Denmark, Norway 1 and Sweden). Panel B: studies 1, 2 and 3 (Denmark, Norway 2 and Sweden).

References: Study 1: Sweden and Norway 1: *Razaz et al*.[12] **Study 2: Norway 2 and Taiwan: Meng** *et al*.[13] **Study 3: Denmark: Christensen et al.**[11]

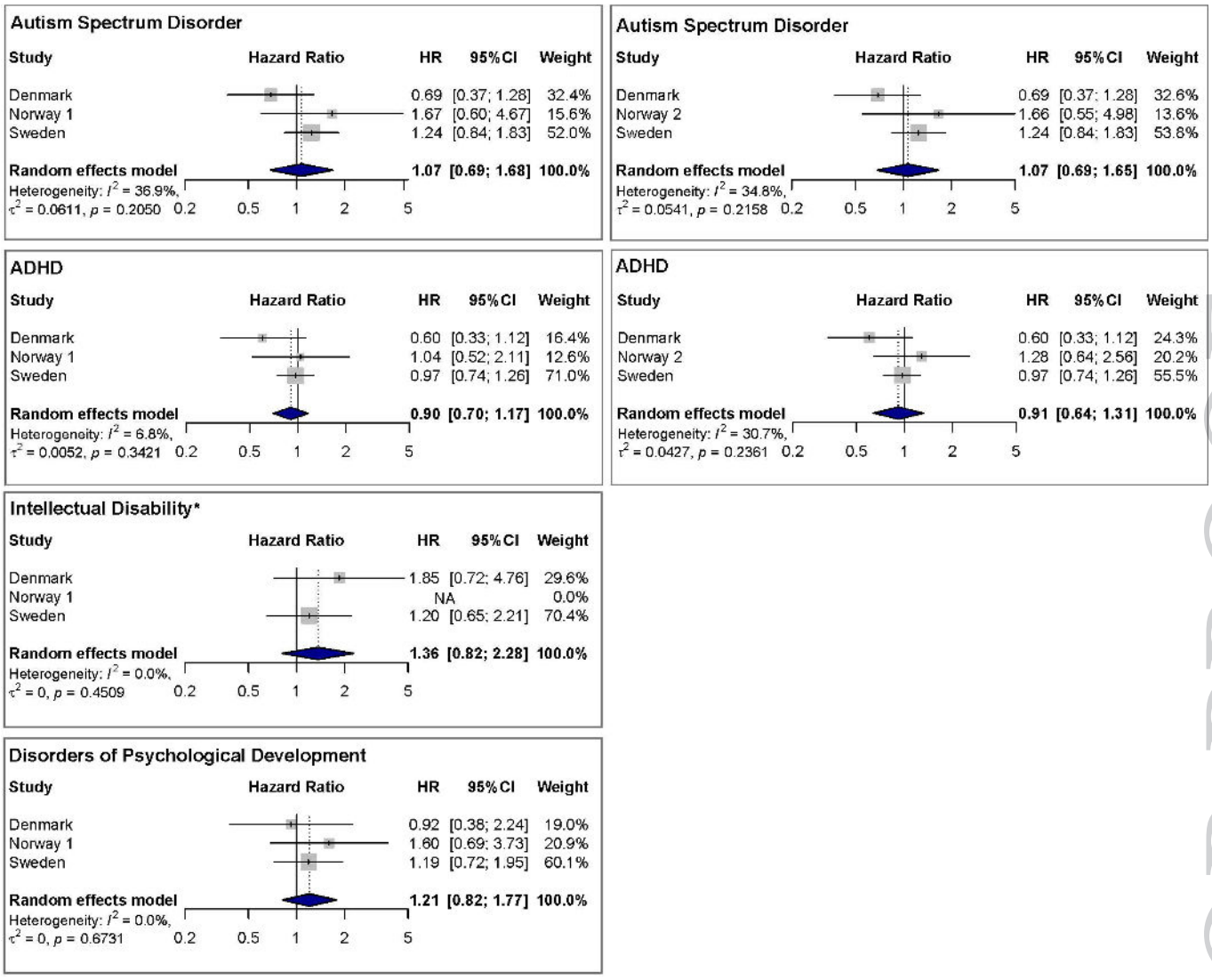

Figure 2 HRs of autism spectrum disorders, ADHD, intellectual disability and disorders of psychological development in children of fathers who used valproate in monotherapy compared with children of fathers who used lamotrigine or levetiracetam in monotherapy during spermatogenesis. Panel A: studies 1 and 3 (Denmark, Norway 1 and Sweden). Panel B: studies 1, 2 and 3 (Denmark, Norway 2 and Sweden).

References: Study 1: Sweden and Norway 1: Razaz *et al*.[12] Study 2: Norway 2 and Taiwan: Meng *et al*.[13] Study 3: Denmark: Christensen *et al*.[11] ADHD, attention-deficit/hyperactivity disorder.

When extending the meta-analysis with results from Taiwan, the pooled HR of NDDs was similar to the pooled HR based on data from Denmark, Norway and Sweden only (figure 1);[11–13] the pooled HR of any NDD was 1.06 (95% CI 0.88 to 1.27; I^2=0.0%) in studies 1, 2 and 3 (Sweden, Norway 1, Taiwan and Denmark) and 1.04 (95% CI 0.87 to 1.25; I^2=0.0%) in studies 1, 2 and 3 (Sweden, Norway 2, Taiwan and Denmark; figure 3).

Risk of specific neurodevelopmental disorders

When extending the meta-analysis of specific NDDs with data from Taiwan, the pooled HR for offspring risk of ADHD was 0.91 (95% CI 0.73 to 1.13; I^2=0.0%), in studies 1, 2 and 3 (Sweden, Norway 1, Denmark **and Taiwan**) (online supplemental figure 3) and 0.93 (95% CI 0.75 to 1.17; I^2=0.0%), in studies 1, 2 and 3 (Sweden, Norway 2, Denmark **and Taiwan**) (online supplemental figure 3). There were no other specific NDDs that allowed additional meta-analyses across the studies included.

Analyses restricted to offspring of fathers with epilepsy

When extending the meta-analysis restricted to offspring of **fathers with epilepsy** with results **from Taiwan**, the pooled HR of any NDD was 1.30 (95% CI 1.00 to 1.70; I^2=0.0%) in studies 1, 2 and 3 (Sweden, Norway 1, Taiwan and Denmark) and 1.27 (95% CI 0.97 to 1.67; I^2=0.0%) in studies 1, 2 and 3 (Sweden, Norway 2, Taiwan and Denmark) (online supplemental figure 4).

Additional analyses

Studies allowing combination therapy during spermatogenesis

In additional analyses of NDDs in children of fathers who used valproate compared with children of fathers who used lamotrigine or levetiracetam allowing combination therapy during spermatogenesis, data were available from Study 2 (Norway and Taiwan)[13] and Study 3 (Denmark).[11] In this analysis, the pooled HR of any NDD was 0.93 (95% CI 0.75 to 1.16; I^2=0.0%) (online supplemental figure 5)

Meta-analyses including non-peer-reviewed data

In the non-peer-reviewed French study by Botton *et al*,[17] authors report that after taking propensity score into account, the overall incidence of NDDs was significantly higher among children exposed to paternal use of valproate than among children exposed to paternal use of lamotrigine or levetiracetam (aHR 1.24 (95% CI 1.07 to 1.44)).[17] However, in analyses restricted to monotherapy exposure (ie, similar to the IQVIA study), the aHR was 1.17 (95% CI 0.98 to 1.40).[17] We meta-analysed this result with the available data from Norway, Denmark, Sweden and Taiwan[11–13] (online supplemental figure 6). The pooled HR was 1.11 (95% CI 0.98 to 1.27; I^2=0.0%) using data from studies 1 and 3 (Denmark, Norway 1, Sweden and Taiwan) and the non-peer-reviewed study from France, and the pooled HR was 1.11 (95% CI 0.97 to 1.26; I^2=0.0%) using data from studies 1, 2 and 3 (Denmark, Norway 2, Taiwan and Sweden) and the non-peer-reviewed study from France. When including results from studies allowing combination therapy during spermatogenesis, that is, Study 2 (Norway and Taiwan),[13] Study 3 (Denmark),[11] and the non-peer-reviewed study from France,[17] the pooled HR was 1.07 (95% CI 0.89 to 1.28; I^2=42.7%) (online supplemental figure 7).

Meta-analyses with data from the IQVIA study

We meta-analysed the results from the IQVIA study[5 6] (Denmark, Norway and Sweden), with the results from Taiwan[13] and the results from the non-peer-reviewed study from France[17] (online supplemental figure 8). In this meta-analysis, the pooled HR was 1.24 (95% CI 1.06 to 1.44; I^2=0.0%).

As this is the first version of the living review, there are no changes in included studies or pooled estimates relative to a previous version.

DISCUSSION

This living meta-analysis presents more precise estimates of the risk of NDDs in children with paternal valproate versus lamotrigine or levetiracetam exposure during spermatogenesis, suggesting no increased risk associated with paternal use of valproate during spermatogenesis. This meta-analysis incorporates all available data from Denmark, Norway and Sweden, with the addition of data from Taiwan.[13] These findings substantiate conclusions from previous individual replication studies based on data from Denmark, Norway and Sweden[10–13] and do not replicate an increased risk reported by IQVIA.[2–6] The findings of this new meta-analysis therefore do not support the conclusions reached by EMA and MHRA regarding precautionary measures for the treatment of male patients with valproate,[1 7] but align with the conclusions of a recent systematic review of risks associated with paternal use of antiseizure medication.[22]

In the IQVIA study of offspring neurodevelopmental risk, the crude Cox regression models (not excluding outliers) showed a HR of 0.94 (95% CI 0.60 to 1.46) in Denmark, 1.16 (95% CI 0.76 to 1.76) in Sweden and 1.60 (95% CI 0.81 to 3.15) in Norway.[2–6] These crude HRs are comparable to the crude HRs for the individual countries in the Nordic cohorts included in this meta-analysis (0.99 (95% CI 0.68 to 1.44) in Denmark, 0.96 (95% CI 0.77 to 1.19) in Sweden, 1.28 (95% CI 0.74 to 2.22) in Norway 1 and 0.94 (95% CI 0.57 to 1.56) in Norway 2). However, the results of the inverse probability of treatment weighting propensity score-weighted Cox regression models used in the IQVIA study suggested that the crude results could have been affected by downward confounding bias (ie, negative confounding),[2–6] with higher HRs in the three countries (1.34 (95% CI 0.79 to 2.25) in Denmark, 1.54 (95% CI 0.95 to 2.51) in Sweden and 1.76 (95% CI 0.83 to 3.71) in Norway, with a pooled HR among all three countries of 1.50 (95% CI 1.09 to 2.07)).[2–6] In the current meta-analysis, none of the CIs of the pooled risk estimates (HR=1.05 (95% CI 0.87 to 1.27) and HR=1.03 (0.85 to 1.24)) overlapped with the pooled risk estimate from the IQVIA study.[2–6] Thus, while the cohort and exposure definitions of studies included in this meta-analysis and the IQVIA study produce similar crude risk estimates, differences in adjustment and statistical modelling likely explain the different adjusted estimates and conclusions. However, the number of exposed children also varies between studies included in this meta-analysis (table 1)[10–13] and the IQVIA study (table 2);[2–6] thus, further efforts to try to understand the differences are much needed as also acknowledged by EMA.[14 15] Although part of the analytical code from the IQVIA study was published, we do not think that the description of the IQVIA data and analyses is sufficiently transparent to judge which of the studies are the most robust. Currently, there is disagreement[8 9] about the interpretation and conclusions reached by EMA and MHRA[1 7] after reviewing the findings from the IQVIA study.[2–6]

This updated meta-analysis of recently published studies from Denmark,[11] Sweden[12] and Norway[12 13] provides precise risk estimates with low heterogeneity across studies. Although we assessed studies with two different adjustments and statistical modelling approaches (Cox regression with covariate adjustment in studies 1[12] and 3,[11] and pooled logistic regression with propensity score fine stratification weighting in study 2[13]), this had no impact on our results. Also, including studies allowing combination therapy during spermatogenesis and including findings from populations not included in the IQVIA study (ie, Taiwan[13]

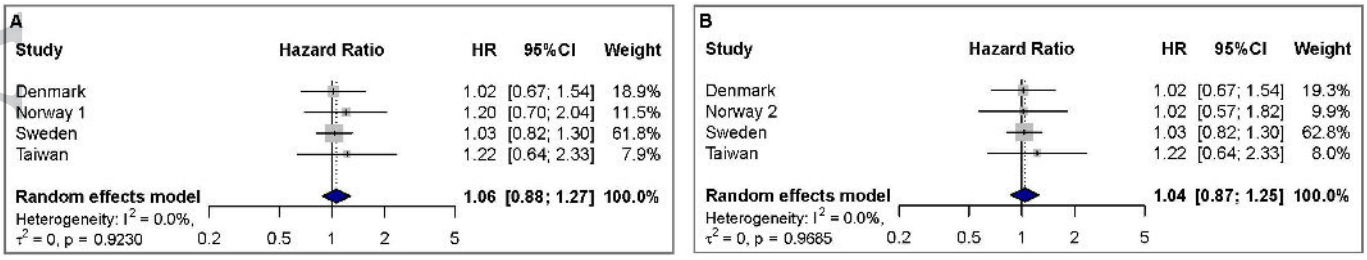

Figure 3 HRs of **neurodevelopmental disorders** (composite outcome) in children of fathers who used valproate in monotherapy compared with children of fathers who used lamotrigine or levetiracetam in monotherapy during spermatogenesis. Panel A: studies 1, 2 and 3 (Denmark, Norway 1, Sweden **and Taiwan**), Panel B: studies 1, 2 and 3 (Denmark, Norway 2, Sweden **and Taiwan**).

References: Study 1: Sweden and Norway 1: Razaz *et al*.[12] Study 2: Norway 2 and Taiwan: Meng et al.[13] Study 3: Denmark: Christensen *et al*.[11]

and France[17]) did not alter our findings. Thus, the inclusion of demographically and geographically distinct populations across the Nordic region, together with data from Taiwan, suggests that the findings may be extrapolated to different healthcare systems, genetic backgrounds and environmental contexts, thereby strengthening the robustness and generalisability of the results.

The studies included in this meta-analysis[11–13] draw on high-quality, population-based cohort studies using comprehensive national registry data with extensive adjustment for confounding factors, thereby minimising the risk of bias. However, these strengths also apply to the study performed by IQVIA[2–4 6] and do therefore not shed light on reasons for the differing conclusions.

The differences in overall results are most likely due to differences in the analyses of the original data. Both in the study from Denmark[11] and in the IQVIA study,[2–4] the analytical code has been published, and additional information about the IQVIA study is presented in supplement to the Colas *et al*[6] study (ie, the peer-reviewed publication of the IQVIA study). However, even with this granularity, it has not been possible to ascertain which specific factors account for the differences observed in the original data analyses across the studies. In a replication study using data from Denmark,[11] we attempted to mirror the individual analytical steps of the IQVIA study;[2–4] however, even in these detailed analyses, we were unable to disentangle the source of the discrepancies.

In this meta-analysis, we present NDD risk estimates for children born to fathers using valproate during spermatogenesis relative to the NDD risk in children born to fathers using lamotrigine or levetiracetam, but it would be relevant to also compare with the risk of NDDs in the general population. However, estimates for this comparison were not presented in any of the studies included in the meta-analysis. However, in a previous replication study by Christensen *et al*,[10] the risk of NDDs in valproate-exposed children was compared with the risk of NDDs in children unexposed to valproate, that is, roughly identical to the general population. In this analysis, the risk of NDDs was not higher in children exposed to valproate than in children unexposed to valproate (aHR=1.10, 95% CI 0.88 to 1.37), suggesting that the underlying risks in the two populations were similar, once adjusted for relevant confounding variables.[10]

In the present study, we present several parallel meta-analyses, to ensure inclusion of all relevant studies in the evidence synthesis, while avoiding inclusion of overlapping populations in a single analysis. Thus, this resulted in parallel analyses of data from Denmark and Sweden with Norway 1 and 2[11–13] (the main analyses enabling direct comparison between the replication studies and the IQVIA study[2–4]) and in the study by Colas *et al*[6] (also data from Denmark, Sweden and Norway) with data from Taiwan and France.

In this current meta-analysis, the eligibility criteria regarding exposure were chosen to replicate the study design used by IQVIA[2–4 6] (ie, paternal monotherapy exposure to valproate compared with lamotrigine/levetiracetam). We identified a previous study using Swedish register data of paternal use of antiseizure medication and offspring risk of NDDs,[23] and a study from Norway based on self-reported paternal epilepsy and use of antiseizure medication and risk of autistic traits at 18 and 36 months of age.[15] These studies, however, did not specifically report on outcomes after paternal exposure to valproate compared with lamotrigine/levetiracetam,[23 24] making comparison with the IQVIA study and the current meta-analysis challenging. In addition to these peer-reviewed studies, a recent population-based study report from France was brought to our attention.[17] Using data from the National Health Data System, the authors followed 2.8 million children born in France between 2010 and 2015.[17] After propensity score matching, authors report a non-significant 17% increased risk of NDDs following paternal monotherapy exposure to valproate compared with lamotrigine or levetiracetam (HR 1.17 (95% CI 0.98 to 1.40)).[17] This risk estimate is lower than that reported by IQVIA (HR 1.50 (95% CI 1.09 to 2.07)); however, it is higher than that reported in our meta-analysis (figure 1). The pooling of the French study results with our meta-analysis did not identify an increased risk (online supplemental figure 6 and 7). In contrast, when the IQVIA study results[2–4 6] were included, the pooled suggested an increased risk (online supplemental figure 8). Thus, adding the non-peer-reviewed French study[17] did not resolve the discrepancy between the IQVIA study[2–4 6] and the replication studies based on data from Denmark, Norway and Sweden, with additional data from Taiwan.[10–13]

The risk estimates included in this meta-analysis compared valproate monotherapy with an active comparator group (lamotrigine/levetiracetam) also used in monotherapy. This restriction excluded other estimates with greater statistical power that might have provided more precise results, such as those involving polytherapy or unexposed population controls. Nevertheless, estimates including polytherapy and population controls did not suggest that paternal use of valproate was linked to offspring neurodevelopmental outcomes in previous studies.[10–13] We applied a random-effects model to account for potential heterogeneity between studies arising from differences in study design, analytical approaches, populations and healthcare settings. While heterogeneity was low for analyses considering the composite NDD outcome, it was somewhat higher in analyses of specific NDDs.

The risk estimates of NDDs were higher when limiting the meta-analyses to include only offspring of fathers with epilepsy (online supplemental figure 2). However, the proportion of offspring that was included in the analyses varied among the individual countries and by drug exposure. The proportions with paternal epilepsy for valproate were 56.4% for Sweden, 74.5% for Norway 1, 62.1% for Norway 2, 30.1% for Taiwan and 77.0% for Denmark, whereas the proportions with paternal epilepsy for lamotrigine/levetiracetam were 34.0% for Sweden, 53.9% for Norway 1, 42.6% for Norway 2, 49.0% for Taiwan and 52.6% for Denmark.[11–13] Additionally, the indications for paternal use of valproate may overlap, for example, in Norway 2,[13] the mean number of indications for paternal valproate use was 1.4, suggesting that indications for paternal valproate use may overlap. These differences between the individual countries and even internally within the same country (Norway 1+2) could potentially explain some of the differences between the countries in the analyses restricted to the offspring of fathers with epilepsy.

Several limitations should be acknowledged. First, the individual analyses of specific NDDs were based on small case numbers, as reflected by the wide CIs and, for example for ID, we were only able to include estimates from two countries, which limit the certainty of disorder-specific associations. Second, all included studies adjusted for key confounders, but residual confounding due to unmeasured or imperfectly measured factors cannot be excluded. All pooled risk estimates had CIs including the null, but there could still be residual confounding, for example, from underlying genetic susceptibility to NDDs that differ between fathers who use valproate and fathers who use lamotrigine or levetiracetam.[25] Third, we tried to align with the IQVIA study, but differences in exposure definitions, outcome ascertainment, follow-up time, and

particularly adjustment procedures, covariate inclusion and definitions may have introduced variability in the effect estimates, as suggested by the similarities of crude but not adjusted risk estimates. Fourth, we conducted a formal systematic literature review (online supplemental figure 1), but some relevant studies may not have been identified. However, given the small number of population-based data sources with father-child linkages addressing this very specific question (monotherapy exposure to valproate vs lamotrigine/levetiracetam), it is unlikely that major studies were missed. Finally, the meta-analysis relied on published aggregate data rather than on individual participant data due to legal restrictions in sharing and pooling individual data, which restricted the ability to perform harmonised adjustments or subgroup analyses. However, the IQVIA study also relied on pooled analyses of aggregated results; thus, we do not think that this limitation explains the difference between this meta-analysis and the IQVIA study.[2–4 6]

Implications of the results for practice, policy and future research

Epilepsy is a prevalent neurological disorder in males of fertile age,[26–29] and valproate is likely the most efficacious medication for generalised epilepsies.[30 31] Epilepsy is a serious disorder with an associated life expectancy that on average is 10 years shorter compared with the general population.[32] A recent study suggested potential harm associated with valproate withdrawal; valproate withdrawal was linked to higher risks of emergency visits, hospital admissions, falls, injuries, burns and new-onset depression, corresponding to a 1–7% higher risk compared with those remaining on valproate.[16] The lack of replication of the original IQVIA findings across independent population-based studies from Denmark, Sweden and Norway raises questions about whether paternal valproate exposure during spermatogenesis affects NDDs in human offspring. Given the significant and far-reaching clinical implications of the EMA's[1] and the MHRA's[7] precautionary measures, the absence of reproducible evidence supporting the original signal,[10–13] and new data from France,[17] the warning and restrictions of the use of valproate in males of fertile age should be reconsidered to determine whether they remain proportionate to the available evidence.[9] Further comparative analyses are needed to clarify the methodological or data-related reasons for the discrepancy between the IQVIA[2–4 6] findings and subsequent studies with similar design.[10–13] The ongoing review initiated by the PRAC,[14] the additional studies commissioned by the MAHs for valproate[15] and other independent investigations[17] are therefore of critical importance.

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Contributors All authors initiated the study, obtained funding and participated in the design of the study. BBT constructed the dataset, analysed the data, had full access to all study data and takes responsibility for the integrity of the data and the accuracy of the data analysis. JC prepared the first draft and the revised versions. All authors interpreted the results, revised the manuscript and approved the final version of the manuscript. The corresponding author (JC) attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted. JC is responsible for the overall content as the guarantor.

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