Author:
Jain, Kritika

Title:
Anti-seizure medication prescription during preconception period and pregnancy with risk of orofacial clefts in offspring

A UK CPRD GOLD population-based study

Anti-seizure medication prescription during preconception period and pregnancy with risk of orofacial clefts in offspring: A UK CPRD GOLD population-based study

Student number: [redacted]

A dissertation submitted to the University of Bristol in accordance with the requirements of the degree of Master of Science by advanced study in Public Health in the Faculty of Health Sciences.

Population Health Sciences, Bristol Medical School, September 2022

Dissertation Declaration

I declare that the work in this report was carried out in accordance with the requirements of the University's Regulations and Code of Practice for Taught Programmes and that it has not been submitted for any other academic award. Except where indicated by specific reference in the text, this work is my own work. Work done in collaboration with, or with the assistance of others, is indicated as such. I have identified all material in this report which is not my own work through appropriate referencing and acknowledgement. Where I have quoted from the work of others, I have included the source in the references/bibliography. Any views expressed in the dissertation are those of the author.

SIGNED: ……Kritika Jain……. DATE: ……11 September 2022…….

(an electronic signature will be taken as confirmation of declaration)

Abstract

Background

Anti-seizure medications (ASM) are widely used during pregnancy to prevent adverse maternal and foetal outcomes resulting from inadequate seizure management and non-epileptic conditions. As the knowledge of ASM teratogenicity expands, practitioners face a challenge in balancing the detrimental effects of ASM use during pregnancy. Our study aims to evaluate the association between epilepsy and ASM prescriptions as monotherapy and polytherapy in women during the preconception and pregnancy period with the risk of orofacial clefts (OFCs) in offspring.

Methods

A population-based cohort study was conducted using the United Kingdom (UK) Clinical Practice Research Datalink (CPRD) GOLD database, with cohort including women having pregnancy start date between 1st January 1995 and 31st December 2018. The final cohort consisted of 518,050 livebirths. Epilepsy in women and ASM prescriptions as monotherapy and/or polytherapy during the preconception period, pregnancy, and first trimester were evaluated with OFC in offspring as the primary outcome, using logistic regression models.

Findings

Valproate prescription during preconception (aOR=4.34, 95% CI=0.45-42.27), and pregnancy (aOR=4.97, 95% CI=0.51-48.38) was associated with an increased risk of OFCs in offspring. However, strength of the evidence for an association was lacking. Prescription with carbamazepine, pregabalin, lamotrigine, and levetiracetam presented with raised odds, but the wide confidence intervals suggested lack of strong evidence for association. No evidence was found for gabapentin, phenytoin, and topiramate prescriptions.

Interpretation

Our study did not discover substantial evidence for relationship between epilepsy and ASM prescriptions in women with OFC in offspring, indicating further research to evaluate the ASM safety during pregnancy.

Introduction

Epilepsy is the most prevalent neurological disorder globally, affecting approximately one million women of reproductive age, and nearly 1% of all pregnant women.[1-2] Over the years, anti-seizure medications (ASMs) have been used for epilepsy treatment in pregnant women because of the higher risk of foetal loss and inadequate neurodevelopment in the foetus due to poor seizure control.[3] With the advent of newer ASMs, e.g., lamotrigine, gabapentin, and levetiracetam, and an increase in the number of non-epileptic indications (e.g., bipolar disorders, neuropathic pain), ASM use among women of reproductive age has increased.[2,4-6] A study revealed that ASM use in pregnant women increased from 15.7 to 21.9 per 1000 deliveries from 2001 to 2007 in the United States, attributable to both the increase in the number of non-epileptic indications and the development of newer ASMs,[4] thus increasing the rate of foetal exposure to ASMs. Studies by Veiby et al. and Dean et al. indicated that roughly 33.5% and 87% of the offspring born to epileptic mothers respectively were exposed to ASMs in-utero.[7-8]

Physicians encounter the challenge of managing epilepsy during pregnancy and assessing the undesirable maternal and child outcomes linked to uncontrolled epilepsy and ASM use. In 1968, Meadow addressed the issue of congenital malformations (CM) such as cleft lip (CL) and cleft palate (CP), congenital heart lesions, and skeletal abnormalities in children born to epileptic mothers and taking a combination of ASMs.[9] Though, 90% of the children born to epileptic women have no anomalies,[1] it has been documented that epilepsy in women and ASM use during gestation may increase the risk of CM and neurodevelopmental disorders in offspring compared to offspring of women with untreated or no epilepsy.[1,6-8,10-13] A Swedish study indicated that children exposed to ASMs in-utero had a 17% increased risk of CM (RR=1.17; 95% CI=0.75-1.25) as compared to unexposed children.[14]

CL and CP are the second most common CM in children, following cardiac defects,[10] with a prevalence of one in every 700 livebirths worldwide.[15] Furthermore, the anomaly is associated with impaired speech, feeding difficulties, and poor cognition in children. As the fusion of maxillary and palatine processes for facial development occurs between the sixth and twelfth week of gestation, teratogenic medication use during the first trimester (FT) may result in cleft anomalies in offspring.[15] A Norwegian study revealed no association between ASM use during pregnancy and orofacial clefts (OFC) in offspring.[12] Lamotrigine and topiramate prescriptions early in pregnancy was associated with a 10-fold higher risk of CL and/or CP in offspring, while valproate monotherapy elevated the risk of cleft palate by 5-fold.[16] According to EUROCAT (European Concerted Action on Congenital Anomalies and Twins) registries-based studies, lamotrigine monotherapy during pregnancy was associated with a 31% increased odds of all OFC

(adj.OR=1.31; 95% CI=0.73-2.33) and a 69% increased odds of isolated CP (adj.OR=1.69; 95% CI=0.69-4.15) in babies.[17]

However, several methodological shortcomings make previous studies susceptible to bias. First, some studies failed to account for possible confounding factors, e.g., mother's socioeconomic position, maternal age, and indications for ASM use (e.g., epilepsy, psychiatric conditions), which may have caused biased estimates.[7,10,12,18] Second, cohort selection in pregnancy and epilepsy registry-based studies relies on self-enrolment by the women, which may cause differences in the women's characteristics in the study as compared to the general population. This lack of systematic or random sample selection may contribute to selection bias and decreased generalizability.[19] Additionally, lack of an internal control group in some studies prevented comparison between ASM treatment and no treatment within the same population, resulting in bias.[20]

The purpose of our study was to evaluate the association between ASM prescription during the preconception period and FT with the risk of OFC in offspring using the UK CPRD GOLD database. We also examined the effects of epilepsy, ASM prescription during pregnancy, ASM monotherapy, and ASM polytherapy during the FT of pregnancy with OFC in offspring.

Methods

Data sources

Data was obtained from CPRD GOLD, CPRD pregnancy register, CPRD mother-baby link dataset, Hospital Episode Statistics (HES) database, the Office for National Statistics (ONS) death certificate data, and Index of Multiple Deprivation (IMD) data.

The CPRD database includes primary care data on demographics, prescriptions, clinical events, and hospital admissions for approximately 6.9% (4.4 million active patients) of the total UK population, sourced from 674 UK general practices (GPs) and is representative of the UK population in terms of age, gender, and ethnicity.[21] The data was supplemented by linkages to HES, ONS, and IMD, covering 75% of UK practices. The HES database includes information on admissions, accidents and emergency attendances, diagnosis, and maternity data (coded using international classification of diseases (ICD) version 10) for all NHS-funded healthcare services in England from 1997, excluding data on medication prescriptions. IMD data provides information on a single deprivation score, derived from the postcodes of patients' residences or GP addresses.[22]

All pregnancies identified in the CPRD GOLD database for women aged 11 to 49 years are recorded in the Pregnancy Register, together with details on the pregnancy's outcome and anticipated start and end dates, based on the last menstrual cycle and pregnancy-related codes. The mother-baby link dataset contained information regarding live births and children enrolled with the same GP as their mother.[22]

Study design and cohort selection

A population-based observational cohort study design was used to examine the risk of OFC in children born to epileptic mothers and/or women prescribed ASMs before and during pregnancy. The study population consisted of women with a pregnancy start date between 1st January 1995 and 31st December 2018. We limited cohort selection to women registered with an "up-to-standard" GP for a minimum of 365 days before the estimated pregnancy start date until the pregnancy end date, to ensure adequate time to record women's baseline characteristics and ASM prescription before and during pregnancy. We only included pregnancies with mother-baby linkage data to retain maternal exposure status and offspring outcomes, and excluded mothers with missing data on age. To maximise study power, children and mothers with and without HES data were also included. The final study cohort consisted of 518,050 children.

Outcome

The diagnosis of OFC in the offspring at any age was used as the primary outcome for our study. The cases were identified from the CPRD and HES databases using Read codes (used to describe clinical terms in the CPRD) and ICD-10 codes, respectively (supplementary tables-S1 and S2).

Exposures

An algorithm was developed to identify epilepsy in mothers before the pregnancy start date. We used information from primary care data on ASM prescriptions in women from 365 days before the pregnancy start date until the pregnancy end date. ASM prescription was defined as any prescription with the anatomical therapeutic chemical codes N03A and N05BA09 (for clobazam).

Primary exposure:

The primary exposures in women were: 1) ASM prescriptions with a start or end date in the preconception period; preconception period was defined as the period starting from three months before pregnancy start date until the pregnancy start date; and 2) ASM prescriptions with a start or end

date within the FT of the pregnancy; FT was defined as the first 90 days following the pregnancy start date.

We investigated the ASM classes separately, which included carbamazepine, gabapentin, lamotrigine, levetiracetam, phenytoin, pregabalin, topiramate, and valproate. All other ASMs were included in "other ASMs" category (see supplementary methods).

Secondary exposure:

The secondary exposures included: 1) Diagnosis of epilepsy in the mothers before the pregnancy start date; 2) ASM prescriptions with a start or end date within the pregnancy period; 3) ASM monotherapy for each ASM class during the preconception period, pregnancy, and FT; 4) ASM prescription anytime from the preconception period to pregnancy end date; and 5) polytherapy in the FT (full definitions are presented in the supplementary methods).

Covariates

The characteristics associated with ASM prescription in mothers and risk of OFC in the offspring (potential confounding variables) were adjusted for in the analytical models. Minimally adjusted models included maternal age, marital status, ethnicity, and IMD quintile. The fully adjusted models were further adjusted for area of residence, maternal body mass index (BMI), smoking status of the mother, evidence of hazardous drinking behavior, seizure events in the year before pregnancy, use of anti-psychotics, antidepressants, multivitamins, and folic acid in the year before pregnancy, use of illicit drugs during pregnancy, gravidity, and indications for ASM use, i.e., diagnosis of epilepsy, other somatic and psychiatric conditions in the women before pregnancy (see supplementary table-S3 for definitions).

Statistical analysis

The characteristics of the mothers with epilepsy and those with or without ASM prescription during the preconception period, pregnancy, and FT were described.

Primary analysis:

We used logistic regression models using STATA-17 software to evaluate the risk of OFC in children born to mothers subjected to primary exposures as compared to children born to unexposed women. We calculated the Odds Ratios (OR) and 95% Confidence Intervals (CI) for unadjusted, minimally adjusted, and fully adjusted models and repeated for each ASM class separately.

Secondary analysis:

We analysed the effect of secondary exposures in the women and the development of OFC in their offspring as compared to children of unexposed women. Details are presented in the supplementary methods. All analyses were performed using logistic regression models, adjusted for covariates and repeated for each ASM type. The results were presented as ORs with a 95% CI.

Ethical consideration

Access to CPRD data, including UK Primary Care Data, and linked data such as HES, was approved following protocol submission to CPRD's Research Data Governance process (protocol number 20_000228).

Results

Cohort description

Table-1 describes the descriptive statistics according to the diagnosis of epilepsy and ASM prescription during the preconception period, pregnancy, and FT in the study cohort. Among the women enrolled in the study, approximately 1.2% had a diagnosis of epilepsy before the pregnancy start date. Those with the diagnosis of epilepsy were more likely to be younger, not in a partnership, be of white ethnic origin, be in the highest quintile of deprivation, be obese, be smokers, be prescribed with antipsychotics and antidepressants in the year before pregnancy, and suffer from other somatic and psychiatric conditions.

Approximately 0.8% of the women were prescribed ASMs during the preconception period, pregnancy, and FT. The ASM prescription during FT accounted for 93% of all ASMs prescribed anytime during pregnancy. Those prescribed with ASMs were more likely to have a pregnancy start date between 2013 and 2018, at least one seizure event in the year before pregnancy, and diagnosis of other somatic and psychiatric conditions.

Primary analysis

In our study, lamotrigine was the most common ASM to be prescribed during preconception and FT. Table-2 and figure-1 depict the number of women prescribed with specific ASMs of interest and ORs for the ASM prescription during the preconception period. There was strong evidence for an increased risk of OFCs in children born to women prescribed with valproate (unadjusted OR (uOR)=3.47, 95% CI=1.29-9.29) as compared to children of women not prescribed with valproate during the preconception period. Upon adjusting for potential confounders, the odds for the OFC in children born to mothers prescribed

with valproate became 4.3 times. However, the strength of the evidence for an association decreased (fully adjusted OR (aOR)=4.34, 95% CI=0.45-42.27). Prescription of carbamazepine (uOR=1.94, 95% CI=0.62-6.03), pregabalin (aOR=2.75, 95% CI=0.37-20.39), lamotrigine (aOR=1.72, 95% CI=0.17-17.63), and "other ASMs" (uOR=2.08, 95% CI=0.29-14.85) showed raised ORs, but evidence for an association was weak. Prescription of gabapentin (uOR=0.66, 95% CI=0.09-4.7), levetiracetam, phenytoin, and topiramate during the preconception period did not show any association with OFC in offspring.

Table-2 and figure-2 present the findings for the association between the ASM prescription in FT and OFC. Prescription of valproate in FT showed little evidence for association with OFC in children in unadjusted, minimally adjusted and fully adjusted models. However, the effect size was approximately five-times more in exposed children as compared to the unexposed (aOR=5.41, 95% CI=0.56-52.25). Carbamazepine (uOR=2.09, 95% CI=0.67-6.53), levetiracetam (uOR=2.86, 95% CI=0.71-11.49), lamotrigine (aOR=1.82, 95% CI=0.17-18.82), pregabalin (aOR=3.15, 95% CI=0.42-23.59), and "other ASMs" (uOR=2.35, 95% CI=0.33-16.76) presented with increased odds of OFC in children born to mothers prescribed with the respective ASMs, but there is a lack of strong evidence for an association. Phenytoin and topiramate exposure groups did not have cases of OFC in children.

Secondary analysis

Table-3 shows the number of exposed women and ORs for epilepsy in women and ASM prescriptions during pregnancy with OFC in children. 0.27% of children born to women with epilepsy were diagnosed with OFC, as compared to 0.19% children of unexposed women. Our study did not find any evidence for an association between epilepsy in women and OFC in offspring after adjusting for covariates (minimally adjusted OR (maOR)=0.96, 95% CI=0.31-2.99; aOR=0.83, 95% CI=0.25-2.78).

Figure-3 shows the ORs for ASM prescription during pregnancy. Levetiracetam prescription during pregnancy showed strong evidence of OFC in children in unadjusted models (uOR=3.72, 95% CI=1.19-11.61). Adjusting for potential confounders increased the size estimates, but no longer suggested evidence for an association (aOR=5.33, 95% CI=0.49-58.36). Prescription of valproate in mothers during pregnancy also showed increased ORs for association with OFC in children, but there is a lack of strong evidence for an association (aOR=4.97, 95% CI=0.51-48.38). Results for carbamazepine, pregabalin, lamotrigine, and "other ASMs" prescriptions showed increased odds for association with OFC, but the evidence for the same was weak. There was no association between gabapentin, topiramate, or phenytoin prescriptions during pregnancy with OFC in children.

The results for the ASM monotherapy, ASM prescription anytime from preconception period to pregnancy end date, and ASM polytherapy during FT can be found in supplementary results and tables.

Discussion

Summary of findings and comparison with previous studies

In our study, 1.2% of pregnant women had epilepsy, and prevalence of OFC in children was 0.2% (N=1,006). ASM prescriptions among women increased by 2-3% between 2007-2012 and 2013-2018 periods, which is comparable to previous findings.[4] Previous studies showed varied results for CM, notably clefts in the offspring of epileptic mothers,[1-2] however, our investigation found no association between OFCs in children born to epileptic mothers.

In our study, lamotrigine was the most frequently prescribed ASM during pregnancy, supporting the previous studies[10,23-24] and findings of the UK Cleft Collective database, which showed that the majority of women were administered lamotrigine (0.3%) during the FT of pregnancy. The decreased risk of CM associated with lamotrigine in comparison to other ASMs like valproate and topiramate might explain why it is increasingly prescribed to pregnant women.[23] However, some studies showed that lamotrigine exposure during pregnancy raises the risk of clefts in offspring by 69-100%.[17,23] In contrast, a study by Blotiere et al. found no instances of CL and/or CP in offspring exposed to lamotrigine compared to unexposed children.[10] Although we observed elevated ORs for lamotrigine prescription throughout the preconception and pregnancy periods, the evidence for an association with OFC in children was weak. This is possibly attributed to the small number of children who were diagnosed with the outcome of interest, reducing the power of our study.

Prior investigations have presented inconsistent evidence for carbamazepine teratogenicity.[10,23,25] Our study, however, found weak evidence for an increased likelihood of OFC in carbamazepine-exposed offspring over unexposed pregnancies. Moreover, despite reports of a decline in valproate prescription in pregnancy registries in Australia, Europe, and the UK primary care database,[24,26] it was the fourth most commonly prescribed ASM in our study. We discovered that valproate prescription during preconception and FT was associated with an increased risk of OFC in exposed children, which is consistent with earlier studies demonstrating valproate's teratogenicity both in monotherapy and polytherapy.[10,18,23] Since the FT of gestation is crucial for facial development in the foetus,[15] our study suggests avoidance of valproate prescription in women during this period.

Though previous studies do not provide strong evidence for levetiracetam teratogenicity,[18,23] our findings suggest that prenatal exposure to levetiracetam was associated with a higher risk of OFC in

offspring. Consequently, our results contradict the reports by the Commission on Human Medicine, suggesting that levetiracetam is the safest ASM to prescribe during pregnancy.[27] However, in our study, there were no incidences of OFC in the exposed group when levetiracetam prescribing was restricted to monotherapy during pregnancy, suggesting that the association found earlier could be attributable to the synergistic effect of co-prescription with another ASM.

Despite studies confirming the teratogenic potential of phenytoin and topiramate,[18,23,28] no cases of OFC were found in children exposed to these medicines in-utero in our study. Therefore, we cannot comment on the risk of OFCs in these exposed groups. The results of our study also support the findings of previous studies on the teratogenic potential of ASM polytherapy in the FT of pregnancy.[23]

Due to the wide CI and inadequate number of cases of OFC, our study is unable to make definitive conclusions on the effect of ASMs in-utero. However, the trends indicate a positive association between the outcome and exposures.

Strengths and limitations

Our study had multiple advantages. First, this was a population-based study with a sample size of 518,050 children, increasing the precision and accuracy of the results. However, we cannot neglect the small number of individuals in the exposure and outcome groups, reducing the power of our study to detect a true association. Second, the CPRD database is representative of the UK population, which increases the external validity and generalizability of our findings. We also observed that the CPRD had a prevalence of approximately 1% for epilepsy in women, 0.8% for ASM prescriptions during pregnancy, and 0.19% for OFC in children, which is similar to the prevalence in the general population.[1,24,27] This represents the good diagnostic sensitivity of our study and reduces the possibility of underestimation of results. As the CPRD database contains primary care data from GPs, our study may have been free of selection bias, increasing its external validity. Third, we used a control group from the same database as the cases to ensure comparable baseline characteristics across exposed and non-exposed groups. Fourth, our study accounted for potential confounders, e.g., maternal age, use of other medications, and indications of ASM use (e.g., epilepsy, somatic and psychiatric conditions), thus limiting the probability of confounding due to indication and increasing the accuracy and internal validity of the study. However, residual confounding in the study might bias the results. Fifth, we assessed the impact of individual ASM types in polytherapy and monotherapy, which would help in shaping the ASM prescription guidelines for clinicians. Lastly, we examined the effects of ASMs based on the timing of prescriptions, i.e., preconception, pregnancy, and FT. Preconception and FT period are essential for

foetal development; hence it is crucial to investigate the effects of medications on the women during these timeframes.

However, our study also had limitations. First, CPRD has incomplete information on over-the-counter prescriptions, women's adherence to ASMs, filled prescriptions, or secondary care prescriptions.[21] This might cause a non-differential misclassification of exposure status and consequently underestimate the findings. Secondly, despite a large sample size, few women were prescribed topiramate and phenytoin; hence, no conclusions can be drawn from the absence of outcomes in these exposure groups. Third, our database excluded information on stillbirths, abortions, and miscarriages, which could lead to biased findings. For example, if abortions were a result of the identification of OFC in the foetus through frequent prenatal screening among exposed women, our results may be underestimated. Fourth, previous studies suggest an association between parental and offspring cleft.[29] However, potential genetic confounding owing to familial inheritance of clefts was not controlled for in our study. Fifth, the data available on ASM dosages prescribed to women was insufficient and we could not make an inference about its association with OFC in offspring. Sixth, we did not analyse the different types of clefts in children or if the diagnosis was a symptom of an ASM-related syndrome, thus limiting our ability to make conclusions about the aetiology of clefts and CM. Lastly, CPRD does not contain information on pregnant women in prisons, private practices, or homeless women.[21] Also, missing data on marital status, BMI, ethnicity, and smoking status may further impair the accuracy and robustness of findings (see supplementary results).

Future work

In our study, levetiracetam prescription in women showed association with OFC in offspring, however, the results were confounded due to co-prescription with other ASMs. Therefore, additional research is required to investigate the impact of different combinations of ASMs on mothers and foetuses. Similarly, there is a need for further research to assess the relationship between ASM dosages prescribed and maternal ASM blood levels with the risk of CM in offspring.

Conclusion

This study highlighted balancing seizure management and treatment of other ASM indications during pregnancy with ASM therapeutic safety. Our findings recommend avoiding valproate prescriptions during pregnancy if seizure control can be accomplished with safer ASMs like gabapentin and lamotrigine. After the introduction of valproate, concerns were raised about birth abnormalities in babies born to mothers using the medication. This tightened valproate prescription laws, resulting in a

ban on valproate prescriptions among pregnant females from March 2018, until they are registered in a pregnancy prevention programme.[10,27] The outcomes of our study may assist in shaping medical practice and decision-making for ASM prescription in pregnant women.

Acknowledgement

I would like to thank my supervisors, who have been a constant pillar of support during the duration of my dissertation. In addition, I would like to thank them for assisting me with the ethical approval and providing me with the database on exposure, outcome, and other variables for my dissertation. I would also like to thank my personal tutor, Ms. Karen Coulman, who supported and encouraged me throughout the MSc programme and dissertation stage. This dissertation has improved my abilities to conduct quantitative analysis using STATA and to work with large databases.

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Tables

Table-1: Maternal characteristics separated by epilepsy and prescription of ASMs during the preconception, pregnancy and first trimester.

	Total N (%)	**No Epilepsy N (%)**	**Epilepsy N (%)**	**No ASM prescription in preconception period N (%)**	**Any ASM prescription in preconception period N (%)**	**No ASM during pregnancy N (%)**	**Any ASM during pregnancy N (%)**	**No ASM prescription during first trimester N (%)**	**Any ASM prescription during first trimester N (%)**
	N=518,050	**N=511,542 (98.75%)**	**N=6,508 (1.25%)**	**N=513,875 (99.2%)**	**N=4,175 (0.8%)**	**N=514,070 (99.2%)**	**N=3,980 (0.8%)**	**N=514,324 (99.3%)**	**N=3,726 (0.7%)**
Year of pregnancy start									
1995-2000	40,047 (7.7%)	39,565 (7.7%)	482 (7.4%)	39,845 (7.8%)	202 (4.8%)	39,830 (7.7%)	217 (5.5%)	39,852 (7.7%)	195 (5.2%)
2001-2006	152,434 (29.4%)	150,589 (29.4%)	1,845 (28.3%)	151,569 (29.5%)	865 (20.7%)	151,561 (29.5%)	873 (21.9%)	151,636 (29.5%)	798 (21.4%)
2007-2012	202,568 (39.1%)	199,997 (39.1%)	2,571 (39.5%)	201,063 (39.1%)	1,505 (36.0%)	201,163 (39.1%)	1,405 (35.3%)	201,254 (39.1%)	1,314 (35.3%)
2013-2018	123,001 (23.7%)	121,391 (23.7%)	1,610 (24.7%)	121,398 (23.6%)	1,603 (38.4%)	121,516 (23.6%)	1,485 (37.3%)	121,582 (23.6%)	1,419 (38.1%)
Maternal age (years)									
<18	12,117 (2.3%)	11,984 (2.3%)	133 (2.0%)	12,072 (2.3%)	45 (1.1%)	12,075 (2.3%)	42 (1.1%)	12,078 (2.3%)	39 (1.0%)
18-24	104,446 (20.2%)	102,940 (20.1%)	1,506 (23.1%)	103,670 (20.2%)	776 (18.6%)	103,665 (20.2%)	781 (19.6%)	103,728 (20.2%)	718 (19.3%)
25-29	143,633 (27.7%)	141,764 (27.7%)	1,869 (28.7%)	142,449 (27.7%)	1,184 (28.4%)	142,502 (27.7%)	1,131 (28.4%)	142,577 (27.7%)	1,056 (28.3%)
30-34	160,404 (31.0%)	158,551 (31.0%)	1,853 (28.5%)	159,127 (31.0%)	1,277 (30.6%)	159,218 (31.0%)	1,186 (29.8%)	159,282 (31.0%)	1,122 (30.1%)
>=35	97,450 (18.8%)	96,303 (18.8%)	1,147 (17.6%)	96,557 (18.8%)	893 (21.4%)	96,610 (18.8%)	840 (21.1%)	96,659 (18.8%)	791 (21.2%)

	Total N (%)	No Epilepsy N (%)	Epilepsy N (%)	No ASM prescription in preconception period N (%)	Any ASM prescription in preconception period N (%)	No ASM during pregnancy N (%)	Any ASM during pregnancy N (%)	No ASM prescription during first trimester N (%)	Any ASM prescription during first trimester N (%)
	N=518,050	**N=511,542 (98.75%)**	**N=6,508 (1.25%)**	**N=513,875 (99.2%)**	**N=4,175 (0.8%)**	**N=514,070 (99.2%)**	**N=3,980 (0.8%)**	**N=514,324 (99.3%)**	**N=3,726 (0.7%)**
Marital Status									
In a partnership	115,534 (22.3%)	114,141 (22.3%)	1,393 (21.4%)	114,679 (22.3%)	855 (20.5%)	114,715 (22.3%)	819 (20.6%)	114,770 (22.3%)	764 (20.5%)
Previously in a partnership	3,017 (0.6%)	2,989 (0.6%)	28 (0.4%)	2,986 (0.6%)	31 (0.7%)	2,987 (0.6%)	30 (0.8%)	2,987 (0.6%)	30 (0.8%)
Single	65,130 (12.6%)	64,324 (12.6%)	806 (12.4%)	64,517 (12.6%)	613 (14.7%)	64,552 (12.6%)	578 (14.5%)	64,586 (12.6%)	544 (14.6%)
Missing	334,369 (64.5%)	330,088 (64.5%)	4,281 (65.8%)	331,693 (64.5%)	2,676 (64.1%)	331,816 (64.5%)	2,553 (64.1%)	331,981 (64.5%)	2,388 (64.1%)
Ethnicity									
White	339,325 (65.5%)	334,895 (65.5%)	4,430 (68.1%)	336,568 (65.5%)	2,757 (66.0%)	336,725 (65.5%)	2,600 (65.3%)	336,895 (65.5%)	2,430 (65.2%)
South Asian	17,892 (3.5%)	17,763 (3.5%)	129 (2.0%)	17,809 (3.5%)	83 (2.0%)	17,810 (3.5%)	82 (2.1%)	17,819 (3.5%)	73 (2.0%)
Black	8,344 (1.6%)	8,297 (1.6%)	47 (0.7%)	8,303 (1.6%)	41 (1.0%)	8,307 (1.6%)	37 (0.9%)	8,307 (1.6%)	37 (1.0%)
Other	5,878 (1.1%)	5,844 (1.1%)	34 (0.5%)	5,845 (1.1%)	33 (0.8%)	5,846 (1.1%)	32 (0.8%)	5,846 (1.1%)	32 (0.9%)
Mixed	3,379 (0.7%)	3,351 (0.7%)	28 (0.4%)	3,357 (0.7%)	22 (0.5%)	3,360 (0.7%)	19 (0.5%)	3,362 (0.7%)	17 (0.5%)
Missing	143,232 (27.6%)	141,392 (27.6%)	1,840 (28.3%)	141,993 (27.6%)	1,239 (29.7%)	142,022 (27.6%)	1,210 (30.4%)	142,095 (27.6%)	1,137 (30.5%)

	Total N (%)	No Epilepsy N (%)	Epilepsy N (%)	No ASM prescription in preconception period N (%)	Any ASM prescription in preconception period N (%)	No ASM during pregnancy N (%)	Any ASM during pregnancy N (%)	No ASM prescription during first trimester N (%)	Any ASM prescription during first trimester N (%)
	N=518,050	**N=511,542 (98.75%)**	**N=6,508 (1.25%)**	**N=513,875 (99.2%)**	**N=4,175 (0.8%)**	**N=514,070 (99.2%)**	**N=3,980 (0.8%)**	**N=514,324 (99.3%)**	**N=3,726 (0.7%)**
Practice Region									
East Midlands	18,504 (3.6%)	18,276 (3.6%)	228 (3.5%)	18,407 (3.6%)	97 (2.3%)	18,402 (3.6%)	102 (2.6%)	18,414 (3.6%)	90 (2.4%)
East of England	39,346 (7.6%)	38,875 (7.6%)	471 (7.2%)	39,089 (7.6%)	257 (6.2%)	39,107 (7.6%)	239 (6.0%)	39,123 (7.6%)	223 (6.0%)
London	38,415 (7.4%)	38,000 (7.4%)	415 (6.4%)	38,177 (7.4%)	238 (5.7%)	38,185 (7.4%)	230 (5.8%)	38,200 (7.4%)	215 (5.8%)
North East	9,270 (1.8%)	9,150 (1.8%)	120 (1.8%)	9,193 (1.8%)	77 (1.8%)	9,200 (1.8%)	70 (1.8%)	9,205 (1.8%)	65 (1.7%)
North West	54,719 (10.6%)	53,993 (10.6%)	726 (11.2%)	54,316 (10.6%)	403 (9.7%)	54,340 (10.6%)	379 (9.5%)	54,368 (10.6%)	351 (9.4%)
Northern Ireland	27,247 (5.3%)	26,871 (5.3%)	376 (5.8%)	26,910 (5.2%)	337 (8.1%)	26,926 (5.2%)	321 (8.1%)	26,937 (5.2%)	310 (8.3%)
Scotland	84,083 (16.2%)	83,087 (16.2%)	996 (15.3%)	83,194 (16.2%)	889 (21.3%)	83,244 (16.2%)	839 (21.1%)	83,289 (16.2%)	794 (21.3%)
South Central	51,821 (10.0%)	51,174 (10.0%)	647 (9.9%)	51,449 (10.0%)	372 (8.9%)	51,463 (10.0%)	358 (9.0%)	51,484 (10.0%)	337 (9.0%)
South East Coast	46,548 (9.0%)	46,013 (9.0%)	535 (8.2%)	46,209 (9.0%)	339 (8.1%)	46,230 (9.0%)	318 (8.0%)	46,247 (9.0%)	301 (8.1%)
South West	38,612 (7.5%)	38,082 (7.4%)	530 (8.1%)	38,376 (7.5%)	236 (5.7%)	38,379 (7.5%)	233 (5.9%)	38,403 (7.5%)	209 (5.6%)
Wales	51,513 (9.9%)	50,786 (9.9%)	727 (11.2%)	50,964 (9.9%)	549 (13.1%)	50,989 (9.9%)	524 (13.2%)	51,021 (9.9%)	492 (13.2%)
West Midlands	41,996 (8.1%)	41,454 (8.1%)	542 (8.3%)	41,702 (8.1%)	294 (7.0%)	41,717 (8.1%)	279 (7.0%)	41,735 (8.1%)	261 (7.0%)
Yorkshire & The Humber	15,976 (3.1%)	15,781 (3.1%)	195 (3.0%)	15,889 (3.1%)	87 (2.1%)	15,888 (3.1%)	88 (2.2%)	15,898 (3.1%)	78 (2.1%)

	Total N (%)	No Epilepsy N (%)	Epilepsy N (%)	No ASM prescription in preconception period N (%)	Any ASM prescription in preconception period N (%)	No ASM during pregnancy N (%)	Any ASM during pregnancy N (%)	No ASM prescription during first trimester N (%)	Any ASM prescription during first trimester N (%)
	N=518,050	**N=511,542 (98.75%)**	**N=6,508 (1.25%)**	**N=513,875 (99.2%)**	**N=4,175 (0.8%)**	**N=514,070 (99.2%)**	**N=3,980 (0.8%)**	**N=514,324 (99.3%)**	**N=3,726 (0.7%)**
Maternal IMD status									
1 - Least deprived	99,719 (19.2%)	98,726 (19.3%)	993 (15.3%)	99,099 (19.3%)	620 (14.9%)	99,132 (19.3%)	587 (14.7%)	99,161 (19.3%)	558 (15.0%)
2	92,779 (17.9%)	91,768 (17.9%)	1,011 (15.5%)	92,123 (17.9%)	656 (15.7%)	92,172 (17.9%)	607 (15.3%)	92,209 (17.9%)	570 (15.3%)
3	100,299 (19.4%)	99,051 (19.4%)	1,248 (19.2%)	99,523 (19.4%)	776 (18.6%)	99,573 (19.4%)	726 (18.2%)	99,619 (19.4%)	680 (18.3%)
4	102,255 (19.7%)	100,806 (19.7%)	1,449 (22.3%)	101,337 (19.7%)	918 (22.0%)	101,363 (19.7%)	892 (22.4%)	101,418 (19.7%)	837 (22.5%)
5 - Most deprived	122,998 (23.7%)	121,191 (23.7%)	1,807 (27.8%)	121,793 (23.7%)	1,205 (28.9%)	121,830 (23.7%)	1,168 (29.3%)	121,917 (23.7%)	1,081 (29.0%)
BMI									
Underweight, <18 kg/m^2	15,484 (3.0%)	15,295 (3.0%)	189 (2.9%)	15,372 (3.0%)	112 (2.7%)	15,371 (3.0%)	113 (2.8%)	15,381 (3.0%)	103 (2.8%)
Normal weight, 18-<25 kg/m^2	233,973 (45.2%)	231,380 (45.2%)	2,593 (39.8%)	232,473 (45.2%)	1,500 (35.9%)	232,536 (45.2%)	1,437 (36.1%)	232,631 (45.2%)	1,342 (36.0%)
Overweight, 25-<30 kg/m^2	125,414 (24.2%)	123,778 (24.2%)	1,636 (25.1%)	124,419 (24.2%)	995 (23.8%)	124,467 (24.2%)	947 (23.8%)	124,531 (24.2%)	883 (23.7%)
Obese, >= 35 kg/m^2	98,235 (19.0%)	96,636 (18.9%)	1,599 (24.6%)	96,950 (18.9%)	1,285 (30.8%)	97,024 (18.9%)	1,211 (30.4%)	97,093 (18.9%)	1,142 (30.6%)
Missing	44,944 (8.7%)	44,453 (8.7%)	491 (7.5%)	44,661 (8.7%)	283 (6.8%)	44,672 (8.7%)	272 (6.8%)	44,688 (8.7%)	256 (6.9%)

	Total N (%)	No Epilepsy N (%)	Epilepsy N (%)	No ASM prescription in preconception period N (%)	Any ASM prescription in preconception period N (%)	No ASM during pregnancy N (%)	Any ASM during pregnancy N (%)	No ASM prescription during first trimester N (%)	Any ASM prescription during first trimester N (%)
	N=518,050	**N=511,542 (98.75%)**	**N=6,508 (1.25%)**	**N=513,875 (99.2%)**	**N=4,175 (0.8%)**	**N=514,070 (99.2%)**	**N=3,980 (0.8%)**	**N=514,324 (99.3%)**	**N=3,726 (0.7%)**
Smoking status during pregnancy									
Non-smoker	216,973 (41.9%)	214,589 (41.9%)	2,384 (36.6%)	215,494 (41.9%)	1,479 (35.4%)	215,585 (41.9%)	1,388 (34.9%)	215,673 (41.9%)	1,300 (34.9%)
Current smoker	139,844 (27.0%)	137,730 (26.9%)	2,114 (32.5%)	138,461 (26.9%)	1,383 (33.1%)	138,487 (26.9%)	1,357 (34.1%)	138,583 (26.9%)	1,261 (33.8%)
Ex-smoker	144,416 (27.9%)	142,577 (27.9%)	1,839 (28.3%)	143,172 (27.9%)	1,244 (29.8%)	143,253 (27.9%)	1,163 (29.2%)	143,318 (27.9%)	1,098 (29.5%)
Missing	16,817 (3.2%)	16,646 (3.3%)	171 (2.6%)	16,748 (3.3%)	69 (1.7%)	16,745 (3.3%)	72 (1.8%)	16,750 (3.3%)	67 (1.8%)
Evidence of alcohol problems during pregnancy (binary)	4,855 (0.9%)	4,785 (0.9%)	70 (1.1%)	4,783 (0.9%)	72 (1.7%)	4,794 (0.9%)	61 (1.5%)	4,797 (0.9%)	58 (1.6%)
Evidence of illicit drug use in pregnancy	1,058 (0.2%)	1,035 (0.2%)	23 (0.4%)	1,009 (0.2%)	49 (1.2%)	1,009 (0.2%)	49 (1.2%)	1,014 (0.2%)	44 (1.2%)
Number of seizure events in CPRD and HES in the year before pregnancy									
0	517,412 (99.9%)	511,306 (100.0%)	6,106 (93.8%)	513,538 (99.9%)	3,874 (92.8%)	513,748 (99.9%)	3,664 (92.1%)	513,980 (99.9%)	3,432 (92.1%)
1	460 (0.1%)	186 (0.0%)	274 (4.2%)	265 (0.1%)	195 (4.7%)	250 (0.0%)	210 (5.3%)	268 (0.1%)	192 (5.2%)
2	117 (0.0%)	34 (0.0%)	83 (1.3%)	45 (0.0%)	72 (1.7%)	47 (0.0%)	70 (1.8%)	47 (0.0%)	70 (1.9%)
3+	61 (0.0%)	16 (0.0%)	45 (0.7%)	27 (0.0%)	34 (0.8%)	25 (0.0%)	36 (0.9%)	29 (0.0%)	32 (0.9%)

	Total N (%)	No Epilepsy N (%)	Epilepsy N (%)	No ASM prescription in preconception period N (%)	Any ASM prescription in preconception period N (%)	No ASM during pregnancy N (%)	Any ASM during pregnancy N (%)	No ASM prescription during first trimester N (%)	Any ASM prescription during first trimester N (%)
	N=518,050	**N=511,542 (98.75%)**	**N=6,508 (1.25%)**	**N=513,875 (99.2%)**	**N=4,175 (0.8%)**	**N=514,070 (99.2%)**	**N=3,980 (0.8%)**	**N=514,324 (99.3%)**	**N=3,726 (0.7%)**
Antidepressant use in the year before pregnancy (binary)	48,465 (9.4%)	47,476 (9.3%)	989 (15.2%)	47,197 (9.2%)	1,268 (30.4%)	47,214 (9.2%)	1,251 (31.4%)	47,286 (9.2%)	1,179 (31.6%)
Multivitamin use in the year before pregnancy (binary)	323 (0.1%)	320 (0.1%)	3 (0.0%)	320 (0.1%)	3 (0.1%)	320 (0.1%)	3 (0.1%)	320 (0.1%)	3 (0.1%)
Folic acid use in the year before pregnancy (binary)	156,585 (30.2%)	152,971 (29.9%)	3,614 (55.5%)	153,665 (29.9%)	2,920 (69.9%)	153,671 (29.9%)	2,914 (73.2%)	153,817 (29.9%)	2,768 (74.3%)
Vomiting or prescription for antiemetics during pregnancy	64,948 (12.5%)	63,909 (12.5%)	1,039 (16.0%)	63,994 (12.5%)	954 (22.9%)	64,045 (12.5%)	903 (22.7%)	64,101 (12.5%)	847 (22.7%)
Gravidity									
0	154,867 (29.9%)	153,011 (29.9%)	1,856 (28.5%)	153,642 (29.9%)	1,225 (29.3%)	153,700 (29.9%)	1,167 (29.3%)	153,765 (29.9%)	1,102 (29.6%)
1	143,273 (27.7%)	141,617 (27.7%)	1,656 (25.4%)	142,235 (27.7%)	1,038 (24.9%)	142,297 (27.7%)	976 (24.5%)	142,363 (27.7%)	910 (24.4%)
2	99,072 (19.1%)	97,887 (19.1%)	1,185 (18.2%)	98,335 (19.1%)	737 (17.7%)	98,365 (19.1%)	707 (17.8%)	98,416 (19.1%)	656 (17.6%)
3+	120,838 (23.3%)	119,027 (23.3%)	1,811 (27.8%)	119,663 (23.3%)	1,175 (28.1%)	119,708 (23.3%)	1,130 (28.4%)	119,780 (23.3%)	1,058 (28.4%)
Other somatic conditions	70,279 (13.6%)	68,923 (13.5%)	1,356 (20.8%)	68,884 (13.4%)	1,395 (33.4%)	69,092 (13.4%)	1,187 (29.8%)	69,151 (13.4%)	1,128 (30.3%)
Other psychiatric conditions	185,470 (35.8%)	182,251 (35.6%)	3,219 (49.5%)	182,795 (35.6%)	2,675 (64.1%)	183,006 (35.6%)	2,464 (61.9%)	183,154 (35.6%)	2,316 (62.2%)

Table-2: Odds ratios with 95% confidence interval for orofacial cleft according to anti-seizure medication prescription during preconception period and first trimester of pregnancy.

Outcome	Exposure	N in exposure group	uOR (95% CI)[a]	maOR (95% CI)[b]	aOR (95% CI)[c]
Orofacial Cleft	**ASM prescription in preconception period**				
	Carbamazepine	800	1.94 (0.62-6.03)	..	..
	Gabapentin	778	0.66 (0.09-4.7)	..	..
	Levetiracetam	356	1	..	..
	Lamotrigine	1131	1.37 (0.44-4.25)	1.85 (0.26-13.22)	1.72 (0.17-17.63)
	Phenytoin	73	1	..	..
	Pregabalin	541	1.91 (0.47-7.67)	3.74 (0.52-26.89)	2.75 (0.37-20.39)
	Topiramate	263	1	..	..
	Valproate	598	3.47 (1.29-9.29)	4.02 (0.56-28.90)	4.34 (0.45-42.27)
	Other ASMs	248	2.08 (0.29-14.85)	..	..
Orofacial Cleft	**ASM prescription during first trimester**				
	Carbamazepine	739	2.09 (0.67-6.53)	..	..
	Gabapentin	600	0.86 (0.12-6.11)	..	..
	Levetiracetam	362	2.86 (0.71-11.49)	..	..
	Lamotrigine	1133	0.91 (0.23-3.64)	1.92 (0.27-13.73)	1.82 (0.17-18.82)
	Phenytoin	64	1	..	..
	Pregabalin	447	2.31 (0.57-9.29)	4.72 (0.65-34.07)	3.15 (0.42-23.59)
	Topiramate	203	1	..	..
	Valproate	517	3.01 (0.96-9.37)	4.69 (0.65-33.84)	5.41 (0.56-52.25)
	Other ASMs	220	2.35 (0.33-16.76)	..	..

a- uOR: unadjusted odds ratio.
b- maOR: minimally adjusted odds ratio; adjusted for maternal age, marital status, ethnicity and IMD quintile.
c- aOR: fully adjusted odds ratio; adjusted for all covariates and indications of ASM prescription in women (epilepsy, other somatic and psychiatric conditions).
.. The models did not converge upon adjustment with covariates.
Note: The number of children diagnosed with the outcome of interest, i.e., OFC, cannot be depicted in exposure and reference groups because, under the CPRD guidelines, cases less than 5 cannot be reported, preserving the confidentiality at the reporting stage.[30]

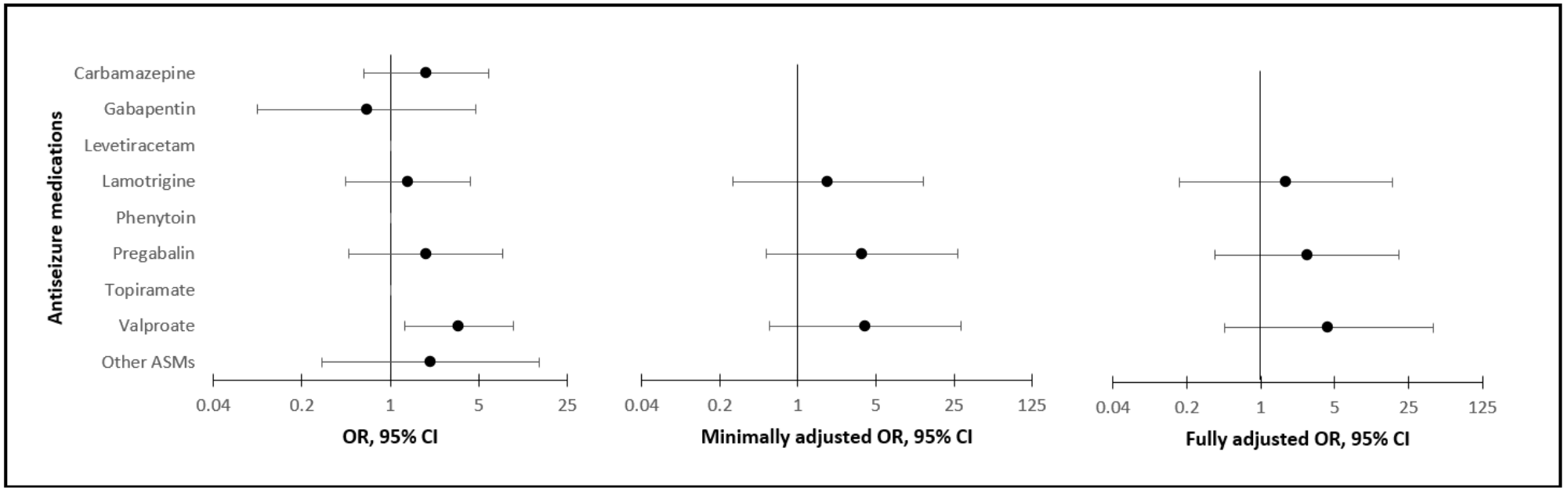
Table-3 : Odds ratios with 95% confidence interval for orofacial cleft according to epilepsy and prescription of anti-seizure medications during pregnancy.

Outcome	**Exposure**	**N in exposure group**	**uOR (95% CI)** [a]	**maOR (95% CI)**[b]	**aOR (95% CI)**[c]
Orofacial Cleft	**Epilepsy**	6508	1.43 (0.89-2.28)	0.96 (0.31-2.99)	0.83 (0.25-2.78)*
Orofacial Cleft	**ASM prescription during pregnancy**				
	Carbamazepine	806	1.92 (0.62-5.98)	..	..
	Gabapentin	629	0.82 (0.11-5.82)	..	..
	Levetiracetam	418	3.72 (1.19-11.61)	5.72 (0.79-41.26)	5.33 (0.49-58.36)
	Lamotrigine	1207	0.85 (0.21-3.42)	1.78 (0.25-12.78)	1.69 (0.17-17.04)
	Phenytoin	73	1	..	..
	Pregabalin	457	2.26 (0.56-9.08)	4.61 (0.64-33.19)	3.09 (0.41-23.14)
	Topiramate	211	1	..	..
	Valproate	568	2.73 (0.88-8.52)	4.14 (0.57-29.81)	4.97 (0.51-48.38)
	Other ASMs	283	1.82 (0.25-13.01)	..	..

a- uOR: unadjusted odds ratio.
b- maOR: minimally adjusted odds ratio; adjusted for maternal age, marital status, ethnicity and IMD quintile.
c- aOR: fully adjusted odds ratio; adjusted for all covariates and indications of ASM prescription in women (epilepsy, other somatic and psychiatric conditions).
.. The models did not converge upon adjustment with covariates.
*The fully adjusted model for epilepsy exposure was adjusted for all covariates and other indications for ASM prescription, i.e., other somatic and psychiatric conditions.
Note: The number of children diagnosed with the outcome of interest, i.e., OFC, cannot be depicted in exposure and reference groups because, under the CPRD guidelines, cases less than 5 cannot be reported, preserving the confidentiality at the reporting stage.[30]

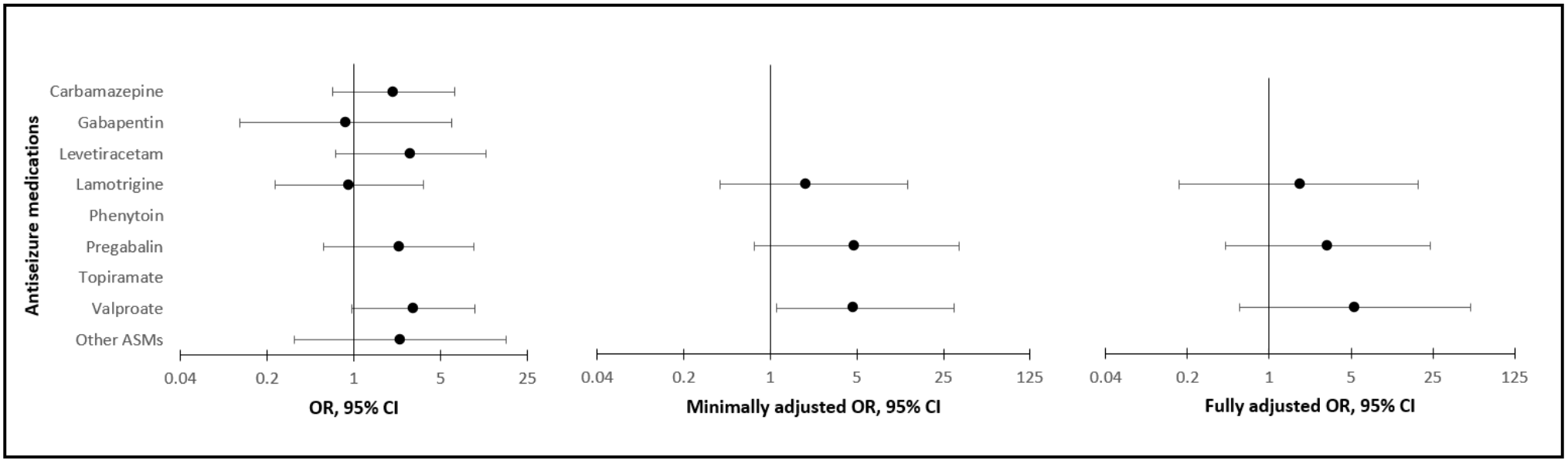
Figures

Figure-1: Forest plot depicting odds ratio (OR) with 95% confidence intervals (CI) for orofacial cleft in children for ASM prescription during the preconception period.



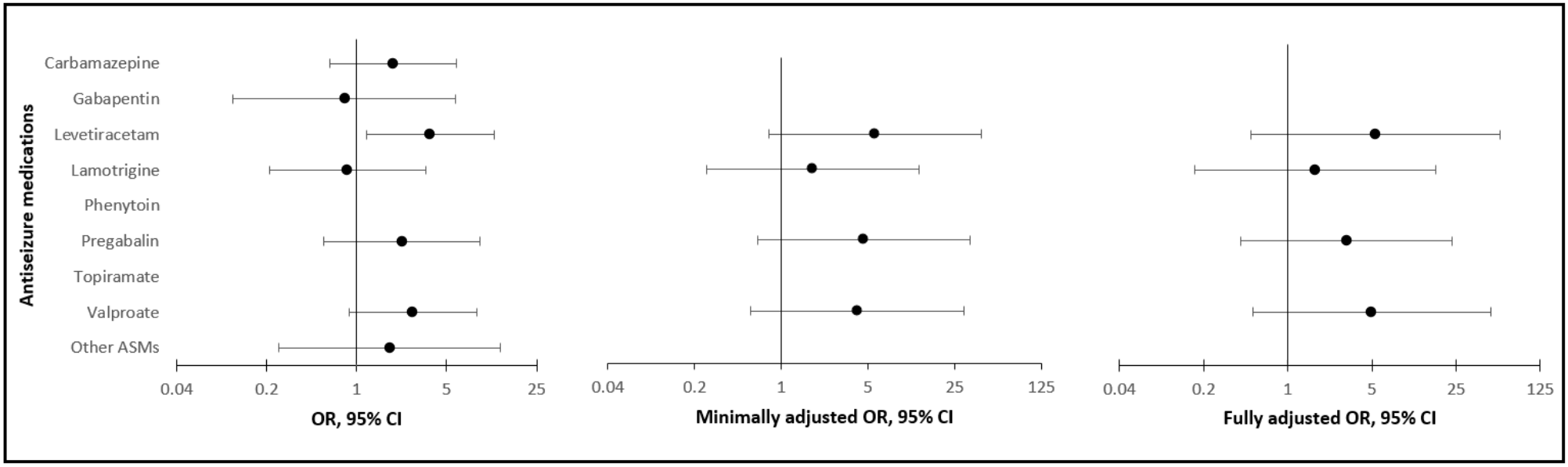
- OR is adjusted for maternal age, marital status, ethnicity and IMD quintile for minimally adjusted model.
- Fully adjusted models further included epilepsy, diagnosis of other somatic conditions and psychiatric conditions, maternal area of residence, smoking status, BMI of mother, evidence of hazardous drinking during pregnancy, seizure events in the year before pregnancy, use of antipsychotics, antidepressants, multivitamins and folic acid in the year before pregnancy, gravidity, and illicit drug use during pregnancy.
- Individuals exposed to levetiracetam, phenytoin, and topiramate did not have any cases of OFC in the study cohort.
- Minimally and fully adjusted models did not converge for carbamazepine, gabapentin, and other ASMs.

Figure-2: Forest plot depicting odds ratio (OR) with 95% confidence intervals for orofacial cleft in children for ASM prescription during first trimester of pregnancy.



- OR is adjusted for maternal age, marital status, ethnicity and IMD quintile for minimally adjusted model.
- Fully adjusted models further included epilepsy, diagnosis of other somatic conditions and psychiatric conditions, maternal area of residence, smoking status, BMI of mother, evidence of hazardous drinking during pregnancy, seizure events in the year before pregnancy, use of antipsychotics, antidepressants, multivitamins and folic acid in the year before pregnancy, gravidity, and illicit drug use during pregnancy.
- Individuals exposed to phenytoin, and topiramate did not have any cases of OFC in the study cohort.
- Minimally and fully adjusted models did not converge for carbamazepine, gabapentin, and other ASMs

Figure-3: Forest plot depicting odds ratio (OR) with 95% confidence intervals (CI) for orofacial cleft in children for ASM prescription during pregnancy.



- OR is adjusted for maternal age, marital status, ethnicity and IMD quintile for minimally adjusted model.
- Fully adjusted models further included epilepsy, diagnosis of other somatic conditions and psychiatric conditions, maternal area of residence, smoking status, BMI of mother, evidence of hazardous drinking during pregnancy, seizure events in the year before pregnancy, use of antipsychotics, antidepressants, multivitamins and folic acid in the year before pregnancy, gravidity, and illicit drug use during pregnancy.
- Individuals exposed to phenytoin, and topiramate did not have any cases of OFC in the study cohort.
- Minimally and fully adjusted models did not converge for carbamazepine, gabapentin, and other ASMs.

Supplementary Material

Supplementary Methods

Other antiseizure medications

The "other ASMs" category included the following ASMs: ethosuximide, felbamate, lacosamide, primidone, oxcarbazepine, perampanel, phenobarbital, , retigabine, rufinamide, sulthiame, tiagabine, vigabatrin, zonisamide, clonazepam, beclamide, stiripentol, mesuximide, phenacemide, ethotoin, pheneturide, cenobamate, barbexaclone, , carisbamate, ethadione, progabide, clobazam, brivaracetam, eslicarbazepine.

Definition of secondary exposures

1. Epilepsy in the mothers were defined based on one of the following criteria:

- Mothers having a Read code for epilepsy or two seizure events more than 24 hours apart in primary care data and/or ICD-10 codes for epilepsy or two seizure events more than 24 hours apart in the HES in-patient, out-patient or emergency data. OR;
- Prescription of epilepsy specific medications: Epilim, Brivaracetam, Brivaracetam, Eslicarbazepine, Ethosuximide, Felbamate, Fenfluramine, Lacosamide, Levetiracetam, Mesuximide, Oxcarbazepine, Perampanel, Phenobarbital, Phenytoin, Retigabine, Rufinamide, Stiripentol, Sulthiame, Tiagabine, Vigabatrin, Zonisamide. OR;
- Same day co-prescribing of epilepsy specific medication: i) Clobazam and an ASM or ii) rectal administration of diazepam and an ASM or iii) intranasal administration of Midazolam and ASM.

2. ASM monotherapy was defined as prescription of only one ASM at a given time period.
3. Polytherapy was defined as prescription of two or more different ASM classes.

Secondary analysis

We evaluated the effect of 1) Epilepsy in women with OFC in offspring as compared to children born to non-epileptic mothers; 2) ASM prescription during the pregnancy period compared to no prescription with the ASM of interest during pregnancy period; 3) ASM monotherapy during the preconception period, pregnancy, and FT as compared to no ASM prescription during these periods; 4) ASM prescription anytime between preconception period to end of pregnancy as compared to no prescription with ASM of interest anytime from three months prior to pregnancy up to pregnancy end

date; and 5) polytherapy during FT as compared to: i) monotherapy during FT, ii) no ASM prescription during FT.

Supplementary Results

Missing data in CPRD

Our study sample consisted of missing data for marital status, ethnicity, BMI, and smoking status of the mothers. Approximately 60%, 28%, 7%, and 0.2% of the women had missing data for marital status, ethnicity, BMI and smoking status respectively. Excluding the missing data from the analysis resulted in a reduced sample size in adjusted models, possibly decreasing the precision and level of confidence of the final results.

ASM prescription anytime between preconception period to pregnancy end date

Table-S4 depicts the ORs for OFC in children born to mothers prescribed with ASMs anytime between preconception period to pregnancy end date, and those prescribed with polytherapy during FT. There is strong evidence of relationship for OFC in children born to women prescribed levetiracetam (uOR=3.57, 95% CI=1.14-11.12) or valproate (uOR=3.06, 95% CI=1.14-8.2) anytime from preconception period to pregnancy completion, compared to children born to mothers not prescribed the respective ASM. Adjustment for the confounding variables weakened the evidence for an association, but the findings showed a consistent positive association for levetiracetam (aOR=5.14, 95% CI=0.47-56.63) and valproate (aOR=3.93, 95% CI= 0.41-37.84) and OFC in children. The prescription of carbamazepine, lamotrigine, pregabalin, and “other ASMs” during this period was associated with higher estimates of association, although the findings lacked strong evidence for an association. Any other ASM in women was not related to OFCs during this period.

ASM polytherapy

Around 13% of women were prescribed with ASM polytherapy during the FT. There is strong evidence for an association between mothers prescribed with ASM polytherapy during FT of pregnancy and OFC in children as compared to 1) children born to mothers prescribed with ASM monotherapy during FT (uOR=5.38, 95% CI=1.44-20.11), and 2) children born to mothers with no ASM prescription during FT (uOR=4.28, 95% CI=1.59-11.48). The models did not converge upon adjustments with potential confounding variables.

ASM monotherapy

Table-S5 depicts the ORs for ASM monotherapy. Upon limiting the ASM prescription to only one ASM, prescription of valproate in preconception period showed strong evidence of an association with the OFC in children as compared to children born to mothers prescribed with no ASM during that period (uOR=3.41, 95% CI=1.09-10.64). Adjustment with potential confounding factors increased the odds of OFC in children to five times (maOR=5.07, 95% CI=0.70-36.57) and seven times (aOR=7.10, 95% CI=0.64-79.12) in minimally adjusted and fully adjusted models respectively, however, the strength of the evidence for an association decreased. Prescription with lamotrigine and pregabalin also showed increased odds for association with OFC in offspring (lamotrigine: aOR=2.52, 95% CI=0.20-31.55; pregabalin: aOR=3.27, 95% CI=0.55-24.43). The wide confidence intervals, however, do not provide enough evidence for the association. Carbamazepine, levetiracetam, phenytoin, and topiramate exposure groups did not have cases of outcome. Exposure to gabapentin did not show evidence of an association.

During the pregnancy period, only prescription of pregabalin and lamotrigine as monotherapy showed association with OFC in children, but a lack of evidence for an association cannot be neglected (lamotrigine: aOR=2.45, 95% CI=0.21-28.50; pregabalin: aOR=3.72, 95% CI=0.49-28.10). No other ASM prescription was shown to be associated with OFCs in children.

Valproate monotherapy during FT depicted an eight times increased likelihood of OFCs in children (aOR=8.37, 95% CI=0.75-92.85). However, large confidence intervals and overlapping of null value decreased the evidence strength. Pregabalin and lamotrigine were found to have positive association with OFCs, but lacked strong evidence of an association. Gabapentin prescription in mothers showed no association with OFC in offspring.

Supplementary Tables

Table S1: List of Read codes in CPRD use to identify OFC in offspring.

Medcode	Read code	Read term
1679	7525000	Primary repair of cleft palate, unspecified
2020	7502.11	Repair of cleft lip operations
2027	P91..00	Cleft lip (harelip)
2170	P90..00	Cleft palate
5374	P9...00	Cleft palate and lip
5386	P92..00	Cleft palate with cleft lip
6341	7525.12	Repair of cleft palate
8002	7409500	Rhinoplasty for cleft lip nasal deformity
9809	7409	Correction of cleft lip nasal deformity
14974	7502D00	Repair of bilateral cleft lip unspecified
15364	P90z.00	Cleft palate NOS
16457	P910.00	Cleft lip, unspecified
17207	14H3.00	H/O: cleft lip
20542	7525100	Revision of repair of cleft palate
21043	14H2.00	H/O: cleft palate
21245	7502300	Unilateral lip adhesion
21363	7409000	Primary correction of cleft lip nasal deformity
23683	7525012	Langenbeck repair of cleft palate
23714	7502A11	Rep bilat cleft lip Millard
23739	7502900	Repair of unilateral cleft lip unspecified
24026	7502100	Revision of primary closure of cleft lip
24102	7502000	Primary closure of cleft lip, unspecified
24846	P909.00	Cleft uvula
25740	P908.11	Cleft soft palate NOS
30249	7525700	Repair of cleft soft palate with intra-velar veloplasty
30957	P914.00	Bilateral incomplete cleft lip
31584	7525300	Repair of cleft hard palate with bipedicled flaps
32465	7409700	Septoplasty for cleft lip nasal deformity
33902	P92A.00	Cleft hard palate with cleft lip, bilateral
34024	7525500	Repair of anterior cleft palate with local flap
34071	7502012	Millard cleft lip correction
35374	P91z.00	Cleft lip NOS
37071	7525711	Rep anterior cleft palate local flap
37079	7525400	Repair of cleft soft palate with Z-plasty
38873	P901.11	Cleft hard palate, unilateral
42208	P90A.00	Cleft soft palate, bilateral
42525	7502C11	Manchester bilateral cleft lip repair
44977	P923.00	Bilateral complete cleft palate with cleft lip
45313	P906.00	Central incomplete cleft palate
47845	7525600	Repair of anterior cleft palate with vomerine flap
48070	Pyu4100	[X]Unspecified cleft palate with cleft lip, bilateral

Medcode	Read code	Read term
48870	7.50E+03	Synchronous bilateral cleft lip repair
48948	P903.00	Bilateral complete cleft palate
49350	7409100	Secondary correction of cleft lip nasal deformity
49751	7502700	Repair of unilateral cleft lip with triangular flap
49874	7409600	Septorhinoplasty for cleft lip nasal deformity
50430	P9z..00	Cleft palate or cleft lip NOS
51058	7525411	Furlow repair cleft palate
51196	7525800	Repair cleft soft palate with other musculature correction
51301	P920.00	Cleft palate with cleft lip, unspecified
51377	P908.00	Incomplete cleft palate NOS
52827	P915.00	Central cleft lip
54012	P912.00	Unilateral incomplete cleft lip
54144	P922.00	Unilateral incomplete cleft palate with cleft lip
54721	P913.00	Bilateral complete cleft lip
54973	7502C12	Veau type III bilateral cleft lip repair
54974	7525213	Veau flap repair cleft palate
56520	7502611	Millard repair unilateral cleft lip
57490	P902.12	Cleft soft palate, unilateral
58885	P900.00	Cleft palate, unspecified
58977	7502F00	Asynchronous bilateral cleft lip repair
60496	7502014	Tenison cleft lip repair
62102	7502400	Bilateral lip adhesion
62321	P92B.00	Cleft hard palate with cleft lip, unilateral
62690	P924.00	Bilateral incomplete cleft palate with cleft lip
62987	P921.00	Unilateral complete cleft palate with cleft lip
63658	7409200	Correction of cleft lip nasal tip deformity
63930	P911.00	Unilateral complete cleft lip
64549	P90B.00	Cleft hard palate, bilateral
65623	P907.11	Cleft hard palate NOS
65664	7502600	Repair unilateral cleft lip - rotation advancement flap technique
65866	7502500	Repair of unilateral cleft lip using straight line technique
65887	7525200	Repair cleft hard palate post based axial transposition flap
65948	7525013	Wardill repair of cleft palate
68166	P906.11	Cleft soft palate, central
68398	P92z.00	Cleft palate with cleft lip NOS
69454	7502800	Repair unilateral cleft lip with quadrilateral flap
69871	7502011	Lemesurier cleft lip repair
71457	7525311	Langenbeck repair cleft palate
72027	Pyu4.00	[X]Cleft lip and cleft palate
73531	P901.00	Unilateral complete cleft palate
73558	P902.00	Unilateral incomplete cleft palate
90923	7525011	Kilner repair of cleft palate
93030	P907.00	Complete cleft palate NOS
93641	Pyu4000	[X]Cleft palate, unspecified, bilateral
93972	P928.00	Cleft hard palate with cleft soft palate, unilateral

Medcode	Read code	Read term
96645	7502713	Tennyson repair unilateral cleft lip
97477	P904.11	Cleft soft palate, bilateral
97631	P902.11	Cleft uvula
98506	7502B00	Repair of bilateral cleft lip with quadrilateral flap
99908	7525212	Wardill repair cleft palate
100787	P905.00	Central complete cleft palate
100946	7502811	Repair unilateral cleft lip with quadrilateral flap
101223	P90C.00	Cleft hard palate, unilateral
103535	7502A00	Repair bilateral cleft lip - rotation advancement flap tech
106078	P904.00	Bilateral incomplete cleft palate
110201	7502712	Skoog repair unilateral cleft lip
112480	P905.11	Cleft hard palate, central
112758	P927.00	Cleft hard palate with cleft soft palate, bilateral
113211	7502711	Randall repair unilateral cleft lip
114094	7502013	Randall cleft lip repair
115221	7502511	Kilner repair unilateral cleft lip

Table-S2: List of ICD-10 codes from HES database used to identify OFC in offspring.

Code	alt_code	Description
Q35	Q35	Cleft palate
Q35.1	Q351	Cleft hard palate
Q35.3	Q353	Cleft soft palate
Q35.5	Q355	Cleft hard palate with cleft soft palate
Q35.7	Q357	Cleft uvula
Q35.9	Q359	Cleft palate, unspecified
Q36	Q36	Cleft lip
Q36.0	Q360	Cleft lip, bilateral
Q36.1	Q361	Cleft lip, median
Q36.9	Q369	Cleft lip, unilateral
Q37	Q37	Cleft palate with cleft lip
Q37.0	Q370	Cleft hard palate with bilateral cleft lip
Q37.1	Q371	Cleft hard palate with unilateral cleft lip
Q37.2	Q372	Cleft soft palate with bilateral cleft lip
Q37.3	Q373	Cleft soft palate with unilateral cleft lip
Q37.4	Q374	Cleft hard and soft palate with bilateral cleft lip
Q37.5	Q375	Cleft hard and soft palate with unilateral cleft lip
Q37.8	Q378	Unspecified cleft palate with bilateral cleft lip
Q37.9	Q379	Unspecified cleft palate with unilateral cleft lip

Table-S3: Definitions of covariates used in the adjusted models.

Covariate	Definition	Type
Maternal age	Age of women at the pregnancy start date as defined by the pregnancy register, classified in the following categories: <18 years; 18-24 years; 25-29 years; 30-34 years and >=35 years.	Categorical
Maternal ethnicity	A previously published algorithm was used to identify ethnicities of the women in the study cohort.[1] The ethnicities included were white, south Asian, Black, Other, Mixed. All the women with unknown ethnicities were coded as missing.	Categorical
Area of Residence	The geographical region of the mother's GP was identified using the CPRD practice file. CPRD practice file was used to identify area of residence or geographical region of mother's GP. Regions were categorised as: East midlands, east of England, London, north east, north west, Northern Ireland, Scotland, south-central, south-east coast, south west, Wales, west midlands, and Yorkshire and the Humber.	Categorical
Index of Multiple Deprivation (IMD)	Linkages with deprivation data was used to gather information on patient-level IMD quintiles for patients living in England. Practice-level IMD data was used for patients living in Scotland, Wales and Northern Ireland.	Quintiles
Body mass index (BMI) of women at the start of pregnancy	The BMI information of mothers at the start of pregnancy was identified and categorised as: underweight (<18 Kg/m^2); Normal weight (18-25 Kg/m^2); Overweight (25-30 Kg/m^2); and Obese (>30 Kg/m^2).	Categorical
Smoking status during pregnancy	Smoking status during the pregnancy was identified using the clinical codes and smoking-related data in the CPRD. Mothers were classified into: non-smokers; current smokers, and ex-smokers based on smoking records present for pregnancy period or most recent records in the 10 years before pregnancy.	Categorical
Evidence of alcohol problems during pregnancy	The evidence for hazardous drinking behaviour was identified using maternal clinical file, clinical details file in CPRD and read codes for prescription of treatment for severe alcohol use. Consumption of >=43 units/week or a prescription for high alcohol use were used to define hazardous drinking. Records for 5 years prior to pregnancy start were used if no information on drinking habits was available for pregnancy period.	Binary
Marital status	Patient file data provided with information on marital status of the mother and was classified as: single, in a partnership, and previously in a partnership. All women with the unknown marital status or no data were grouped as under "unknown".	Categorical
Illicit drug use during pregnancy	The following methods were used to identify use of illicit drug use by the women during pregnancy: 1) Read codes in mother's medical records; 2) Relevant Read codes in mother's additional clinical details; 3) mother's prescription records for treatment of illicit drug use.	Binary

Covariate	Definition	Type
Gravidity at pregnancy start	Gravidity was defined as total number of live births and pregnancies terminated at <6 months or did not result in live births. The information was gathered from the pregnancy register for the period before pregnancy start date and was categorised into 0, 1, 2 and >=3.	Categorical
Number of seizure events in the year before pregnancy	Seizure events in the year before pregnancy start date was used to identify the severity of epilepsy in the mothers. The information was gathered from: 1) Read codes in clinical or referral CPRD files; 2) ICD-10 codes in HES APC dataset; 3) A&E diagnosis of epilepsy related central nervous system condition in HES dataset. The events were categorised as 0, 1, 2 and >=3 events.	Categorical
Medications prescribed during 365 days before pregnancy start date	Information from therapy file was used to identify medication prescription in the year before pregnancy. Separate binary variables were created for: multivitamins, folic acid, antipsychotics, and antidepressants.	Binary
Other somatic conditions	Read codes from CPRD and ICD-10 codes from the HES database were used to identify fibromyalgia, essential tremor, restless leg and migraine and categorised into a single category as “other somatic conditions”.	Binary
Other psychiatric conditions	Read codes from CPRD and ICD-10 codes from the HES database were used to identify bipolar disorders, anxiety disorders, other mood affective disorders, psychosis and other psychiatric indications and categorised into a single category on “other psychiatric conditions”.	Binary

Table-S4: Odds ratios with 95% confidence interval for orofacial cleft according to anti-seizure medications prescription anytime between preconception period and pregnancy end date; and polytherapy during first trimester.

Outcome	Exposure	N in exposure group	uOR (95% CI)[a]	maOR (95% CI)[b]	aOR (95% CI)[c]
Orofacial Cleft	**ASM prescription anytime between preconception period and pregnancy end date**				
	Carbamazepine	906	1.71 (0.55-5.32)	..	..
	Gabapentin	926	0.55 (0.08-3.94)	..	..
	Levetiracetam	436	3.57 (1.14-11.12)	5.51 (0.76-39.72)	5.14 (0.47-56.63)
	Lamotrigine	1269	1.22 (0.39-3.79)	1.66 (0.23-11.91)	1.54 (0.16-15.32)
	Phenytoin	82	1	..	..
	Pregabalin	610	1.69 (0.42-6.79)	3.36 (0.47-24.15)	2.45 (0.33-18.19)
	Topiramate	290	1	..	..
	Valproate	677	3.06 (1.14-8.2)	3.45 (0.48-24.81)	3.93 (0.41-37.84)
	Other ASMs	329	1.57 (0.22-11.17)	..	..
Orofacial Cleft	**Polytherapy as compared to monotherapy during first trimester**	485	5.38 (1.44-20.11)	..	..
Orofacial Cleft	**Polytherapy as compared to no ASM during first trimester**	485	4.28 (1.59-11.48)	..	..

a- uOR: unadjusted odds ratio.
b- maOR: minimally adjusted odds ratio; adjusted for maternal age, marital status, ethnicity and IMD quintile.
c- aOR: fully adjusted odds ratio; adjusted for all covariates and indications of ASM prescription in women (epilepsy, other somatic and psychiatric conditions).
.. The models did not converge upon adjustment with covariates.
Note: The number of children diagnosed with the outcome of interest, i.e., OFC, cannot be depicted in exposure and reference groups because, under the CPRD guidelines, cases less than 5 cannot be reported, preserving the confidentiality at the reporting stage.[30]

Table-S5: Odds ratios with 95% confidence interval for orofacial cleft according to monotherapy of anti-seizure medications during the preconception period, pregnancy and first trimester.

Outcome	**Exposure**	**N in exposure group**	**uOR (95% CI)[a]**	**maOR (95% CI)[b]**	**aOR (95% CI)[c]**
Orofacial Cleft	**ASM monotherapy during preconception period**				
	Carbamazepine	599	1	..	..
	Gabapentin	707	0.73 (0.10-5.19)	..	..
	Levetiracetam	170	1	..	..
	Lamotrigine	886	1.17 (0.29-4.67)	2.32 (0.32-16.63)	2.52 (0.20-31.35)
	Phenytoin	46	1	..	..
	Pregabalin	487	2.13 (0.53-8.54)	4.39 (0.61-31.72)	3.27 (0.55-24.43)
	Topiramate	200	1	..	..
	Valproate	456	3.41 (1.09-10.64)	5.07 (0.70-36.57)	7.10 (0.64-79.12)
Orofacial Cleft	**ASM monotherapy during pregnancy**				
	Carbamazepine	602	1	..	..
	Gabapentin	564	0.91 (0.13-6.51)	..	..
	Levetiracetam	193	1	..	..
	Lamotrigine	939	0.55 (0.07-3.90)	2.37 (0.33-16.98)	2.45 (0.21-28.50)
	Phenytoin	46	1	..	..
	Pregabalin	408	2.54 (0.63-10.18)	5.38 (0.74-38.84)	3.72 (0.49-28.10)
	Topiramate	154	1	..	..
	Valproate	423	1	..	..

Outcome	Exposure	N in exposure group	uOR (95% CI)[a]	maOR (95% CI)[b]	aOR (95% CI)[c]
Orofacial cleft	**ASM monotherapy during first trimester**				
	Carbamazepine	554	1	..	..
	Gabapentin	540	0.95 (0.13-6.80)	..	..
	Levetiracetam	178	1	..	..
	Lamotrigine	921	0.56 (0.08-3.98)	2.36 (0.33-16.94)	2.57 (0.21-31.76)
	Phenytoin	44	1	..	..
	Pregabalin	401	2.58 (0.64-10.37)	5.51 (0.76-39.80)	3.79 (0.50-28.68)
	Topiramate	151	1	..	..
	Valproate	389	1.33 (0.19-9.45)	5.93 (0.82-42.85)	8.37 (0.75-92.85)

a- uOR: unadjusted odds ratio.
b- maOR: minimally adjusted odds ratio; adjusted for maternal age, marital status, ethnicity and IMD quintile.
c- aOR: fully adjusted odds ratio; adjusted for all covariates and indications of ASM prescription in women (epilepsy, other somatic and psychiatric conditions).
.. The models did not converge upon adjustment with covariate.
Note: The number of children diagnosed with the outcome of interest, i.e., OFC, cannot be depicted in exposure and reference groups because, under the CPRD guidelines, cases less than 5 cannot be reported, preserving the confidentiality at the reporting stage.[30]

References

1 Mathur R, Bhaskaran K, Chaturvedi N, et al. Completeness and Usability of Ethnicity Data in Uk-Based Primary Care and Hospital Databases. J Public Health. 2014;36(4):684-92. Available from:10.1093/pubmed/fdt