

Pregnancy, baby, and childhood outcomes from using anti-seizure medication during pregnancy

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This file contains all reviewer reports in order by version, followed by all author rebuttals in order by version.

Version 0:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

The paper describes a large population-based retrospective cohort study based on routinely collected information for all singleton pregnancies in Scotland conceived 2010-2023 that assessed the risk of adverse pregnancy and infant outcomes following exposure to anti-seizure medications (ASM) during pregnancy compared with an unexposed referent. Given it is often necessary for women to continue treatment with ASM during pregnancy due to the chronic and serious nature of the underlying condition that itself can increase risk of adverse outcomes, as well as many pregnancies being unplanned, this topic remains highly pertinent generating key information to inform treatment decisions by patients and healthcare providers. Overall this paper provides valuable evidence across a broad range of ASMs and indications, though the paper would benefit from some additional clarifications and context.

Major comments:

Introduction: The introduction states that “Evidence on the safety of other ASMs (e.g., lamotrigine and levetiracetam) during pregnancy is less certain”. There is substantial evidence on these ASMs, especially in epilepsy, generated through through single and multi-drug pregnancy registries (e.g., EURAP and the North American Anti-Epileptic Drug pregnancy registry), as well as multiple other study types (e.g., cohort studies in the Clinical Practice Research Datalink and EUROCAT case control study). For major malformations these showed a reassuring safety profile in pregnancy for well over a decade so this statement is not completely correct. Generally, with the newer ASMs it is more about accumulating larger sample sizes to study broader and rarer outcomes as well as patterns of risk by dose and duration of use.

Covariates: Do hospital discharge records only capture inpatient stays or specialist outpatient visits as well? Depending on the scope of medical information captured, this could increase the risk of residual confounding and potentially introduce systematic bias with the ability to adequately adjust only for more serious comorbidities that lead to a hospital-based healthcare encounter.

Development outcomes: Developmental outcomes are discussed with respect to ASD and ADHD, but it's not clear whether the developmental outcome assessment routinely collected at 27-30 months of age are strongly predictive of ASD, ADHD etc. Could you further elaborate on these assessments and/or reflect in the discussion section how much these outcomes can be represent longer term development delays or conditions.

Limitations: The study assesses a number of ASMs as well as a number of adverse outcomes. Given the multiple testing it may be possible that some positive associations may be reported by chance. Would you consider acknowledging this in the limitations section?

Study design: Please specify the length of follow up for each cohort

Minor comments:

Statistics: How did the authors account for the matching with replacement in the statistical models?

Statistics: Did the authors account for multiple pregnancies in the same woman?

Discussion: High dose folic acid – given lower dose folic acid may be obtained over the counter, there may be misclassification of categories for no folic acid and lower dose folic acid. This may affect interpretation of the high dose folic acid analyses. Was this considered in the interpretation of data?

Reviewer #2

(Remarks to the Author)

This interesting study conducted a retrospective analysis using a large population-based cohort of 923,440 singleton pregnancies in Scotland to examine whether exposure to antiepileptic medications (ASM) is associated with an increase risk of pregnancy loss, structural congenital malformations, and developmental concerns. This is a crucial area of concern given the rising use of these medications among pregnant women, particularly second-generation of ASMs such as gabapentin and pregabalin, for which the results of existing studies are inconsistent. The authors identified an unexpected association between gabapentinoid exposure and early childhood developmental concerns.

While the study presents numerous analytic findings and addresses an important topic, I have several concerns:

1. The authors should clearly define how the estimated date of conception was determined (based on gestational age at pregnancy end date, ultrasound, etc). A single ASM filled prescription during this exposure window is sufficient for an individual to be classified as exposed. This implies that an individual with only one prescription filled overlapping the 28 days prior to conception (who was estimated), but with no subsequent prescriptions, would still be considered exposed in the analyses. This likely leads to exposure misclassification, which should be addressed - ideally through a sensitivity analysis that defines exposure as having at least two prescriptions during the specified period.

Accurate timing of exposure is crucial, and the exposure window used in this study does not appear to be appropriate for the three outcomes assessed. The relevant exposure window for structural malformations ends no later than the end of the first trimester. In contrast, for childhood developmental concerns outcome, the critical exposure period is closer to the end of pregnancy (around the 20th week of gestation), corresponding to the onset of synaptogenesis.

2. Regarding the first outcome, pregnancy loss, it is important to recognize that spontaneous miscarriage, stillbirth, and induced or planned abortion all represent pregnancy termination, but differ significantly in timing, underlying causes, and intent. I do not agree with the decision to pool these events into a single outcome and recommend that they be analyzed separately to ensure more accurate and meaningful interpretations.

3. The diagnostic codes used to identify the cases (for all outcomes) should be provided, along with the ATC codes used to define exposure.

4. The comparator groups are not clearly defined in the analysis by type of ASM used in monotherapy. Are the comparator groups consistently pregnancies with no ASM exposure during the exposure window, or pregnancies not exposed to the specific ASM under study? This distinction should be clearly specified, as it is not currently clear in the manuscript.

5. Covariates section: please add ICD-9 or 10 as well as ATC codes used for the identification of all covariates.

Overall, this manuscript is difficult to read. While I acknowledge that a large number of analyses were conducted, several sections - particularly 'Statistical Analyses', 'Results', and especially the 'Discussion' - are challenging to follow.

In the 'Statistical Analyses' section, I recommend adding a subheading for the sensitivity analyses. Currently, terms such as 'In primary analyses' and 'Primary analyses' are used inconsistently, which makes the structure unclear. This section would benefit from being rewritten with clearly defined subsections. There is also no information provided on the methods used to compare the characteristics of exposed and unexposed pregnancies (results presented in Table 1). This should be described at the beginning of the 'Statistical Analyses' section. These presentation order should be reflected also in the result section presentation throughout the manuscript. The 'Discussion' section should be completely revised. The first paragraph does not summarize any results. Subsequently, the comparisons with previous studies are presented in a disorganized manner. The section would benefit from a more structured and coherent discussion, including a more substantial analysis of the study's strengths and limitations. It is also unclear how the date of conception was estimated. If gestational age at the end of the pregnancy was not available, this limitation should be explicitly discussed. Furthermore, the limitations of the exposure definition should also be addressed. The discussion should include a reflection on the biological plausibility of the associations found. Finally, the section lacks a proper conclusion, which should be presented as the final paragraph.

Version 1:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

Many thanks to the authors for their thorough responses to my comments. Based on review of the responses and updated manuscript, these comments have been answered and the updated manuscript is now a more balanced overview of this complex study.

One minor clarification. The comment on the statistical methods for matching with replacement versus without replacement was related to whether additional adjustments were made for the method of matching with replacement. The author response focused on the rationale for matching with replacement which is clear rather than any additional statistical adjustment. If this detail is available it can be added to the manuscript, but this is a minor point.

Reviewer #2

(Remarks to the Author)

I would like to sincerely thank you for your thorough and thoughtful review of our manuscript. Your insightful comments and suggestions have significantly contributed to enhancing the quality of our work. I am pleased to see that all the points I raised have been effectively addressed. The revised version is much stronger, and I now consider it ready for publication.

Thank you once again for your valuable collaboration and dedication to maintaining the excellence of our research.

Version 2:

Reviewer comments:

Reviewer #1

(Remarks to the Author)

I have no further comments and thank the authors for their thorough review and consideration of comments made during the course of the review process.

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Point-by-point response to reviewers

Reviewer #1 (Remarks to the Author):

The paper describes a large population-based retrospective cohort study based on routinely collected information for all singleton pregnancies in Scotland conceived 2010-2023 that assessed the risk of adverse pregnancy and infant outcomes following exposure to anti-seizure medications (ASM) during pregnancy compared with an unexposed referent. Given it is often necessary for women to continue treatment with ASM during pregnancy due to the chronic and serious nature of the underlying condition that itself can increase risk of adverse outcomes, as well as many pregnancies being unplanned, this topic remains highly pertinent generating key information to inform treatment decisions by patients and healthcare providers. Overall this paper provides valuable evidence across a broad range of ASMs and indications, though the paper would benefit from some additional clarifications and context.

Thank you for your thoughtful and constructive comments on our manuscript. We are pleased that you found the study to be of value, particularly considering the clinical importance of balancing the need for effective treatment of indicating conditions with the potential risks associated with anti-seizure medication (ASM) use during pregnancy. We welcome your suggestions regarding the need for additional clarifications and context, and we have carefully addressed each point in our responses below. We believe these revisions have strengthened the manuscript and improved clarity.

Major comments:

Introduction: The introduction states that “Evidence on the safety of other ASMs (e.g., lamotrigine and levetiracetam) during pregnancy is less certain”. There is substantial evidence on these ASMs, especially in epilepsy, generated through single and multi-drug pregnancy registries (e.g., EURAP and the North American Anti-Epileptic Drug pregnancy registry), as well as multiple other study types (e.g., cohort studies in the Clinical Practice Research Datalink and EUROCAT case control study). For major malformations these showed a reassuring safety profile in pregnancy for well over a decade so this statement is not completely correct. Generally, with the newer ASMs it is more about accumulating larger sample sizes to study broader and rarer outcomes as well as patterns of risk by dose and duration of use.

This is a helpful correction, thank you. We have amended the introduction (see lines 71-76 and 81-83 in the revised manuscript with all tracked changes displayed) to reflect your comments:

“Evidence on the safety of some of the other ASMs during pregnancy is less certain. There is substantial evidence that lamotrigine and levetiracetam show a reassuring safety profile with regards to major congenital conditions^{18,19}; however, conclusive data on outcomes such as intrauterine growth restrictions or neurodevelopmental concerns remains relatively scarce, especially for newer ASMs and ASMs that are not as widely used as valproate, topiramate, levetiracetam, or lamotrigine²⁰.”

“Consequently, comprehensive real-world evidence on the safety of some ASMs (particularly the newer ASMs such as lamotrigine and levetiracetam) during pregnancy is still lacking²⁶⁻²⁸.”

Covariates: Do hospital discharge records only capture inpatient stays or specialist outpatient visits as well? Depending on the scope of medical information captured, this could increase the risk of residual confounding and potentially introduce systematic bias with the ability to adequately adjust only for more serious comorbidities that lead to a hospital-based healthcare encounter.

Thank you for raising this important point. In our study, we utilised data from the Scottish Morbidity Record datasets, specifically SMR01, SMR02, and SMR04, to identify indications for ASM use and comorbidities. These datasets capture information on patients discharged from an episode of inpatient or day case hospital-based care only. They do not include information from specialist outpatient visits. SMR02 collects data on patients discharged from maternity/obstetric care (antenatal, delivery, or postnatal). SMR04 collects data on patients discharged from mental health/psychiatric care. SMR01 collects data on patients discharged from all other acute specialties.

Outpatient attendance records in Scotland (SMR00) do not include ICD-10 diagnostic coding, and as such, we were unable to use these for identifying indications and comorbidities. We acknowledge that this may limit our ability to identify less severe or chronic conditions managed exclusively in outpatient settings. To help mitigate this limitation, we incorporated primary care prescribing data into our definitions of indicating condition (for example using prior prescription of anti-psychotic medication and/or a discharge diagnosis of a relevant mental health condition when identifying women with a mental health condition indicating ASM use). However, we recognise that residual confounding may persist, particularly for conditions that do not lead to hospitalisation or prescribing.

We have added the following clarification to the methods (see lines 215-218):

“Indications for ASM use, chronic comorbidity, and alcohol and drug misuse were identified using hospital in-patient and day case discharge records in the five years preceding the estimated date of conception up to 14 days after pregnancy end date (Supplementary Table 3, Supplementary Table 4).”

We have also added the following limitation to the discussion (see lines 632-633):

“Our hospital data did not include outpatient appointments, so we may have missed milder indications or comorbidities.”

Development outcomes: Developmental outcomes are discussed with respect to ASD and ADHD, but it's not clear whether the developmental outcome assessment routinely collected at 27-30 months of age are strongly predictive of ASD, ADHD etc. Could you further elaborate on these assessments and/or reflect in the discussion section how much these outcomes can be represent longer term development delays or conditions.

Thank you for raising this important point. We agree that developmental concerns identified at the child health reviews that are universally offered to pre-school children in Scotland are distinct from a formal diagnosis of a neurodevelopmental condition such as autism spectrum disorder (ASD) or attention-deficit/hyperactivity disorder (ADHD). The results of a child health review present a snapshot of a child's development at a certain age (in our case, 27-30 months). Concerns recorded at a review reflect delay in a child meeting the developmental milestones that would be expected at that age. Such delay may (broadly) resolve over time, or the child may go on to receive a formal diagnosis of a neurodevelopmental condition.

As noted in our paper (existing text in lines 148-151), child health reviews are provided by specialist nurses and the developmental assessment carried during reviews comprises a structured discussion with parents to establish a developmental history and elicit any parental concerns, observation of the child, and completion of a validated developmental assessment questionnaire.

The Ages & Stages Questionnaire (ASQ-3) is the main questionnaire used in Scotland. Guidance on the provision of 27-30 month child health reviews (including developmental assessment) was first issued in Scotland in 2012 (see: [The Scottish Child Health Programme: Guidance on the 27-30 month child health review - gov.scot](#)) and reviews for this age group commenced in April 2013 (see [\[ARCHIVED CONTENT\] Child Health | Child Health Programme | Child Health Systems Programme Pre-School \(CHSP Pre-School\) | Health Topics | ISD Scotland](#)).

The ASQ-3 is not intended to be diagnostic and does not specifically screen for conditions such as ASD or ADHD. However, scores below established cut-offs are moderately predictive of later developmental difficulties, including cognitive, language, and behavioural problems. Some studies in other settings have shown associations between low ASQ-3 scores in early childhood and later diagnoses of ASD or ADHD (for example, see [Early Developmental Signs in Children with Autism Spectrum Disorder: Results from the Japan Environment and Children's Study - PubMed](#)), though predictive values vary by domain and population. We do not have a register of individuals with ASD or ADHD in Scotland, so we cannot accurately assess the predictive validity of ASQ-3 in relation to these conditions in our study population.

We have added text to the methods to clarify the purpose of the ASQ-3-based assessments (see lines 152-154):

“Questionnaires seek to identify delay in meeting expected developmental milestones and do not specifically screen for conditions such as autism or ADHD which are typically diagnosed later in life^{41,42}.”

We have also strengthened our statement in the discussion noting that the evidence we present on the association between ASM exposure and early developmental concerns differs from the existing evidence examining the association with specific neurodevelopmental conditions (see lines 549-554):

“Existing evidence on ASM exposure during pregnancy and resulting developmental outcomes in exposed children tends to reflect neurodevelopmental conditions such as autism, ADHD, and intellectual disability diagnosed later in childhood^{41, 59}, rather than early ‘concerns’ (reflecting potentially transient delay in reaching expected milestones and/or parent or nurse concerns) examined in our study.”

Limitations: The study assesses a number of ASMs as well as a number of adverse outcomes. Given the multiple testing it may be possible that some positive associations may be reported by chance. Would you consider acknowledging this in the limitations section?

While the primary analyses were hypothesis-driven, we acknowledge that spurious associations cannot be entirely excluded. We have added this to the limitations (see lines 642-643):

“However, we assessed multiple exposures and outcomes, increasing the likelihood of chance findings.”

Study design: Please specify the length of follow up for each cohort

We have amended the methods (see lines 171-175) to note follow-up length as:

“Cohorts were followed until pregnancy end (pregnancy cohorts) or, for live births, the baby’s first birthday [allowing for pre- or post-natal diagnosis of a congenital condition] (baby cohorts), and age 32 months [the upper age limit for delivery of the 27-30 month review] (live birth cohorts).”

Minor comments:

Statistics: How did the authors account for the matching with replacement in the statistical models?

By using a conditional logistic regression model (see lines 242-243), which estimates the common stratum- and covariate-specific odds ratio by stratifying on matching factors while adjusting for other confounders as covariates. Regarding replacement,

there weren't enough unexposed comparators to achieve the prespecified 1:10 matching ratio by matching without replacement. Although matching with replacement decreases statistical efficiency if the same individual is repeatedly included as an unexposed comparator, if the number of unexposed is much larger than that of the exposed (which it is in our case given our 1:10 ratio), choosing with or without replacement would not make a substantive difference in the estimated odds ratios (see doi: [10.37737/ace.22005](https://doi.org/10.37737/ace.22005)).

Statistics: Did the authors account for multiple pregnancies in the same woman?

Yes. There are two interpretations of multiple pregnancies; a pregnancy with more than one baby (i.e., twins, triplets, etc) or sequential pregnancies to the same woman. We accounted for the former by restricting the study population to singleton pregnancies. We accounted for the latter by dropping sequential pregnancies to the same woman within a matched unit. Where exposure status was discordant between sequential pregnancies within a matched unit, the exposed pregnancy was preferentially kept. We have added text reflecting this to the methods (see lines 204-207):

“Sequential pregnancies to the same woman within a matched unit were dropped to account for non-independence. Where exposure status was discordant between sequential pregnancies within a matched unit, the exposed pregnancy was retained.”

Discussion: High dose folic acid – given lower dose folic acid may be obtained over the counter, there may be misclassification of categories for no folic acid and lower dose folic acid. This may affect interpretation of the high dose folic acid analyses. Was this considered in the interpretation of data?

We recognise the important point you make and yes, we did consider this. The following existing text in the methods notes that, on the basis of the national prescription records we had access to, we were only able to classify women as receiving, or not receiving, high dose folic acid, and that the ‘no high dose folic acid’ group will likely include some women receiving standard dose supplements and some receiving no supplements (see lines 225-233):

“In supplementary analyses, maternal receipt of high dose (5mg per day) folic acid supplements was assessed as a potential effect modifier. Receipt of high dose folic acid was derived from prescription records... In Scotland, standard dose (400mcg per day) folic acid supplements are provided directly by maternity services to women (or can be purchased over the counter at pharmacies) with no prescription required. We were therefore unable to tell whether women who did not receive high dose supplements received standard dose or no supplements.”

Throughout the paper, we reiterate that, when considering receipt of high dose folic acid, the comparator group is likely to include women receiving standard dose or no supplements (for example, see existing text in lines 269-273):

“Thirdly, we included maternal high dose folic acid in models, and an interaction term between maternal high dose folic acid and ASM exposure, to assess whether receipt of high dose folic acid (compared to no or standard dose) modified the association between ASM exposure and outcomes.”

Finally, in our discussion we reflect that our lack of evidence of effect modification by high dose folic acid on the association between ASM exposure and our outcomes may indicate little incremental benefit of high dose compared to standard dose folic acid (if many women in the comparator group received standard dose supplements) (see existing text in lines 603-608):

“We found no evidence that receipt of high dose folic acid around the time of conception (compared to no or standard dose) modified the association between ASM exposure and congenital conditions, and evidence that it attenuated the association with developmental concerns for Any ASM and carbamazepine only. These results may reflect inadequate power to detect interactions and/or relatively little benefit of high, compared to standard, dose supplementation.”

Reviewer #2 (Remarks to the Author):

This interesting study conducted a retrospective analysis using a large population-based cohort of 923,440 singleton pregnancies in Scotland to examine whether exposure to antiseizure medications (ASM) is associated with an increase risk of pregnancy loss, structural congenital malformations, and developmental concerns. This is a crucial area of concern given the rising use of these medications among pregnant women, particularly second-generation of ASMs such as gabapentin and pregabalin, for which the results of existing studies are inconsistent. The authors identified an unexpected association between gabapentinoid exposure and early childhood developmental concerns. While the study presents numerous analytic findings and addresses an important topic, I have several concerns.

Thank you for your helpful and comprehensive feedback on our manuscript. We are pleased that you found the study to be of interest and recognise the importance of examining the safety of ASMs, particularly gabapentin and pregabalin, in pregnancy. We have carefully considered your specific comments and suggestions below, and we believe the resulting revisions have further strengthened the manuscript.

1. The authors should clearly define how the estimated date of conception was determined (based of gestational age at pregnancy end date, ultrasound, etc).

We have strengthened the data sources section of our methods to ensure that references giving detailed information on each national dataset used in our study (including the Scottish Linked Pregnancy and Baby Dataset, SLiPBD) are provided at this first mention of each source (see existing text in lines 122-135).

In the cohorts section of our methods we have clarified that all cohorts were drawn based on singleton status and estimated date of conception (EDC) as recorded in SLiPBD (for example, see lines 156-159):

“Three sets of cohorts were drawn from the national pregnancy and baby dataset, SLiPBD, to examine each outcome of interest. Pregnancy cohorts (used to examine the pregnancy loss outcome) included all singleton pregnancies with an estimated date of conception from 1 April 2010 until 2 July 2023.”

As SLiPBD draws data from a wide range of other existing national health datasets, the provenance of the EDC varies depending on the woman's antenatal booking status and pregnancy outcome. In general:

- For pregnancies where the woman booked for antenatal care (regardless of subsequent pregnancy outcome), the EDC will be derived from the date of booking and the gestation in completed weeks at booking as determined at a first trimester booking ultrasound scan in accordance with international guidelines (see Methods for Estimating the Due Date | ACOG) (as recorded on the antenatal booking record).
- For unbooked pregnancies ending in a termination, the EDC will be derived from the date of termination and the gestation in completed weeks at termination based on either an ultrasound scan or the last menstrual period (LMP) if no scan was done (as recorded on the termination notification record).
- For unbooked pregnancies ending in a miscarriage, the EDC will be derived from the date of miscarriage and either the gestation in completed weeks at miscarriage based on an ultrasound scan or the LMP (as recorded on the hospital discharge record), or on an imputed gestation in completed weeks at miscarriage (generally set to 10 weeks, as discharge records relating to care for a miscarriage may lack information on gestation).

Broadly speaking, this means that the EDC will be highly accurate for pregnancies ending in a delivery, moderately accurate for pregnancies ending in a termination, and least accurate for pregnancies ending in a miscarriage. Further information is provided on this in our data resource paper on SLiPBD which is referenced in this paper (Data resource profile: Scottish Linked Pregnancy and Baby Dataset (SLiPBD) - PMC).

We have added summary information on this to the cohorts section of our methods (see lines 159-165):

“The estimated date of conception as recorded in SLiPBD is derived from information on source records providing the date of antenatal booking or end of pregnancy and the gestation in completed weeks at booking or the end of pregnancy. The gestation information is generally based on a first trimester ultrasound scan, but in some situations may be based on the last menstrual period (in particular for pregnancies ending in termination) or imputed based on the pregnancy outcome type (in particular for pregnancies ending in miscarriage).”

A single ASM filled prescription during this exposure window is sufficient for an individual to be classified as exposed. This implies that an individual with only one prescription filled overlapping the 28 days prior to conception (who was estimated), but with no subsequent prescriptions, would still be considered exposed in the analyses. This likely leads to exposure misclassification, which should be addressed - ideally through a sensitivity analysis that defines exposure as having at least two prescriptions during the specified period.

We agree that it is important to consider the possibility of exposure misclassification, however we do not think this is likely to be a major limitation to our study for the following reasons.

There are two main factors that may drive exposure misclassification: inaccuracy in the EDC (and hence inaccuracy in the timing of prescription in relation to the pregnancy) and the relationship between a prescription being issued and the medication being taken.

As set out in our response to the previous comment, the EDC will be highly accurate for the substantial majority of pregnancies in our study, in particular those ending in a delivery.

In terms of whether women receiving prescriptions in the 28 days prior to the EDC should be considered exposed, we note the following. In Scotland, the typical duration of supply per ASM prescription in the national prescribing dataset is 28 days, with some being for 56 days. When classifying exposure status, we only ‘counted’ prescriptions issued that were subsequently dispensed to the patient. The average lag between an ASM prescription being issued and it being dispensed was 4 days. It is therefore highly likely that a woman with an ASM prescription issued in the 28 days prior to EDC would still have supply remaining at the point of conception.

Nevertheless, in response to this comment, we have undertaken additional analyses to examine how many women were classed as exposed on the basis of receiving a single prescription in the 28 days prior to the EDC (the ‘pre-conception period’). Of the 11,011 pregnancies in our pregnancy cohort classed as exposed to Any ASM, 1,466 (13%) received only a single prescription in the pre-conception period. 5,444 (49%) received their first prescription in the preconception period then went on to have at least one further prescription during pregnancy (EDC to end of pregnancy).

The remaining 4,101 (37%) received their first prescription during pregnancy. This shows that being classed as exposed on the basis of receiving a single prescription in the 28 days prior to the EDC is relatively uncommon.

We do acknowledge that, in common with all pharmacoepidemiology studies relying on routine prescribing data, we cannot say for certain when, or whether, women dispensed an ASM actually took the medication. The extent of this form of exposure misclassification is unquantifiable, however we do note that in general exposure misclassification would be expected to bias findings towards the null. This means that any such misclassification would tend to result in the associations we observe between ASM use and the outcomes studied being underestimates.

We have strengthened the text relating to the possibility of exposure misclassification in the exposures section of our methods (see lines 177-185):

“Exposure ‘in pregnancy’ was defined as a prescription for a specified ASM issued at any point from 28 days prior to the estimated date of conception up to pregnancy end date (pregnancy and live birth cohorts) or 19 weeks and 6 days (19+6 weeks) gestation (or pregnancy end date, if sooner) (baby cohorts). Prescriptions issued were restricted to those subsequently dispensed to minimise exposure misclassification. The typical duration of supply per ASM prescription recorded on the national prescribing dataset is at least 28 days, with an average lag of 4 days between the prescription being issued and it being dispensed. It is therefore highly likely that a women prescribed an ASM in the 28 days prior to the estimated date of conception would still have supply remaining at the point of conception.”

And in the limitations section of our discussion (see lines 634-642):

“Some exposure misclassification may have occurred (for example, a pregnancy being classified as exposed to an ASM when it was not) for reasons including inaccuracy in the estimated date of conception or a woman delaying or not taking her prescribed medication. To mitigate this as far as possible, we aligned our exposure periods with international standards where available, and only ‘counted’ prescriptions that were subsequently dispensed. Any remaining exposure misclassification (in particular that relating to women not taking their dispensed medication) would be expected to bias findings towards the null, suggesting that the associations we observed were, if anything, underestimated.”

Accurate timing of exposure is crucial, and the exposure window used in this study does not appear to be appropriate for the three outcomes assessed. The relevant exposure window for structural malformations ends no later than the end of the first trimester.

We agree that organogenesis is complete by the end of the first trimester, hence that represents the critical period for teratogenic exposures. However, in line with international guidance from The Brighton Collaboration Congenital Anomalies

Working Group (Congenital anomalies: Case definition and guidelines for data collection, analysis, and presentation of immunization safety data - ScienceDirect), we used the broader exposure window of up to 19⁺⁶ when considering ASM exposure and structural congenital conditions to allow for any errors in relevant dates.

However, in light of your comment, we have undertaken additional analyses to examine timing of exposure in our baby cohort (used to assess the congenital condition outcome). Of the 8,370 fetuses exposed to Any ASM in our baby cohort, 8,137 (97.2%) had at least one prescription issued at <12⁺⁰ weeks gestation, confirming that the substantial majority were likely exposed during the most clinically relevant window.

In contrast, for childhood developmental concerns outcome, the critical exposure period is closer to the end of pregnancy (around the 20th week of gestation), corresponding to the onset of synaptogenesis.

We agree that synaptogenesis occurs in the second half of pregnancy, however we would argue that exposures at any point in pregnancy could conceivably affect early childhood development. To our knowledge, there is no international standard for defining the clinically relevant window for exposures in pregnancy affecting childhood development, nor are the biological mechanisms (which may go beyond disruption of synaptogenesis) fully understood. For example, fetal alcohol spectrum disorder (FASD) is characterised by neurocognitive and behavioural disabilities resulting from maternal alcohol consumption in pregnancy. For FASD, prenatal exposure is defined as confirmed or unknown maternal alcohol consumption at any point during pregnancy (see Children and young people exposed prenatally to alcohol).

However, in light of your comment, we have undertaken additional analyses to examine timing of exposure in our live birth cohort (used to assess the early childhood developmental concern outcome). Of the 4,890 live births exposed to Any ASM in our live births cohort, 3,135 (64.1%) had at least one prescription issued at ≥16⁺⁰ weeks gestation, indicating that the woman would likely have ongoing supply at 20⁺⁰ weeks given the typical prescription duration and the lag between prescription and dispensing. Hence, whilst most first exposures occur in the pre-conception or early pregnancy period, many women (and hence their babies) continue to be exposed into later pregnancy.

As noted above, we have added the following text to the limitations section of our discussion (see lines 634-642):

“Some exposure misclassification may have occurred (for example, a pregnancy being classified as exposed to an ASM when it was not) for reasons including inaccuracy in the estimated date of conception or a woman delaying or not taking her prescribed medication. To mitigate this as far as possible, we aligned our exposure

periods with international standards where available, and only 'counted' prescriptions that were subsequently dispensed. Any remaining exposure misclassification (in particular that relating to women not taking their dispensed medication) would be expected to bias findings towards the null, suggesting that the associations we observed were, if anything, underestimated."

Our conclusions for live births therefore remain the same; that is, our unexpected finding of an association between gabapentinoids and early childhood development concerns indicates an initial safety signal that should be studied further.

2. Regarding the first outcome, pregnancy loss, it is important to recognize that spontaneous miscarriage, stillbirth, and induced or planned abortion all represent pregnancy termination, but differ significantly in timing, underlying causes, and intent. I do not agree with the decision to pool these events into a single outcome and recommend that they be analyzed separately to ensure more accurate and meaningful interpretations.

We agree that ASM exposure may affect the risk of spontaneous pregnancy loss and/or of termination of pregnancy, and that modelling any pregnancy loss as a composite outcome means it is not possible to disentangle these two possible pathways. However, there are compelling methodological reasons to treat pregnancy loss as a composite outcome. The main reason is that spontaneous loss and termination of pregnancy are competing risks (i.e., a pregnancy that ends in a spontaneous loss cannot end in a termination, and vice versa) and it is not possible to account for competing risks in regression models analysing categorical outcomes (such as the conditional logistic regression used in our study). Modelling the different types of pregnancy loss (relative to live birth) separately therefore may produce counter-intuitive or misleading results. For example, if women exposed to an ASM in pregnancy are very likely to terminate their pregnancy, the separate models may show a raised odds ratio for termination of pregnancy but a spuriously low odds ratio for spontaneous loss which (erroneously) could suggest a protective effect of ASMs.

Nevertheless, in response to your comment we have undertaken additional supplementary analyses, modelling the odds ratio of spontaneous loss and, separately, termination of pregnancy – both compared to live birth – in pregnancy cohorts using multinomial conditional logistic regression. These new models are technically 'correct' in that they reflect the binary nature of the pregnancy outcome information in the separate models and our matched cohort study design, however they do not (and cannot) take account of the fact that the different types of pregnancy loss are competing risks. For this reason, we have retained the 'any pregnancy loss' results in the main paper and provided the separate results as additional, off-protocol, supplementary material (see Supplementary Figure 5 and Supplementary Table 13). We have added the following text to our methods, results, and discussion sections (see lines 279-282, 386-394, 495-507, and 644-651):

“We conducted an additional off-protocol supplementary analysis in response to reviewer comments. For this analysis, we modelled the odds ratio of termination of pregnancy and, separately, spontaneous loss compared to live birth in pregnancy cohorts using conditional multinomial logistic regression.”

“In additional analyses examining termination of pregnancy and spontaneous loss (compared to live birth) separately, results were similar to primary analyses. However, they were less certain (in particular for spontaneous loss) due to the smaller numbers involved when modelling these outcomes separately (compared to together as a single composite outcome) (Supplementary Table 13, Supplementary Figure 5). In adjusted analyses, exposure to Any ASM, gabapentin, and pregabalin remained significantly associated with an increased odds of both termination of pregnancy and spontaneous loss. Exposure to valproate and topiramate remained significantly associated with termination of pregnancy, but not spontaneous loss.”

“In primary analyses (including all pregnancies exposed to an ASM) we found an association between Any ASM and several ASM monotherapies and any pregnancy loss. As previously stated, in our per-protocol analyses we examined any pregnancy loss as our outcome of interest. We chose this approach as spontaneous loss (in particular, early miscarriage) and termination of pregnancy act as competing risks, making the results of modelling specific types of pregnancy loss in isolation difficult to interpret. This approach does mean that any associations found between ASM exposure and pregnancy loss may reflect associations with spontaneous loss (reflecting biological risk) and/or women’s decisions to continue or terminate a pregnancy (mainly reflecting reproductive choices). However, in the additional supplementary analyses undertaken in response to reviewer comments, we generally observed that associations between ASM exposure and any pregnancy loss seen in our primary analyses reflected an association with both spontaneous loss and termination of pregnancy.”

“In our per-protocol analyses, we examined associations between ASM exposure and any pregnancy loss, with termination of pregnancy and spontaneous loss modelled together as a composite outcome due to competing risk between these types of pregnancy loss and the loss of precision seen when modelling smaller numbers of different types of loss separately. We modelled these outcomes separately in additional supplementary analyses to attempt to disentangle the effects of ASM exposure on spontaneous loss as opposed to reproductive choices, but the results from this multinomial modelling should be interpreted with caution due to the persistent issue of competing risk.”

3. The diagnostic codes used to identify of the cases (for all outcomes) should be provided, along with the ATC codes used to define exposure.

Pregnancy outcomes (live birth, spontaneous loss, termination of pregnancy) were identified using hard-coded variables from the national pregnancy and baby dataset (SLiPBD), which we reference in the paper.

Congenital condition outcomes (congenital condition group, none) were identified using the diagnostic code list set by the European network of national congenital condition registers (EUROCAT) as implemented in the Scottish national linked dataset of babies with congenital conditions (SLiCCD). We have added the following references which provide full ICD10 code lists for all major congenital conditions, conditions with a genetic basis (for exclusion), and standard groups of conditions (for example, congenital heart disease) (see line 126-130): [Guidelines for data registration | European Platform on Rare Disease Registration and Congenital conditions in Scotland - 2000 to 2021 - Congenital conditions in Scotland - Publications - Public Health Scotland](#).

Early childhood development outcomes (type of concern, none) were identified using hard-coded variables from the national child health dataset (CHSP Pre-School). We have added a reference to the website where a copy of the data collection form used at the 27-30 month review can be downloaded (see line 132): [Pre-school system - Child health programme - Child health data and intelligence - Early years and young people - Population health - Public Health Scotland](#). We already provide a reference to the policy document providing guidance on delivery of the 27-30 month review, including the developmental assessment (see line 151): [The Scottish Child Health Programme: Guidance on the 27-30 month child health review - gov.scot](#).

The codes (British National Formulary (BNF) and Virtual Therapeutic Moiety (VTM) to define ASM exposure are provided in Supplementary Table 1, which is referenced in the methods (see line 194). We have updated Supplementary Table 1 to include the corresponding Anatomical Therapeutic Chemical (ATC) codes.

4. The comparator groups are not clearly defined in the analysis by type of ASM used in monotherapy. Are the comparator groups consistently pregnancies with no ASM exposure during the exposure window, or pregnancies not exposed to the specific ASM under study? This distinction should be clearly specified, as it is not currently clear in the manuscript.

Thank you for flagging this. We have clarified in the methods section that the unexposed were consistently those with no exposure to any ASM in the 28 days prior to conception up to pregnancy end (see lines 198-201):

“Unexposed pregnancies (matched to pregnancies in the Any ASM or seven monotherapy exposed cohorts) were those with no known prescription for any ASM in the corresponding exposure period.”

5. Covariates section: please added ICD-9 or 10 as well as ATC codes used for the identification of all covariates.

ICD-10 code lists for Maternal chronic comorbidity, Maternal indications for ASM use (Maternal epilepsy, Maternal mental health conditions, Maternal migraine or pain conditions), and Maternal alcohol and drug misuse are provided in Supplementary Tables 2, 3 and 4. BNF sections for Maternal indications for ASM use are provided in Supplementary Table 5, and the corresponding ATC codes have now been added to this table. Supplementary Tables 2-5 are referenced in the methods (see lines 213-221). The BNF sub section and ATC code for Maternal high dose folic acid use have been added to the methods (see lines 227-228).

ICD/ATC codes for all other covariates (Year of conception; Maternal age at conception; Maternal deprivation based on residential postcode at antenatal booking; Maternal parity; Baby sex; Maternal BMI at antenatal booking; Maternal smoking at antenatal booking) are not available as they are sourced from hard-coded variables from national datasets.

Overall, this manuscript is difficult to read. While I acknowledge that a large number of analyses were conducted, several sections - particularly 'Statistical Analyses', 'Results', and especially the 'Discussion' - are challenging to follow. In the 'Statistical Analyses' section, I recommend adding a subheading for the sensitivity analyses. Currently, terms such as 'In primary analyses' and 'Primary analyses' are used inconsistently, which makes the structure unclear. This section would benefit from being rewritten with clearly defined subsections.

We have added further subheadings to the methods and results sections (see lines 235, 254, 380, 400, 425, 452, 467, 496) to improve readability. Specifically, we now refer to all additional analyses (previously referred to as “secondary”, “sensitivity” and “supplementary” analyses) as “supplementary” analyses to more easily differentiate these from our primary analyses. We address your comment on the discussion section in our response below.

There is also no information provided on the methods used to compare the characteristics of exposed and unexposed pregnancies (results presented in Table 1). This should be described at the beginning of the 'Statistical Analyses' section. These presentation order should be reflected also in the result section presentation throughout the manuscript.

We state in the methods that, “For each cohort set and each exposure (Any ASM and the seven monotherapies), the characteristics of exposed pregnancies, the total population of unexposed pregnancies, and the sample of matched unexposed pregnancies were categorised and summarised using counts and percentages” (see lines 236-239). In line with STROBE guidelines (Strengthening the Reporting of Observational Studies in Epidemiology (STROBE): Explanation and Elaboration | Annals of Internal Medicine), we did not formally test the statistical significance of the differences in the distribution of covariates in exposed and unexposed groups shown

in Table 1.

The 'Discussion' section should be completely revised. The first paragraph does not summarize any results. Subsequently, the comparisons with previous studies are presented in a disorganized manner. The section would benefit from a more structured and coherent discussion, including a more substantial analyses of the study's strengths and limitations.

In response to your comment, we have amended the first paragraph in the discussion so this now includes a summary of our results (see lines 481-494). Additionally, we have substantially strengthened the section on study limitations (see lines 654-679).

It is also unclear how the date of conception was estimated. If gestational age at the end of the pregnancy was not available, this limitation should be explicitly discussed. Furthermore, the limitations of the exposure definition should also be addressed.

Please see our response to your first comment.

The discussion should include a reflection on the biological plausibility of the associations found.

In response to your comment, we have added a high-level description of biological mechanisms that may explain a causal relationship for our unexpected finding of associations between gabapentinoids and child development concerns in the results section (see lines 593-597):

“Nevertheless, gabapentinoids are known to cross the placental and blood-brain barrier and may inhibit the release of neurotransmitters^{63,64}. In addition, it has been demonstrated in murine models that gabapentin may interfere with neurogenesis during fetal brain development⁶⁵. The observed associations with child development may therefore be biologically plausible.”

This includes the following new references: Involvement of I-type amino acid transporter 1 in the transport of gabapentin into human placental choriocarcinoma cells, Gabapentinoids: pharmacokinetics, pharmacodynamics and considerations for clinical practice - PMC and Frontiers | Prenatal Exposure to Gabapentin Alters the Development of Ventral Midbrain Dopaminergic Neurons.

Finally, the section lacks a proper conclusion, which should be presented as the final paragraph.

In line with Nature Communications Medicine style and formatting guide ([commsj-med-style-formatting-guide-accept.pdf](#)), a conclusion is provided at the end of the

introduction (see lines 90-98). In addition, we provide a plain language summary at the start of the manuscript (see lines 42-53).

Response to reviewers

Reviewer #1 (Remarks to the Author):

Many thanks to the authors for their thorough responses to my comments. Based on review of the responses and updated manuscript, these comments have been answered and the updated manuscript is now a more balanced overview of this complex study.

We sincerely thank the reviewer for their thoughtful engagement with our manuscript and for acknowledging the revisions made in response to their comments. The constructive feedback has significantly strengthened the clarity and rigor of our work, and we are grateful for the opportunity to improve the manuscript through this collaborative process.

One minor clarification. The comment on the statistical methods for matching with replacement versus without replacement was related to whether additional adjustments were made for the method of matching with replacement. The author response focused on the rationale for matching with replacement which is clear rather than any additional statistical adjustment. If this detail is available it can be added to the manuscript, but this is a minor point.

Thank you for clarifying. We have now added the following text relating to this to the Statistics and reproducibility section of our Methods (lines 234-243). New text (and text moved from the Matching section of the Methods for clarity) is underlined. Line numbers refer to the clean version of the manuscript with no Tracked changes applied.

‘For each cohort set and each exposure, we explored the association between exposure and outcome using univariable and multivariable conditional logistic regression models⁴⁶. Pregnancies were dropped if data for the outcomes were missing. To ensure independence within the matched exposed/unexposed sets that were analysed in conditional logistic regression, if the same unexposed pregnancy was included more than once in the ten matched unexposed equivalents for any one exposed pregnancy, the unexposed equivalent was only retained once in that matched set, with duplicates dropped. Similarly, if sequential pregnancies to the same woman were included within a matched set, only one pregnancy was retained. Where exposure status was discordant between sequential pregnancies within a set, the exposed pregnancy was retained.’

Matching with replacement does mean that the same unexposed pregnancy may be matched to different exposed pregnancies (and hence included in different matched sets), however our use of conditional logistic regression – which analyses matched sets containing exposed and unexposed pregnancies with discordant outcome status – deals with this hence no additional adjustment is required.

Matching with replacement may lead to some reduction in statistical efficiency, however as our number of unexposed pregnancies was much higher than the number of exposed pregnancies (10:1 matching ratio), this would not be expected to have any meaningful impact on our results (please see doi: [10.37737/ace.22005](https://doi.org/10.37737/ace.22005)).

Reviewer #2 (Remarks to the Author):

I would like to sincerely thank you for your thorough and thoughtful review of our manuscript. Your insightful comments and suggestions have significantly contributed to enhancing the quality of our work. I am pleased to see that all the points I raised have been effectively addressed. The revised version is much stronger, and I now consider it ready for publication.

Thank you once again for your valuable collaboration and dedication to maintaining the excellence of our research.

We are grateful for your generous feedback regarding our revised manuscript. Your review and insightful suggestions were instrumental in refining our work, and we appreciate the time and care you invested throughout the process. It is especially encouraging to hear that the revisions have strengthened the manuscript and that all concerns have been satisfactorily addressed. Thank you very much.