PEER REVIEW HISTORY

This paper was submitted to a another journal from BMJ but declined for publication following peer review. The authors addressed the reviewers' comments and submitted the revised paper to BMJ Open. The paper was subsequently accepted for publication at BMJ Open.

ARTICLE DETAILS

TITLE (PROVISIONAL)	Risk of early neurodevelopmental outcomes associated with prenatal exposure to the antiepileptic drugs most commonly used during pregnancy: a French nationwide population-based cohort study
AUTHORS	Blotière, Pierre-Olivier; Miranda, Sara; Weill, Alain; Mikaeloff, Yann; Peyre, Hugo; Ramus, Franck; MAHMOUD, ZUREIK; Coste, Joël; DRAY-SPIRA, ROSEMARY

VERSION 1 – REVIEW

REVIEWER	Bromley, Rebecca University of Manchester, Institute of Human Development
REVIEW RETURNED	15-Aug-2019

GENERAL COMMENTS	Thank for you allowing me to review this manuscript. Dr Blotière and colleagues have undertaken a population based cohort study using a number of French national databases. They include large numbers of antiepileptic drugs exposed children and investigate outcomes contained in the given databases. The most interesting part of this paper is the number of children they have exposed to 'newer' AEDs. I would suggest that the focus of this paper is reconfigured somewhat to focus on the more novel results from the study. The authors give the most wording to the results for valproate, a drug with known impact on brain development and functioning, however their data on pregabalin and other newer drugs are unique. To date no study has investigated children exposed to pregablin, oxcarbazepine or topiramate to this extent. Whilst I understand that the authors have written this highlighting the increased incidence of disorders associated with valproate, the fact that there is no association between some of the newer drugs and the measured neurodevelopmental outcomes is unique and important information. I feel that altering the focus will make this a better paper and be more useful to readers. In this context a nil result is important. Providing information with regards to medications without an association of risk to the developing fetus allows women and neurologists to make their treatment decisions with confidence. Providing more and complete information on the other drugs in the text will help readers understand these results more. Therefore I suggest that the focus of this paper (abstract,

	results, discussion) should give more room the more novel results, even though an effect is not seen. Whilst population datasets contain large numbers of children they are often limited in terms of aspects of the outcome measures. In this case I have concern about the ages of the children. Given the pattern of AED utilization over the years there will inevitably be an older mean age for the valproate and carbamazepine groups in comparison to the more recent drugs. Whilst the hazard ratio takes into consideration the time to the event if the majority of the specific AED group is too young for many to be diagnosed with autism or referred to speech and language therapy this may lead to a false conclusion. I am unable to find any information in the paper or tables about the minimum, maximum and mean age of children in each of the specific AED groups. This is information should be included and comment on this should be made in the discussion by the authors as to whether the age of the newer AED groups could influence the lack of association reported. The paper is well written and the information clearly presented. I have provided a number of specific comments below: Abstract: - See general comment about making the newer AEDs the central report here. - Reporting of the absolute risks would be useful for doctors and patients to help them understand the risks. Introduction: - Page 5 line 6: please add….. '(AEDs)' after antiepileptic drugs as this abbreviation is then used throughout. - Page 5 line 35: please provide the references for lamotrigine. There are also studies however that find an association with lamotrigine and neurodevelopmental outcome and these should be discussed also. - Information on the other drugs looked at such as oxcarbazepine, pregabalin etc should also included. Methods: - Page 7 lines 19-21: I think directing the reader to figure 1 here would be helpful. - Page 8 lines 13-14: please explain to the reader what you mean by '…..the number of days covered' as it is not clear to me. - Page 8 lines 39-44: As noted above, please refer here or in the results to the ages of the specific AED exposed children. - Page 8 lines 26-33: Please provide information on how and why these outcomes were selected. - Page 9 lines 14-15: Please provide a little information as to how the proxies for alcohol and nicotine were calculated – for example on what information they are based. This will help the reader to understand this without having to look up the additional reference paper. Given that nicotine and alcohol are neurobehavioural teratogens this is important information. Results: - As noted above, making the central narrative here the newer AEDs rather than valproate will increase the novelty of this paper.

	- Page 12 line 11-35. What about the dose effects of the other drugs? This is important information we do not yet have – even for lamotrigine fully. Discussion: - Page 12: line 57: This currently states that there was no association between carbamazepine exposure and outcome but in the results it notes that children exposed to this AED were less likely to require a referral to speech and language therapy when the analysis was restricted to the epilepsy group only. Please comment on this. Is this a chance finding, given that this has not bee observed in psychometric studies with detailed language assessments? - Page 14 lines 12-30. The fact that this study only included monotherapy and no siblings could be added as additional strengths. - Page 14 lines 36+: The selection of outcomes should be discussed, it is presumed that this was a top-down selection whereby the availability of outcome determined their inclusion, rather than theory dictating the outcomes selected. It should also be noted that the diagnoses included here are likely the tip of the iceberg with many children not reaching diagnostic thresholds can still have extensive difficulty. Comment on tis would be useful for the readers. Further, only a subsection of neurodevelopmental outcomes are included here and this should be reflected in the conclusions. - Page 15 lines 54+: As noted above, the age of each of the specific groups needs discussion as it is likely to differ across the groups and this may require comment. The reference to the average age of diagnosis of autism at 4 years of age is from an American paper and it would be more worthwhile for the reader to understand the average age of diagnosis in France for each of the outcomes. Tables: The tables are clear and information and compliment the text.

REVIEWER	Leung, Howan The Chinese University of Hong Kong, Medicine & Therapeutics
REVIEW RETURNED	22-Aug-2019

GENERAL COMMENTS	This study examines the exposure of monotherapy (antiepileptic drugs) in a large number of pregnant women and concludes that valproate leads to an increased risk of neurodevelopmental disorder. The results are not new but some newer monotherapies have been included. 1. children with brain malformation at birth were excluded. This may possibly give a favourable picture for drugs which are more likely to cause serious physical malformations. 2. Limitation to first birth only may also lead to the confounding of a younger maternal age. 3. Understandably monotherapy is used most of the time for women of childbearing age. Some previous results such as the increased risk with polytherapy cannot be brought out in this study with such a good study population.

	4. In the outcomes, (1) and (2) are the same. For (3), one may argue if a visit to speech therapists necessarily imply pathology. A screening method based on such visits may be reasonable but using that as outcome may be subject to argument. 5. A comparison arm with a normal reference group may be arguably better than a lamotrigine group. Researchers may be interested to know, based on this large scale study, whether LEV, TPM or GBP may possibly increase the risk of neurodevelopmental disorders 6. In the method section, the authors said that SSRI and other psychiatric drugs have been recorded. Any adjustment in the final results needed. Did SSRI/ psychiatric drugs also increase the risk of neurodevelopmental disorders? The use of psychiatric drugs appears to be not uniform across the different AED groups. 7. Any other AEDs explored in this cohort e.g. lacosamide? (N03AX18) 8. The use of folic acid is not uniform across all the AEDs. LTG and LEV have the highest rate of folic use. Very low for PGB. Any implication on this?

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Comments to the Author

Thank for you allowing me to review this manuscript.

Dr Blotière and colleagues have undertaken a population based cohort study using a number of French national databases. They include large numbers of antiepileptic drugs exposed children and investigate outcomes contained in the given databases. The most interesting part of this paper is the number of children they have exposed to 'newer' AEDs. I would suggest that the focus of this paper is reconfigured somewhat to focus on the more novel results from the study. The authors give the most wording to the results for valproate, a drug with known impact on brain development and functioning, however their data on pregabalin and other newer drugs are unique. To date no study has investigated children exposed to pregablin, oxcarbazepine or topiramate to this extent. Whilst I understand that the authors have written this highlighting the increased incidence of disorders associated with valproate, the fact that there is no association between some of the newer drugs and the measured neurodevelopmental outcomes is unique and important information. I feel that altering the focus will make this a better paper and be more useful to readers. In this context a nil result is important. Providing information with regards to medications without an association of risk to the developing fetus allows women and neurologists to make their treatment decisions with confidence. Providing more and complete information on the other drugs in the text will help readers understand these results more. Therefore I suggest that the focus of this paper (abstract, results, discussion) should give more room the more novel results, even though an effect is not seen.

We thank the reviewer for this comment and have modified the abstract, the "Results" section and the "Discussion" section accordingly (see answers to comments 1 and 11 for more details).

Whilst population datasets contain large numbers of children they are often limited in terms of aspects of the outcome measures. In this case I have concern about the ages of the children. Given the pattern of AED utilization over the years there will inevitably be an older mean age for the valproate and carbamazepine groups in comparison to the more recent drugs. Whilst the hazard ratio takes into consideration the time to the event if the majority of the specific AED group is too young for many to be diagnosed with autism or referred to speech and language therapy this may lead to a false conclusion. I am unable to find any information in the paper or tables about the minimum, maximum and mean age of children in each of the specific AED groups. This is information should be included and comment on this should be made in the discussion by the authors as to whether the age of the newer AED groups could influence the lack of association reported.

We thank the reviewer for this comment and have provided additional information in the “Results” and “Discussion” sections (see answers to comments 8 and 16 for more details).

The paper is well written and the information clearly presented.

I have provided a number of specific comments below:

Abstract:

1- See general comment about making the newer AEDs the central report here.

The abstract has been modified in order to focus on the more novel results from the study.

The last sentence of the “Results” part of the abstract “No other AEDs were associated with increased risks of neurodevelopmental outcomes.” (page 4 line 21) has been moved and rephrased: “None of these AEDs, except VPA, were associated with an increased risk of any of the four neurodevelopmental outcomes investigated.” (page 4 line 17).

The “Conclusion” part of the abstract has also been completely rephrased (page 5 line 1): “*No increased risk of any of the neurodevelopmental outcomes investigated in this study was observed with prenatal exposure to levetiracetam, pregabalin, oxcarbazepine, topiramate, gabapentin, clonazepam or carbamazepine, compared to lamotrigine. However, this study corroborates the well-known association between maternal use of VPA during pregnancy and the risk of neurodevelopmental disorders in the offspring. Longer follow-up is necessary to confirm these findings.*”

2- Reporting of the absolute risks would be useful for doctors and patients to help them understand the risks.

As only early neurodevelopmental disorders could have been identified, reporting absolute risks could give a more favourable picture of the risk associated with AED exposure during pregnancy than they actually are when assessed during a longer follow-up period. We therefore preferred not to report absolute risks in the abstract.

Introduction:

3- Page 5 line 6: please add….. ‘(AEDs)’ after antiepileptic drugs as this abbreviation is then used throughout.

We agree and this has been modified both in the abstract and in the introduction. The abbreviation “AEDs” has been replaced by the words “antiepileptic drugs (AEDs)” in the abstract (page 4 line 3)

and the abbreviation “AEDs” has been added after the words “Antiepileptic drugs” in the introduction (page 6 line 2).

4- Page 5 line 35: please provide the references for lamotrigine. There are also studies however that find an association with lamotrigine and neurodevelopmental outcome and these should be discussed also.

A reference has been provided for lamotrigine in the introduction (page 6 line 14). However, we had already mentioned in the “Comparison with Previous Studies” part of the “Discussion” section the studies finding an association between lamotrigine and neurodevelopmental outcomes, but this has now been developed. The sentence “*Only three studies have shown that children prenatally exposed to lamotrigine had very specific impaired outcomes compared to unexposed children.[18–20]*” has been replaced by: “*Only three studies have shown that prenatal exposure to lamotrigine was associated with impaired specific cognitive skills[19,20] and parental concerns about autistic traits and sentence skills.[21]*” (page 15 line 3).

5- Information on the other drugs looked at such as oxcarbazepine, pregabalin etc should also included.

Additional information on the other drugs has been included in the introduction: the sentence “*Discordant but mainly reassuring data have been published for carbamazepine, while evidence for the other AEDs remains limited.[6]*” has been replaced by “*Discordant but mainly reassuring data have been published for carbamazepine, while evidence for levetiracetam and topiramate remains limited and almost no information is available concerning the other AEDs, particularly clonazepam, oxcarbazepine, gabapentin and pregabalin.[6]”* (page 6 line 15).

However, we had already provided detailed information and references regarding the association between exposure to levetiracetam, topiramate, clonazepam, oxcarbazepine, gabapentin or pregabalin and the risk of neurodevelopmental outcomes in the “Comparison with Previous Studies” part of the “Discussion” section (page 15 line 17 to page 16 line 2).

Methods:

6- Page 7 lines 19-21: I think directing the reader to figure 1 here would be helpful.

We agree and a reference to Figure 1 has been added: the sentence *“These exclusion criteria are reported in the study population flowchart (Figure 1).”* has been included at the end of the “Study population” part of the “Methods” section (page 8 line 15).

7- Page 8 lines 13-14: please explain to the reader what you mean by ‘…..the number of days covered’ as it is not clear to me.

The definition of the “*number of days covered*” has been added at the end of the “Exposure” part of the “Methods” section (page 9 line 13): “*The number of days covered was defined as the sum of the 30-day periods of exposure corresponding to each refill minus the number of days of overlap between two consecutive refills. Only the days overlapping with the pregnancy period were taken into account”.*

8- Page 8 lines 39-44: As noted above, please refer here or in the results to the ages of the specific AED exposed children.

Information about length of follow-up, which is equal to the age at the end of follow-up because children were followed from birth, has been added in the manuscript. Median follow-up and interquartile range have been reported in table 1 for all AEDs (pages 26 and 27) and the following sentence has been added to the first paragraph of the “Main analysis” part of the “Results” section

(page 12 line 12): "*The median follow-up ranged from 3.3 to 4.0 years across all AEDs except clonazepam (4.8 years)*".

9- Page 8 lines 26-33: Please provide information on how and why these outcomes were selected.

We agree with this comment and have added the sentence "*based on the literature but also on their availability in the French health care databases*" to the "Outcomes" part of the "Methods" section (page 9 line 18).

We wrote in the original manuscript in the "Outcomes" part of the "Methods" section (page 9 line 19) that the outcomes were selected by using ICD-10 diagnosis codes corresponding to hospitalizations or long-term diseases (LTD), and that the outcome "visits to a speech therapist" was selected as a proxy for communication-related disorders.

10- Page 9 lines 14-15: Please provide a little information as to how the proxies for alcohol and nicotine were calculated – for example on what information they are based. This will help the reader to understand this without having to look up the additional reference paper. Given that nicotine and alcohol are neurobehavioural teratogens this is important information.

We agree and have added additional information related to the definition of the proxies for alcohol intake and smoking to the "Covariates" part of the "Methods" section (page 10 line 16): *"These proxies were constructed on the basis of hospital discharge diagnoses, LTD diagnoses and the child's hospital discharge diagnoses at birth. We also used specific drug reimbursements for alcohol intake and nicotine replacement therapy reimbursements for smoking."*

Consequently, we also explained in the "Covariates" part of the "Methods" section (page 10 line 13), how the covariate "history of mental and behavioral disorders not related to alcohol or smoking" was defined by adding the words "*which was identified by using hospital discharge and LTD diagnoses*".

Results:

11- As noted above, making the central narrative here the newer AEDs rather than valproate will increase the novelty of this paper.

We thank the reviewer for this comment and we agree. The last paragraph of the "Main analysis" part of the "Results" section (page 12 line 21) has therefore been modified in order to focus on the more novel results from the study: *"Table 2 presents the number of events, crude event rates, IRRs and adjusted HRs for the four outcomes and each of the AEDs studied. Compared to prenatal exposure to lamotrigine, prenatal exposures to all of the AEDs studied, excluding valproic acid, were not found to be associated with an increased risk of any of the four outcomes investigated. By contrast, valproic acid was associated with an increased risk of visits to a speech therapist (HR=1.5[1.1-1.9]) and neurodevelopmental disorders (HR=2.7[1.8-4.0]), particularly pervasive developmental disorders (HR=4.4[2.1-9.3]) and mental retardation (HR=3.1[1.5-6.2])."*

The last two sentences of the first paragraph of the "Sensitivity analyses" part of the "Results" section (page 13 line 11) has also been modified accordingly: "*Prenatal exposure to levetiracetam was not found to be associated with any of the four outcomes investigated and prenatal exposure to valproic acid was associated with all four outcomes, which is in line with the results of the main analysis. Results were different from the main analysis for the association between carbamazepine and the risk of visits to a speech therapist (HR=0.2[0.1-0.7]) (Table 3)."*

The sentence "*Prenatal exposures to carbamazepine, levetiracetam, pregabalin, oxcarbazepine and topiramate were not associated with an increased risk of any of the neurodevelopmental outcomes*

investigated compared to lamotrigine" has been modified and moved to the beginning of the "Main Findings" part of the "Discussion" section (page 14 line 10): *"[…] prenatal exposures to levetiracetam, pregabalin, oxcarbazepine, topiramate, gabapentin, clonazepam and carbamazepine were not associated with an increased risk of any of the early neurodevelopmental outcomes investigated compared to lamotrigine*".

12- Page 12 line 11-35. What about the dose effects of the other drugs? This is important information we do not yet have – even for lamotrigine fully.

Unfortunately, we could not study the dose-response relationship for the other AEDs for 2 reasons. The main reason is an insufficient number of cases: for instance, for the main outcome "Neurodevelopmental disorders" (F70 to F98), the number of cases per tertiles of mean daily doses was most of the time below 3 (levetiracetam, gabapentin, oxcarbazepine, topiramate...). The second reason was the impossibility to find groups sufficiently different from each other in terms of mean daily doses and with a sufficient number of exposed women: for instance, the interquartile range was 0.2 mg for mean daily doses of clonazepam.

We were also not able to study the dose-response relationship for lamotrigine because women exposed to lamotrigine were chosen as the reference group.

Discussion:

13- Page 12: line 57: This currently states that there was no association between carbamazepine exposure and outcome but in the results it notes that children exposed to this AED were less likely to require a referral to speech and language therapy when the analysis was restricted to the epilepsy group only. Please comment on this. Is this a chance finding, given that this has not been observed in psychometric studies with detailed language assessments?

We wrote that "*prenatal exposures to carbamazepine, levetiracetam, pregabalin, oxcarbazepine and topiramate were not associated with an increased risk of any of the early neurodevelopmental outcomes investigated compared to lamotrigine"* because none of these AEDs were found to increase the risk of any of the neurodevelopmental outcomes investigated, in any of the analyses of our study.

However, we agree that carbamazepine was associated with a decreased risk of visits to a speech therapist when the population was restricted to women with epilepsy, and that this should be discussed in the "Discussion" section. For greater clarity, the following sentences have therefore been added to the "Main Findings" part of the "Discussion" section (page 14 line 13): *"The decreased risk of visits to a speech therapist observed with carbamazepine when the population was restricted to women with epilepsy may be a chance finding. This association is based on only 4 children and has never been observed in psychometric studies with detailed language assessments."*

14- Page 14 lines 12-30. The fact that this study only included monotherapy and no siblings could be added as additional strengths.

We thank the reviewer for this comment.

15- Page 14 lines 36+: The selection of outcomes should be discussed, it is presumed that this was a top-down selection whereby the availability of outcome determined their inclusion, rather than theory dictating the outcomes selected.

An answer to this comment has been provided above (see comment 9).

It should also be noted that the diagnoses included here are likely the tip of the iceberg with many children not reaching diagnostic thresholds can still have extensive difficulty. Comment on this would be useful for the readers.

We fully agree with this limitation. We have therefore added the following sentence to the “Limitations” part of the “Discussion” section (page 17 line 16), as well as a corresponding reference: “*In addition, as hospital discharge and LTD diagnoses were used to define outcomes, children not reaching diagnostic thresholds but still having some evidence of impairment were not considered to have experienced the outcomes of interest.[40]”*

40 Thapar A, Cooper M, Rutter M. Neurodevelopmental disorders. Lancet Psychiatry 2017;4:339–46. doi:10.1016/S2215-0366(16)30376-5

Further, only a subsection of neurodevelopmental outcomes are included here and this should be reflected in the conclusions.

We also agree. This limitation has been added to the “Limitations” part of the “Discussion” section (page 17 line 25): “*Further, because the study outcomes were limited to three subtypes of neurodevelopmental disorders (pervasive developmental disorders, mental retardation and visits to a speech therapist as a proxy for communication-related disorders), no conclusion can be drawn concerning all of the other subtypes of neurodevelopmental disorders*.”

16- Page 15 lines 54+: As noted above, the age of each of the specific groups needs discussion as it is likely to differ across the groups and this may require comment.

The age observed at the end of follow-up in each of the specific groups has now been discussed. The following sentences and a new reference have been added to the “Limitations” part of the “Discussion” section (page 18 line 13): “*Except clonazepam for which French health authorities took measures to limit off-label use in November 2011,[45] lengths of follow-up were quite comparable across all AEDs. Children exposed to second-generation AEDs had only slightly shorter follow-ups than children exposed to first-generation AEDs, which should not have influenced the results of this study*”.

45 Agence nationale de sécurité du médicament et des produits de santé (ANSM). Clonazepam: modification of the conditions of prescription or dispensing [Rivotril® (clonazépam) : Modification des conditions de prescription et de délivrance]. 2011.https://ansm.sante.fr/S-informer/Points-d-information-Points-d-information/Rivotril-R-clonazepam-Modification-des-conditions-de-prescription-et-de-delivrance-Point-d-information (accessed 23 Apr 2019).

The reference to the average age of diagnosis of autism at 4 years of age is from an American paper and it would be more worthwhile for the reader to understand the average age of diagnosis in France for each of the outcomes.

The reference to the average age of diagnosis of autism has been replaced by a reference from the French “Third Autism Plan” in the “Limitations” part of the “Discussion” section (page 18 line 6): *“a diagnosis of autism spectrum disorders […] is made at an average age of 3 years and 5 months in France,[43]”.*

43 Third Autism Plan [Troisième Plan Autisme] (2013-2017). https://www.cnsa.fr/documentation/plan-autisme2013.pdf

A reference regarding the management of mental retardation in France has also been added as follows: *“This is especially true for mental retardation: although severe and profound mental retardation can be diagnosed before 3 years old, moderate mental retardation cannot be diagnosed before 4 or 5 years old.[44]”* (page 18 line 9).

44 French National Institute for Health and Medical Research (INSERM). Synthesis of the collective experience “Intellectual disabilities” [Synthèse de l’expertise collective “Déficiences intellectuelles”] (2016). https://www.inserm.fr/information-en-sante/expertises-collectives/deficiences-intellectuelles

Tables:

The tables are clear and information and compliment the text.

Reviewer: 2

Comments to the Author

This study examines the exposure of monotherapy (antiepileptic drugs) in a large number of pregnant women and concludes that valproate leads to an increased risk of neurodevelopmental disorder. The results are not new but some newer monotherapies have been included.

1. children with brain malformation at birth were excluded. This may possibly give a favourable picture for drugs which are more likely to cause serious physical malformations.

We agree that excluding children with brain malformation may result in a lower increased risk of neurodevelopmental disorders for drugs which are more likely to cause brain malformation, such as valproic acid. However, our objective was to study the association between prenatal exposure to AEDs and the risk of neurodevelopmental disorders *per se*. We therefore did not want to take into account neurodevelopmental disorders caused by a brain malformation. We investigated the risk of major congenital malformations separately in another study (Blotière 2019).

Blotière P-O, Raguideau F, Weill A, et al. Risks of 23 specific malformations associated with prenatal exposure to ten antiepileptic drugs. Neurology. 2019.

2. Limitation to first birth only may also lead to the confounding of a younger maternal age.

Maternal age was controlled for in the analyses as it was included in the propensity score model. Confounding by maternal age should therefore be limited.

3. Understandably monotherapy is used most of the time for women of childbearing age. Some previous results such as the increased risk with polytherapy cannot be brought out in this study with such a good study population.

We were not able to study polytherapy in our study due to small numbers of women exposed to polytherapy, especially for individual polytherapy combinations. In addition, data now suggest that polytherapy containing valproic acid, rather than polytherapy *per se*, is associated with poorer neurodevelopmental outcomes (Bromley 2017).

Bromley RL, Baker GA. Fetal antiepileptic drug exposure and cognitive outcomes. Seizure 2017;44:225–31. doi:10.1016/j.seizure.2016.10.006

4. In the outcomes, (1) and (2) are the same. For (3), one may argue if a visit to speech therapists necessarily imply pathology. A screening method based on such visits may be reasonable but using that as outcome may be subject to argument.

We reported in the “Outcome” part of the “Methods” section (page 9 line 21) that the outcomes “*pervasive developmental disorders (F84)”* and “*mental retardation (F70-F79)”* were included in the first outcome “*hospitalization or LTD for neurodevelopmental disorders defined by ICD-10 diagnosis codes F70 to F98*”, but they are not the same. For greater clarity, the sentence *“(1) hospitalization or LTD for neurodevelopmental disorders defined by ICD-10 diagnosis codes F70 to F98; (2) two specific subcategories: pervasive developmental disorders (F84) and mental retardation (F70-F79);”* has been replaced by “*The primary outcomes were hospitalization or LTD for neurodevelopmental disorders (ICD-10 diagnosis codes F70 to F98), but also for two specific subcategories: pervasive developmental disorders (F84) and mental retardation (F70-F79).”* in the “Outcome” part of the “Methods” section (page 9 line 19).

In addition, we fully agree that a visit to a speech therapist does not necessarily imply pathology, even if the outcome “visits to a speech therapist” consists only of treatments performed after speech-language assessment. We have therefore decided to consider the outcome “visits to a speech therapist” as a secondary outcome and comment on this in the “Discussion” section:

- The “Outcome” part of the “Methods” section (page 9 line 22) has been modified accordingly. The sentence *“(3) visits to a speech therapist as a proxy for communication-related disorders.”* has been replaced by “*The secondary outcome was “visits to a speech therapist”, as a proxy for communication-related disorders*”.
- The following words have also been added to the “Limitations” part of the “Discussion” section (page 17 line 22): *“a visit to a speech therapist does not necessarily imply pathology”*.

5. A comparison arm with a normal reference group may be arguably better than a lamotrigine group. Researchers may be interested to know, based on this large scale study, whether LEV, TPM or GBP may possibly increase the risk of neurodevelopmental disorders

We thank the reviewer for the comment and agree that knowing whether LEV, TPM or GBP may possibly increase the risk of neurodevelopmental disorders is a very interesting question.

However, information on the indication of reimbursed drugs is limited in the French health care databases whereas the different indications for AEDs are likely to be associated with increased risks of neurodevelopmental disorders (Thorup 2017, Arruda 2012, Higgins 2015, Shallcross 2014), which is of concern in a non-randomized setting such as this cohort study.

Besides, the differences in terms of indication between unexposed women and women exposed to AEDs can be illustrated by the vast differences in baseline covariates observed between these groups. For instance, prevalence of history of mental and behavioral disorders was four times higher in valproate-exposed women than in non-exposed women, and prevalences of both alcohol intake and history of antipsychotic use were seven times higher in valproate-exposed women than in non-exposed women.

By contrast, women exposed to the different AEDs were much more comparable to lamotrigine-exposed women than to unexposed women in terms of measured baseline covariates. For the same covariates as above, the differences in prevalence between valproate-exposed women and lamotrigine-exposed women were 83%, 23% and 37% respectively.

We therefore chose to use an active comparator group (lamotrigine-exposed women) to mitigate confounding by indication and other unmeasured patient characteristics. Although this reason has already been mentioned in the manuscript in the “Exposure” part of the “Methods” section, we have added the following reference to highlight this important methodological point (page 9 line 5):

16 Lund JL, Richardson DB, Stürmer T. The active comparator, new user study design in pharmacoepidemiology: historical foundations and contemporary application. Curr Epidemiol Rep 2015;2:221–8. doi:10.1007/s40471-015-0053-5

The other reasons which lead us to choose lamotrigine-exposed women as the reference group are, as written in the “Exposure” part of the “Methods” section (page 9 line 6):

- “*lamotrigine is the most commonly used AED in France for the treatment of epilepsy*”
- “*prenatal exposure to lamotrigine has been mostly shown to be associated with favorable neurodevelopmental outcomes*”
- and, more importantly, “*comparing all individual AEDs to lamotrigine addresses a clinically relevant question: which is the safest AED?”*

Thorup AAE, Laursen TM, Munk-Olsen T, et al. Incidence of child and adolescent mental disorders in children aged 0-17 with familial high risk for severe mental illness - A Danish register study. Schizophr Res 2017. doi:10.1016/j.schres.2017.11.009.

Arruda MA, Bigal ME. Migraine and behavior in children: influence of maternal headache frequency. J Headache Pain 2012; 13: 395–400. doi:10.1007/s10194-012-0441-x.

Higgins KS, Birnie KA, Chambers CT, et al. Offspring of parents with chronic pain: a systematic review and meta-analysis of pain, health, psychological, and family outcomes. Pain 2015; 156: 2256–2266. doi:10.1097/j.pain.0000000000000293.

Shallcross R, Bromley RL, Cheyne CP, et al. In utero exposure to levetiracetam vs valproate: development and language at 3 years of age. Neurology 2014; 82: 213–221. doi:10.1212/WNL.0000000000000030.

6. In the method section, the authors said that SSRI and other psychiatric drugs have been recorded. Any adjustment in the final results needed. Did SSRI/ psychiatric drugs also increase the risk of neurodevelopmental disorders? The use of psychiatric drugs appears to be not uniform across the different AED groups.

We mentioned in the “Statistical analyses” part of the “Methods” section (page 11 line 6) that “Exposure to SSRIs”, “exposure to antipsychotic drugs” and “the number of 5th level ATC classes of psychiatric medications”, among other covariates, were included in the propensity score (“*Propensity scores were determined by using logistic regression models including the covariates listed above […]*”). These three covariates have therefore been controlled for in the analyses.

In many studies, exposure to SSRIs during pregnancy was associated with neurodevelopmental disorders in the offspring, especially autism spectrum disorders, but this association may be explained by the underlying maternal psychiatric condition (Kobayashi 2016). Exposure to antipsychotic drugs and the number of 5th level ATC classes of psychiatric medications in the year before pregnancy were controlled for in our analyses as proxies for maternal psychiatric condition, together with history of mental and behavioral disorders, identified by hospital discharge and LTD diagnoses.

We agree that the use of these drugs is not uniform across the different AED groups. That is why these three covariates have been included in the propensity score and therefore controlled for in the analyses.

Kobayashi T, Matsuyama T, Takeuchi M, Ito S. Autism spectrum disorder and prenatal exposure to selective serotonin reuptake inhibitors: A systematic review and meta-analysis. Reprod Toxicol Elmsford N 2016; 65: 170–178. doi:10.1016/j.reprotox.2016.07.016.

7. Any other AEDs explored in this cohort e.g. lacosamide? (N03AX18)

All AEDs available in France were included in this study, but results were reported only for the AEDs most commonly used during pregnancy in monotherapy (lamotrigine, pregabalin, clonazepam, valproic acid, levetiracetam, carbamazepine, topiramate, gabapentin, and oxcarbazepine). The

association between the other AEDs and the selected outcomes could not have been studied because the number of women exposed to these AEDs was insufficient. For greater clarity, the sentence: *"[…] and 133 were exposed to another AED monotherapy (Table 1)*" has been replaced by: "*A total of 133 children were exposed to another AED monotherapy, including phenobarbital (N=84), phenytoin (N=13), lacosamide (N=9), zonisamide (N=8), ethosuximide (N=7) and vigabatrin (N=6)"* in the "Main analysis" part of the "Results" section (page 12 line 11).

8. The use of folic acid is not uniform across all the AEDs. LTG and LEV have the highest rate of folic use. Very low for PGB. Any implication on this?

We agree with this comment. Pre-conception folic acid supplementation differs across the different AED groups. However, this covariate was included in the propensity score and therefore controlled for in the analyses.

VERSION 2 – REVIEW

REVIEWER	Howan Leung The Chinese University of Hong Kong
REVIEW RETURNED	19-Nov-2019

GENERAL COMMENTS	The comments raised have been addressed.

REVIEWER	Rebecca Bromley University of Manchester
REVIEW RETURNED	21-Dec-2019

GENERAL COMMENTS	Thank you for the opportunity to review this revision of the manuscript by Blotière and colleagues. The authors have been very diligent in their response to my previous comments. In particular, the more central reporting of the newer antiepileptic drugs makes this paper appealing to those making treatment decisions with women requiring treatment. I have just two additional comments which have arisen from Blotière's revision of the manuscript. Page 14, Section: Main findings. In the revision the authors write …'and have never been observed in psychometric studies with detailed language assessments.'. Poorer verbal skills were seen in the study by Baker et al 2015 (Neurology 2015 84:382–390) Page 15, Section: Comparison to other studies. The authors incorrectly cite that Bromley and colleagues 2010 (Epilepsia 51(10):2058–2065, 2010) an association with LTG exposure and specific neurodevelopmental outcomes. In fact, this study finds no such association once confounders are adjusted for. Once this two very minor points have been addressed I would happily recommend that this manuscript be accepted in BMJ Open and feel that it would make an important contribution to the area.

VERSION 2 – AUTHOR RESPONSE

Reviewer: 2

Thank you for the opportunity to review this revision of the manuscript by Blotière and colleagues.

The authors have been very diligent in their response to my previous comments. In particular, the more central reporting of the newer antiepileptic drugs makes this paper appealing to those making treatment decisions with women requiring treatment.

I have just two additional comments which have arisen from Blotière's revision of the manuscript.

Page 14, Section: Main findings. In the revision the authors write …'and have never been observed in psychometric studies with detailed language assessments.'. Poorer verbal skills were seen in the study by Baker et al 2015 (Neurology 2015 84:382–390)

The sentence "This association is based on only 4 children and has never been observed in psychometric studies with detailed language assessments." has been replaced by: "This association is based on only 4 children and carbamazepine was associated with reduced verbal abilities in one study.[19]" in the "Main Findings" part of the "Discussion" section (page 15 line 15).

Page 15, Section: Comparison to other studies. The authors incorrectly cite that Bromley and colleagues 2010 (Epilepsia 51(10):2058–2065, 2010) an association with LTG exposure and specific neurodevelopmental outcomes. In fact, this study finds no such association once confounders are adjusted for.

The reference concerning this paper has been removed and the words "Only three studies" have been replaced by "Only two studies" in the first paragraph of the "Comparison with Previous Studies" part of the "Discussion" section (page 16 line 3).

VERSION 3 – REVIEW

REVIEWER	Rebecca Bromley University of Manchester
REVIEW RETURNED	25-Feb-2020

GENERAL COMMENTS	Congratulations to the authors on a very interesting paper.