PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based cohort study of first pregnancies in Norway
AUTHORS	Danielsson, Kim; Borthen, Ingrid; Morken, Nils-Halvdan; Gilhus, Nils

VERSION 1 – REVIEW

REVIEWER	M.F. van Oostwaard IJsselland Ziekenhuis, The Netherlands
REVIEW RETURNED	24-Dec-2017

GENERAL COMMENTS	Review Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based study of first pregnancies Subject This article describes a registry based study on the risk for hypertensive disorders of pregnancy in women with epilepsy, with or without antiepileptic medication, compared to women without epilepsy in their first pregnancy. The authors were able to link different national registries to obtain information on antiepileptic drugs in pregnancy. Originality This study is original in the fact that it addresses the different types of hypertensive syndrome and specific antiepileptic drug used. Clinical applicability: If epilepsy or it's therapy predisposes women to hypertensive disorders of pregnancy, we could council them accordingly and create a close-monitoring setting for these women.

	Overall: This is a well performed original, well numbered and contemporary study, but it's reporting and it's English needs work. Specific remarks: Introduction Page 4 – introduction section. I would like to see a little bit information on the different working-mechanisms of antiepileptic drugs and their relation to hypertensive disorders in recent literature. Materials and Methods Page 6 Line 53- page 7 line 5: *Information about AED use in pregnancy is also recorded in MBRN on the notification form in an available blank space for written text. This information was used to validate the AED use obtained from MBRN compared to NorPD.* – Blank spaces in registries are not usually reliable. I would like to know how often the authors could validate AED in the MBRN? Page 7, line 33-35 *The epilepsy diagnosis in MBRN has previously been found to be valid in 92.3 % of cases.* – So 7.7% was incorrect. Page 7 line 7-15 For a registry based study, much detail was available on possible confounders for hypertensive disorders of pregnancy: maternal age, educational level, chronic disease (kidney disease, hypertension, diabetes mellitus), multifetal pregnancies, BMI, smoking during pregnancy. This is a major asset in the current study. Results Page 9, line 24-29 *When WWE were subcategorized into WWE with AED and WWE without AED, none of the two* *subgroups differed significantly from women without epilepsy for any hypertensive disorder.* It took me a while to understand this sentence. I suggest something like: The occurrence of hypertensive disorders did not differ significantly between … Otherwise I would think this sentence was about baseline characteristics. Page 9, line 44-46:

	Sensitivity analyses. What sensitivity analysis? This was not anticipated in the methods section. Page 10, line 13 and 18: *modify*: I suggest to use something like: 'withdraw' or 'the association disappears' Page 10, line 22: VPA: this abbreviation has not yet been explained in the text, please write: Valproate (VPA). Line 46 NorPD same remark. Page 10, line 44 – page 11, line 6: *To validate the AED data in MBRN, …* Data handling or interpretation should be in the methods section. Or at least before outcome. Discussion Page 12, line 5-7: *We found an increased risk of mild preeclampsia in WWE and the hypertensive complications in WWE consisted mostly of cases with mild preeclampsia.* I would not formulate this conclusion so complex. Confine this conclusion to: '*We found an increased risk of mild preeclampsia in WWE.'* Page 12, line 20-42: *The present study shows that most WWE, and in particular when treated with the new AEDs, do not have additional risks of hypertensive complications.* This paragraph has a bit too much detail for a summary of the main results. Page 12, line 7: *The specified newer AEDs.* I am not a neurologist and am unfamiliar with which AED's are 'newer'. What classifies them as new and what are their characteristics? Was it anticipated that they predisposed to hypertensive disorders? Why? – please elaborate in the Introduction section. Page 12, line 9-12: *WWE on valproate monotherapy was significantly associated with mild preeclampsia, in contrast to other AEDs.* "But this association was absent in BMI>30." Am I correct? Page 12, line 26/27: *Relevant chronic diseases*. Since smoking is not a chronic disease I would suggest 'cardiovascular risk factors' Page 13 Line 36-38: *Potential AED effects on the child are highly important for deciding optimal treatment for WWE.* Redundant information. Page 13, line 42-47: *We found an increased risk of early onset preeclampsia in WWE on levetiracetam, but this should be interpreted with caution ….* Not

	mentioned in the text in the results section, only in table 3. All significant relations between AED and outcome dissolve in the sensitivity analysis. The discussion section may be better to read with less detail. (or elaborate a little on AED in the results section) Page 15, line 15,16: *Preeclampsia shows a decreasing prevalence over time.* Very strong statement and conclusions for the interpretation in the current study. I would be very careful with this. The study referred to shows an overall increase in the prevalence of preeclampsia, with a sudden increase from 1999 forward due to changes in the registration form. In the few years after, the numbers go down a little, but still higher than before 1999. Severe preeclampsia may occur less often due to more aggressive treatment and induction of labor, but this could also be a registration bias. Conclusion Page 17, line 7: *MAJOR clinical importance*? I'll agree to it's clinical importance, but overall WWE comprised 0,79% of the total population and the risk for mild PE was only slightly elevated: RR 1,4 (1,8 in sensitivity analysis). Page 17, line 16-20: *Our study shows that the increased risk does not include most WWE and especially not WWE on modern AEDs, nor does it include severe hypertensive complications.* I don't understand. Does the increased risk not *apply* to WWE? Even at increased risk, fortunately *most* WWE do not develop preeclampsia or other hypertensive disorders.

REVIEWER	John Allotey Queen Mary University of London. United Kingdom
REVIEW RETURNED	12-Jan-2018

GENERAL COMMENTS	The study does not appear to have been prospectively registered on a trial database such as ISRCTN or clinicaltrials.gov, which is recommended to increase transparency in the conduct of trials and studies. Nevertheless, this represents a well-conducted and written study. The methods are well described and the use of a large registry database in combination with data linkage is commended. The authors have worked hard to separate the often-grouped outcome of hypertensive disorder, and estimate the risk of these in women with epilepsy. They have concluded mainly that even though mild pre-eclampsia is increased in women with epilepsy compared to those without, it is not associated with increased maternal or fetal morbidity or mortality in pregnancy and this increased risk can be partly mediated by modifiable external risk factors and comorbidities. This reviewer questions this conclusion, as evidence suggests that pre-eclampsia is a dynamic disease and progresses at different rates for different women. As such, classification as mild pre-eclampsia may be unhelpful for management and the temporal based definitions of pre-eclampsia as early or late more useful. This is because women with diagnosis of pre-eclampsia <34 have up to 20 times higher maternal mortality and morbidity than the late onset disease. Therefore, women with the authors outcome of mild pre-

	eclampsia at <34 weeks are at increased risk of complications than those at >34 weeks pregnancy. Materials and methods, page 5, line 40. In categorising the individual outcomes, is it possible that on the MBRN databases, multiple checkboxes are ticked? If so, how did the authors decide which outcome variable would be prioritized in the analysis for that woman? Consequently, severe pre-eclampsia is a compound variable on its own, with raised blood pressure, early onset pre-eclampsia, eclampsia or HELLP syndrome as definitions of the diagnosis. Do the authors think that this may have an effect on the prevalence of the component outcomes individually reported and as such on the relationship under investigation? Similarly for mild pre-eclampsia and severe pre-eclampsia that occurred at <34 weeks. Did the authors classify these as early onset pre-eclampsia or mild/severe pre-eclampsia? Discussion, page 12 The differences in statistical findings across women without epilepsy vs WWE, WWE without AED, WWE with AED and WWE with polytherapy, may be due to differences in sample sizes across these comparisons. The authors may want to include this point in the discussion.

VERSION 1 – AUTHOR RESPONSE

Editor's comments

- *Please revise the title of your manuscript to include the word 'cohort', as well as the country.*
  Response:

  We have added the word "cohort" and the country in the title. The title now reads: Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population based cohort study of first pregnancies in Norway.

Reviewer 1:

- *Page 4 – introduction section. I would like to see a little bit information on the different working mechanisms of antiepileptic drugs and their relation to hypertensive disorders in recent literature*.
  Response:

  We have added information from previous studies on specific AEDs and possible associations to hypertensive disorders in WWE (page 4, line 18–24 and page 5, line 1-2). There are no studies on working mechanisms for hypertensive complications for the specific AEDs in WWE.

- *Page 6, line 53- page 7 line 5:*
  "Information about AED use in pregnancy is also recorded in MBRN on the notification form in an available blank space for written text. This information was used to validate the AED use

obtained from MBRN compared to NorPD." - Blank spaces in registers are not usually reliable. I would like to know how often the authors could validate AED in the MBRN?

Response:

We agree with the reviewer that blank spaces are unreliable. The actual information has been removed from the results section and added to the methods (page 8, line 5-8).

- *Page 7, line 33-35*
  "The epilepsy diagnosis in MBRN has previously been found to be valid in 92.3 % of cases." – So 7.7 % was incorrect.

  Response:

  Yes, 7.7 % of registered epilepsy in MBRN was not confirmed in hospital medical records. This is now specified in the manuscript.

- *Page 7, line 7-15*
  For a registry based study, much detail was available on possible confounders for hypertensive disorders of pregnancy: maternal age, educational level, chronic diseases (kidney disease, hypertension, diabetes mellitus), multifetal pregnancies, BMI, smomking during pregnancy. This is a major asset in the current study.

  Response:

  Thank you for your remark. This has been added as a strength of our study in the discussion (page 17, line 8-9).

- *Page 9, line 24-29*
  "When WWE were subcategorized into WWE with AED and WWE without AED, none of the two subgroups differed significantly from women without epilepsy for any hypertensive disorder." It took me a while to understand this sentence. I suggest something like: The occurrence of hypertensive disorders did not differ significantly between…
  Otherwise I would think this sentence was about baseline characteristics.
  Response:
  We realize that the sentence can be confusing and have changed it according to the reviewer's suggestion (page 11, line 6-8).

- *Page 9, line 44-46:*
  Sensitivity analyses. What sensitivity analysis? This was not anticipated in the method section.
  Response:
  We have now specified the description of sensitivity analyses in the method section (page 9, lines 7 and 9).

- *Page 10, line 13 an 18:*
  Modify: I suggest to use something like: "withdraw" or "the association disappears"
  Response:
  We have changed the wording for these two sentences according to the reviewer's suggestion. (page 13, line 12-15)

- *Page 10, line 22:*
  VPA: this abbreviation has not yet been explained in the text, please write: Valproate (VPA). Line 46 NorPD same remark.
  Response:
  Thank you for noticing the VPA abbreviation, this was unintentional. We have now changed it to read: valproate. The abbreviation NorPD (Norwegian Prescription Database) is explained under material and methods in the original manuscript (page 6, line 14).

- *Page 10, line 44- page 11, line 6:*
  "To validate the AED data in MBRN," …Data handling or interpretation should be in the methods section. Or at least before outcome.
  Response:
  We have moved the information about data handling to the material and methods section (page 8, line 5-8) and also incorporated the results here.

- *Page 12, line 5-7_*
  "We found an increased risk of mild preeclampsia in WWE and the hypertensive complications in WWE consisted mostly of cases with mild preeclampsia." I would not formulate this conclusion so complex. Confine this conclusion to: "We found an increased risk of mild preeclampsia in WWE."
  Response:
  The sentence has been simplified according to the reviewer's suggestion and now reads: We found an increased risk of mild preeclampsia in WWE.

- *Page 12, line 20-42:*
  "The present study shows that most WWE, and in particular when treated with the new AEDs, do not have additional risks of hypertensive complications" This paragraph has bit too much detail for summary of the main results.
  Response:
  In the discussion we have given a short summary of our main results in the first paragraph. In the second paragraph, referred to by the reviewer, we further comment and discuss these results, thus contributing to a suitable narrative. We have now simplified this paragraph.

- *Page 12, line*
  "The specified newer AEDs." I am not a neurologist and am unfamiliar with which AED's are "newer". What classifies them and what are their characteristics? Was it anticipated that they predisposed to hypertensive disorders? Why? – please elaborate in the introduction section.
  Response:
  We have specified the term "newer" and "older" AEDs in the manuscript. It now reads: "newer AEDs, lamotrigine and levetiracetam" or "older AEDs, carbamazepine and valproate". We have also replaced "modern" AEDs with "newer" for more consequent wording. We have included a paragraph about specified AEDs in the introduction, where previous findings and the paradigm shift towards newer AEDs are now described (page 4, line 18-24 and page 5, line 1-2).

- *Page 12, line 9-12:*
  WWE on valproate monotherapy was significantly associated with mild preeclampsia, in contrast to other AEDs. "But this association was absent in BMI>30." Am I correct?
  Response:
  Yes, this association was not significant in WWE on valproate with BMI > 30, although the prevalence was notably higher (16.7 % in WWE on valproate versus 6.7 % in women without

epilepsy). We suggest that low number of cases may be the reason for lack of significance. These results are now specified (page 13, line 19-22).

- *Page 12, line 26/27:*
  Relevant chronic diseases. Since smoking is not a chronic disease I would suggest 'cardiovascular risk factors'
  Response:
  We agree that smoking, BMI and the included chronic diseases (pre-existing kidney disease, hypertension, diabetes) all influence cardiovascular risk. Thus we have introduced cardiovascular risk factors as a common denominator (page 15, line 12-13), but still analysed them separately. In our study we have performed sensitivity analyses for these variables. An argument for this is the missing cases for the variables smoking and BMI, and the considerable confounding for the variable other chronic disease. These variables have a different impact on the results, and we illustrate this by separating them when mentioned in the results.

- *Page 13 Line 36-38:*
  Potential AED effects on the child are highly important for deciding optimal treatment for WWE. Redundant information.
  Response:
  We agree with the reviewer and have removed this sentence.

- *Page 13, line 42-47:*
  "We found an increased risk of early onset preeclampsia in WWE on levetiracetam, but this should be interpreted with caution" …. Not mentioned in the text in the results section, only in table 3. All significant relations between AED and outcome dissolve in the sensitivity analysis. The discussion section may be better to read with less detail. (or elaborate a little on AED in the results section
  Response:
  We have now removed this sentence.

- *Page 15, line 15,16:*
  Preeclampsia shows a decreasing prevalence over time. Very strong statement and conclusions for the interpretation in the current study. I would be very careful with this. The study referred to shows an overall increase in the prevalence of preeclampsia, with a sudden increase from 1999 forward due to changes in the registration form. In the few years after, the numbers go down a little, but still
  higher than before 1999. Severe preeclampsia may occur less often due to more aggressive treatment and induction of labor, but this could also be a registration bias.
  Response:
  We accept that this statement might be too bold and does not unequivocally support a generalized decrease in preeclampsia. We have modified the sentence and specified our statement for the MBRN data and for the time period for the current study (page 18, line 2-4).

- *Page 17, line 7:*
  MAJOR clinical importance? I'll agree to it's clinical importance, but overall WWE comprised 0,79% of the total population and the risk for mild PE was only slightly elevated: RR 1,4 (1,8 in sensitivity analysis).
  Response:
  We have specified that this clinical importance concerns pregnancies of WWE and have removed the word "major".

- *Page 17, line 16-20:*

Our study shows that the increased risk does not include most WWE and especially not WWE on modern AEDs, nor does it include severe hypertensive complications. I don't understand. Does the increased risk not apply to WWE? Even at increased risk, fortunately most WWE do not develop preeclampsia or other hypertensive disorders.

Response:

We agree that the sentence was confusing. It has been rewritten in our revised manuscript (page 19, line 7-9).

Reviewer 2:

- *This reviewer questions this conclusion, as evidence suggests that pre-eclampsia is a dynamic disease and progresses at different rates for different women. As such, classification as mild pre-eclampsia may be unhelpful for management and the temporal based definitions of pre-eclampsia as early or late more useful. This is because women with diagnosis of pre-eclampsia <34 have up to 20 times higher maternal mortality and morbidity than the late onset disease. Therefore, women with the authors outcome of mild pre-eclampsia at <34 weeks are at increased risk of complications than those at >34 weeks pregnancy.*

  Response:

  The categories of hypertensive disorders in our study included also temporal differences during the pregnancy. If preeclampsia developed < 34 weeks it was categorized into "early onset preeclampsia" and always included in the "severe preeclampsia" group. Therefore our mild preeclampsia group does not include any cases of hypertensive disorders < 34 weeks. This categorization is fundamental for the conclusion that mild preeclampsia is not associated with increased morbidity or mortality. Furthermore, any development from mild preeclampsia to more severe forms was categorized accordingly and no longer as "mild preeclampsia". This has been better clarified in our revised manuscript. (page 6, line 23-24 and page 7, line 6)

- *Materials and methods, page 5, line 40.*
  In categorising the individual outcomes, is it possible that on the MBRN databases, multiple checkboxes are ticked? If so, how did the authors decide which outcome variable would be prioritized in the analysis for that woman?

  Response:

  It is correct that checkboxes are not mutually exclusive in the MBRN notification form. We always prioritized the most severe form of hypertensive complication ticked off. This ensured inclusion of the most severe form and excluded transient diagnoses from gestational hypertension or mild preeclampsia to a more severe form. Only 0.8 % of all recorded hypertensive complications were incorrect double registrations.
  Severe preeclampsia included all cases of early onset preeclampsia (< 34 weeks), eclampsia, and HELLP. This has been better specified in the revised manuscript. (page 6, line 23-24 and page 7, line 6)

- *Consequently, severe pre-eclampsia is a compound variable on its own, with raised blood pressure, early onset pre-eclampsia, eclampsia or HELLP syndrome as definitions of the diagnosis. Do the authors think that this may have an effect on the prevalence of the component outcomes individually reported and as such on the relationship under investigation?*

  Response:

  Severe preeclampsia is also a compound variable in our study. We have analysed associations to severe preeclampsia when early onset preeclampsia, eclampsia and HELLP were excluded from the outcome. There were no significant findings for these analyses. They are not reported in the manuscript.

Validation of hypertensive disorders in the MBRN has not been performed for the different groups of severe hypertensive complications. In the discussion we indicate a possible ascertainment bias for mild preeclampsia in WWE (page 16, line 20-23) and this may influence other outcomes as well. However, if an ascertainment bias is present it would have been more likely to cause a stronger association in WWE, and no such association was found. We have revised the manuscript according to the question from the reviewer and our answer.

- *Similarly for mild pre-eclampsia and severe pre-eclampsia that occurred at <34 weeks. Did the authors classify these as early onset pre-eclampsia or mild/severe pre-eclampsia?*
  Response:
  See our response above.

- *Discussion, page 12*
  The differences in statistical findings across women without epilepsy vs WWE, WWE without AED, WWE with AED and WWE with polytherapy, may be due to differences in sample sizes across these comparisons. The authors may want to include this point in the discussion.
  Response:
  Thank you for your remark. This is an important discussion point and partly addressed on page 15, line 11 and page 18, line 7-9. We have emphasized this by adding a sentence under limitations of our study (page 18, line 9-10).

FORMATTING AMENDMENTS (if any)

- *Required amendments will be listed here; please include these changes in your revised version:*
  -- Kindly embed your table (should be editable). Tables should be placed in the main text where the table is first cited. Tables must be cited in the main text in numerical order. Please note that tables embedded as Excel files within the manuscript are NOT accepted. Do not upload your table separately.
  Response:
  Tables have been embedded in the manuscript.

VERSION 2 – REVIEW

REVIEWER	John Allotey Queen Mary University of London
REVIEW RETURNED	02-Mar-2018

GENERAL COMMENTS	The authors have responded accurately to my queries

REVIEWER	M.F. van Oostwaard IJsselland Ziekenhuis, The Netherlands
REVIEW RETURNED	18-Mar-2018

GENERAL COMMENTS	**Review Revised manuscript antiepileptic drugs and PE** Hypertensive pregnancy complications in women with epilepsy and antiepileptic drugs: a population-based study of first pregnancies

	Overall: Subject Originality and Clinical applicability: see review of the original submitted manuscript. All of the previous remarks have been addressed. Still it's reporting and it's English needs some work. (One will always find new things to comment on, even on previously unremarked sections) **Specific remarks:** Introduction Page 4 – line 9-11 '*Consequences of maternal AED use during pregnancy for fetal malformations and early childhood development have been focused*.' The sentence does not read well. Focused on what? I am not a native speaker, so I would recommend to ask a native speaker for advice. Page 4 – line 16-20 '*For women in fertile age, potential AED effects for the fetus as well as on the pregnancy should be of the highest relevance*.' Suggest: '*interest'* instead of '*relevance'*. Results I would like to see some text about the significant baseline differences in table 1, particularly in preexisting disease. Page 14 – line 7-14: '*When AED use in NorDP data was assessed one and three months before conception, the total AED population remained unchanged. 95% of WWE with AED in NorPD had more than one dispensation during pregnancy, illustrating continuous use throughout pregnancy as one dispensation usually corresponds to more than three months use*.' I think this remark corresponds to the validating of AED use obtained from MBRN compared to NorPD, which has been moved to the methods section. Maybe it is better in pace there. Discussion Page 15 – line 9-11 '*WWE on valproate monotherapy was significantly associated with mild preeclampsia, in contrast to other AEDs'.*

	Women 'was' associated with mild preeclampsia? I suggest: '*Use of valproate monotherapy was significantly associated with mild preeclampsia, in contrast to other AEDs'* Page 15 – line 20-27 '*WWE with AED and WWE without AED had the same prevalence of mild preeclampsia but only WWE without AED had a significantly increased risk. This probably reflects marginal differences influenced by sample size.'* Difficult to understand. I suggest: '*WWE with AED had comparable prevalence of mild preeclampsia to WWE without AED, but did not reach significance. This probably reflects marginal differences influenced by sample size.'* Page 15 – line 26-33 '*Cardiovascular risk factors (smoking, BMI > 30kg/m2, pre-existing kidney disease, hypertension and diabetes) were relevant for hypertensive complications in WWE. The mechanism for the increased risk of hypertensive complications in WWE in first pregnancies could therefore be partly mediated by modifiable external risk factors and comorbidity.'* In the methods section it was described that confounding by relevant chronic diseases (among others) was adjusted for using logistic regression. Also a sensitivity analysis was performed on the subgroup with preexisting disease. Results are described on page 12 line 27-30 (This risk disappeared after stratification and when including smoking or other relevant chronic diseases in sensitivity analyses), but no results of the sensitivity analysis are presented about the relation to the risk for mild preeclampsia. I would like to see a comment on that in the discussion section, as well as a more specific presentation of the sensitivity analysis for relevant chronic diseases and the risk for hypertensive disorders. Page 16 – line 46. '*proceed further'* – I suggest: '*progress'* Page 17 - line 52 – page 18 - line 9. Paragraph about BMI: This is the second time in the discussion section that the influence of BMI is discussed. You may want to unite these sections.

VERSION 2 – AUTHOR RESPONSE

Specific remarks:

Introduction

Page 4 – line 9-11 'Consequences of maternal AED use during pregnancy for fetal malformations and early childhood development have been focused.' The sentence does not read well. Focused on what? I am not a native speaker, so I would recommend to ask a native speaker for advice.

Response:

We have revised the sentence and it now reads:

“Studies have focused on consequences of epilepsy and maternal AED use during pregnancy for fetal malformations and child development.”

Page 4 – line 16-20 ‘For women in fertile age, potential AED effects for the fetus as well as on the pregnancy should be of the highest relevance.’ Suggest: ‘interest’ instead of ‘relevance’.

Response:

The wording in the sentence is changed according to the reviewer’s suggestion.

Results

I would like to see some text about the significant baseline differences in table 1, particularly in preexisting disease.

Response:

We have now added description on baseline differences also in the text of our revised manuscript.

Page 14 – line 7-14: ‘When AED use in NorDP data was assessed one and three months before conception, the total AED population remained unchanged. 95% of WWE with AED in NorPD had more than one dispensation during pregnancy, illustrating continuous use throughout pregnancy as one dispensation usually corresponds to more than three months use.’ I think this remark corresponds to the validating of AED use obtained from MBRN compared to NorPD, which has been moved to the methods section. Maybe it is better in pace there.

Response:

The paragraph is now moved to the methods section.

Discussion

Page 15 – line 9-11 ‘WWE on valproate monotherapy was significantly associated with mild

preeclampsia, in contrast to other AEDs’. Women ‘was’ associated with mild preeclampsia?

I suggest: ‘Use of valproate monotherapy was significantly associated with mild preeclampsia, in contrast to other AEDs’

Response:

The sentence is now revised according to the reviewer’s suggestion.

Page 15 – line 20-27 ‘WWE with AED and WWE without AED had the same prevalence of mild preeclampsia but only WWE without AED had a significantly increased risk. This probably reflects marginal differences influenced by sample size.’ Difficult to understand.

I suggest: ‘WWE with AED had comparable prevalence of mild preeclampsia to WWE without AED,but did not reach significance. This probably reflects marginal differences influenced by sample size.’

Response:

The sentence is now revised according to the reviewer's suggestion.

Page 15 – line 26-33 'Cardiovascular risk factors (smoking, BMI > 30kg/m2, pre-existing kidney disease, hypertension and diabetes) were relevant for hypertensive complications in WWE. The mechanism for the increased risk of hypertensive complications in WWE in first pregnancies could therefore be partly mediated by modifiable external risk factors and comorbidity.' In the methods section it was described that confounding by relevant chronic diseases (among others) was adjusted for using logistic regression.

Also a sensitivity analysis was performed on the subgroup with preexisting disease. Results are described on page 12 line 27-30 (This risk disappeared after stratification and when including smoking or other relevant chronic diseases in sensitivity analyses), but no results of the sensitivity analysis are presented about the relation to the risk for mild preeclampsia.

I would like to see a comment on that in the discussion section, as well as a more specific

presentation of the sensitivity analysis for relevant chronic diseases and the risk for hypertensive disorders.

Response:

Yes, other chronic diseases were included in the regression model and the impact was further analyzed with stratification-based sensitivity analyses. Sensitivity analyses were applied on all outcomes. Sensitivity analyses are presented as footnotes marked with asterisks in the tables and are now further specified. The results marked with asterisks represent results were stratum specific aORs are different and alter significant results. Significant changes in sensitivity analyses are also presented in the manuscript.

Page 16 – line 46. 'proceed further' – I suggest: 'progress'

Response:

The wording in the sentence is changed according to the reviewer's suggestion.

Page 17 - line 52 – page 18 - line 9. Paragraph about BMI: This is the second time in the discussion section that the influence of BMI is discussed. You may want to unite these sections.

Response:

It is true; BMI is discussed in two paragraphs. The first time BMI is discussed is in specific relation to the effects on outcomes. The second time BMI is discussed in relation to limitations of the study, and more importantly, in a more universal population perspective. In our opinion the text is more fluent as it currently stands.