PEER REVIEW HISTORY

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ARTICLE DETAILS

TITLE (PROVISIONAL)	Does caesarean delivery in the first pregnancy increase the risk for adverse outcome in the second? A registry-based cohort study on first and second singleton births in Norway.
AUTHORS	Bjellmo, Solveig; Andersen, Guro; Hjelle, Sissel; Klungsøyr, Kari; Krebs, Lone; Lydersen, Stian; Romundstad, Pål; Vik, Torstein

VERSION 1 – REVIEW

REVIEWER	Sohinee Bhattacharya University of Aberdeen
REVIEW RETURNED	27-Feb-2020

GENERAL COMMENTS	This is an important study using high quality population based data from Norway. below are few suggestions to improve the manuscript: 1. The title should clarify that only second singleton pregnancy outcomes are being considered. 2. Abstract: Please explain what is meant by potential confounding by indication. 3. Introduction: sets the scene well and gives the rationale for the study. 4. Methods: It would be good to have a diagram showing data linkage and which variables were obtained from which register. As all confounding variables adjusted for in the multivariable analysis were at the time of the first pregnancy, how were confounders at the time of the second pregnancy handled? For example if the mother was a smoker during her first pregnancy but gave up smoking at the time of the 2nd pregnancy, the 2nd pregnancy status is likely to have more influence on the outcome of the second pregnancy. More importantly the mode of delivery of the second pregnancy will likely influence the outcome and would also be associated with the previous MOD. I would suggest using Cox or Poisson regression to analyse the data as the study design is cohort and all the primary outcomes are mutually exclusive. This would also take account of the differential in birth intervals. Results are clearly presented but needs to specify which pregnancy confounders are being adjusted for in the tables. It is not clear exactly how high/ low risk of adverse outcomes was classified. Discussion: Authors should discuss in the limitations the probability of chance in finding a statistically significant association when analysing big datasets.

REVIEWER	Pisake Lumbiganon Department of Obstetrics and Gynaecology Faculty of Medicine

	Khon Kaen University Khon Kaen, Thailand
REVIEW RETURNED	03-Mar-2020

GENERAL COMMENTS	This is a very interesting and important analysis. I have the following minor comments: 1. Abstract: Should include early neonatal death as one of the outcomes. 2. In conclusion part of the abstract, “children” is not an appropriate word. Children to me should be a live born baby and can’t be a stillbirth. 3. Introduction, page 4, line 36, consider replacing “newborns” with “babies”. 4. Methods: page 4, line 50, consider replacing “children” with “babies”. 5. Methods: page 5, lane 23-26, “The newborns were linked to their mothers by means of the national identification numbers, yielding maternal sibship files with the mother as the observation unit” what about stillbirth? How could they be linked to their mothers? 6. Methods, page 6, line 47-59, It was not clear how was potential confounding by indication adjusted in the multivariate analysis. 7. Methods: page 5, line 50, what was “postpartum bleeding”? Was it PPH? I don’t see this outcome in Table 4, I saw only “bleeding”. 8. Results: Page 7, line 55-59, and Figure 1, what about the third or more pregnancies? 9. Discussion: page 12, line 48-57, the discussion about the adjustment for indication of CD in the first pregnancy was not very clear.

REVIEWER	Annette Regan Texas A&M University, United States
REVIEW RETURNED	10-Mar-2020

GENERAL COMMENTS	Thank you for the opportunity to review this interesting analysis of Norwegian health registry data to evaluate the risk of perinatal outcomes among births following a previous cesarean vs. a previous vaginal delivery. The study draws from a large, reliable register of births from a high-income country. However, I have a couple of concerns around the analytic approach, which I’m hoping the authors can address: 1. How were the primary study outcomes selected? No evidence was provided in the background to suggest we might expect increased risk of CP for cesarean and this seemed a little strange to me to include perinatal mortality and CP as main outcomes together. Some further background would be very helpful for the reader. 2. I’m not sure the confounding by indication analysis really accomplishes what it intended to do. While I think it is helpful to categorize women into high and low risk pregnancies, it would also seem sensible to me to consider reasoning for cesarean section in analyses. 3. Did the authors factor for method of delivery in the second pregnancy? Sorry if I missed this – but this seems highly relevant

	as we know many of the study outcomes are associated with CD in general and one possible explanation for results is that women with repeat CD are more prone to these issues (i.e., intrapartum stillbirth). 4. Page 8 line 29-44: I think it would make more sense to adjust for IPI rather than exclude women with more recent births, as IPI has been linked with the study outcomes and is known to be associated with the method of delivery in the preceding pregnancy. 5. I think the conclusion that CD should be avoided is potentially unfair, given a large portion of CDs are deemed necessary by clinician guidance. I assume the authors mean elective cesarean where no there is no clinician indication for CD should be avoided – and there are many other studies which have come to the same conclusion. It would be worth clarifying this.

VERSION 1 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Sohinee Bhattacharya

Institution and Country: University of Aberdeen Please state any competing interests or state

'None declared': None declared

This is an important study using high quality population based data from Norway. below are few suggestions to improve the manuscript:

Reply: *We appreciate the reviewer's overall assessment of our manuscript.*

1. The title should clarify that only second singleton pregnancy outcomes are being considered.

Reply: *Thank you for your suggestion. The title has been revised (see above).*

2. Abstract: Please explain what is meant by potential confounding by indication.

Reply: *We have changed the wording in the revised abstract and find it better to explain the meaning of confounding by indication in the main text. Thus, the text in the abstract is changed to:"Adjustment for potential confounders attenuated the ORs somewhat, but the excess risks in the second pregnancy persisted for all outcomes."*

And we have tried to explain confounding by indication better in the main text (page 7) as follows:

“These complications may also affect the choice of mode of delivery in the first pregnancy, leading to potential confounding by indication, partly adjusted for in the logistic regression analyses described above. In addition, we also assessed confounding by indication in stratified analyses within subgroups of pregnancies with high and low risk for adverse outcomes. The high-risk group comprised women with any of the complications in the first pregnancy that in the second pregnancy were considered as primary or secondary outcomes (stillbirth, perinatal mortality, neonatal mortality, SGA, placenta previa, bleeding, uterine rupture, placental abruption, preterm delivery and preeclampsia). The low-risk group included mothers without any of the specified primary or secondary outcomes in the first delivery, and where the first infant was born at term.”

3. Introduction: sets the scene well and gives the rationale for the study.
Reply: *Thank you.*

4. Methods: It would be good to have a diagram showing data linkage and which variables were obtained from which register. As all confounding variables adjusted for in the multivariable analysis were at the time of the first pregnancy, how were confounders at the time of the second pregnancy handled? For example if the mother was a smoker during her first pregnancy but gave up smoking at the time of the 2nd pregnancy, the 2nd pregnancy status is likely to have more influence on the outcome of the second pregnancy. More importantly the mode of delivery of the second pregnancy will likely influence the outcome and would also be associated with the previous MOD. I would suggest using Cox or Poisson regression to analyse the data as the study design is cohort and all the primary outcomes are mutually exclusive. This would also take account of the differential in birth intervals.

Reply: *Thank you for this suggestion. We agree that the reader should have this information. However, since the only variable collected from the CPRN was the CP diagnosis, we have found it better to just describe this in the text avoiding an extra figure, as follows (page 4): “In this population-based cohort study, including all births in Norway between 1996 and 2015, information regarding pregnancy, delivery and the neonatal period was retrieved from the Medical Birth Registry of Norway (MBRN). This information was combined with information on a diagnosis of cerebral palsy recorded in the Cerebral palsy Registry of Norway (CPRN).”*

Regarding the analytic strategy we consider that the variables considered as potential confounders in the first pregnancy must be considered potential mediators if present in the second. Several articles have warned against adjusting for mediators in observational studies of potential causality, see for example (Ananth et al).[1] Thus, we do not consider it appropriate to adjust for these variables in the second. Regarding the regression analyses, we regard logistic regression rather than Cox regression or Poisson regression to be the appropriate choice, as recommended by co-author Stian Lydersen, professor of medical statistics, given the aims of the study and the structure of the data set.

5. Results are clearly presented but needs to specify which pregnancy confounders are being adjusted for in the tables. It is not clear exactly how high/ low risk of adverse outcomes was classified.

Reply*: Thank you for the comment. We have changed the wording in the manuscript (page 7)*

to make this clearer as follows: “The high-risk group comprised women with any of the complications in the first pregnancy that in the second pregnancy were considered as primary or secondary outcomes (stillbirth, perinatal mortality, neonatal mortality, SGA, placenta previa, bleeding, uterine rupture, placental abruption, preterm delivery and preeclampsia). The low-risk group included mothers without any of the specified primary or secondary outcomes in the first delivery, and where the first infant was born at term.”

6. Discussion: Authors should discuss in the limitations the probability of chance in finding a statistically significant association when analysing big datasets.

Reply: *Indeed, in large data sets, small (and clinically unimportant) effects can result in small p-values due to the large sample size. But we have chosen to focus on estimates and confidence intervals rather than p-values. For most outcomes these confidence intervals suggest that it is unlikely that the major findings are chance findings.*

Reviewer: 2

Reviewer Name: Pisake Lumbiganon

Institution and Country:

Department of Obstetrics and Gynaecology Faculty of Medicine Khon Kaen University Khon Kaen, Thailand Please state any competing interests or state 'None declared': None declared

Please leave your comments for the authors below This is a very interesting and important analysis. I have the following minor comments:

Reply: *We appreciate the general assessment of our manuscript.*

1. Abstract: Should include early neonatal death as one of the outcomes.

Reply: *Thank you for this suggestion. In fact, the results regarding early neonatal mortality, although not statistically significant, are more in line with the results regarding intrapartum death, than neonatal mortality was. We have added information regarding the outcome early neonatal mortality to the method section (page 5) the results section (page 9 and 11, table 1 and 3, (and in the supplementary table 1 and 3)) and discussed this finding on page 15 in the manuscript.*

2. In conclusion part of the abstract, "children" is not an appropriate word. Children to me should be a live born baby and can't be a stillbirth.

Reply*: Thank you for your suggestion. We have rephrased the conclusion of the abstract. (i.e. identical to the main conclusion of the paper).*

3. Introduction, page 4, line 36, consider replacing "newborns" with "babies".

Reply*: We have replaced "newborns" with "offspring" (see also our response to comment 5).*

4. Methods: page 4, line 50, consider replacing "children" with "babies".

Reply: *We have changed the text in accordance to comment 4 of the first reviewer and "children" is no longer a part of the text.*

5. Methods: page 5, lane 23-26, "The newborns were linked to their mothers by means of the national identification numbers, yielding maternal sibship files with the mother as the observation unit" what about stillbirth? How could they be linked to their mothers?

Reply*: In the Medical Birth Registry of Norway, all infants (including stillbirths) are registered with the mother's (and the father's) national identification numbers. When generating sibship files including only singletons (as in the present study), the mothers' identification numbers, and the infant's date of birth are used to link each infant to its mother in a sibship file with the mother as the observation unit followed by her successive offspring. The infant's identification numbers are not used, and indeed, stillbirths do not have one.*

We have changed the wording to offspring in the manuscript to make this clearer. We have in addition emphasized that the MBRN also records complications during the pregnancy (including stillbirths) (page 5).

6. Methods, page 6, line 47-59, It was not clear how was potential confounding by indication adjusted in the multivariate analysis.

Reply: *We have tried to clarify this in the text as follows:*

"Since there is a risk of recurrence of adverse outcomes, such as stillbirth, perinatal death, preterm birth, fetal growth restriction and preeclampsia from one delivery to the next, we included complications in the first pregnancy that were defined as adverse outcomes in the second, as potential confounders. These complications may also affect the choice of mode of delivery in the first pregnancy, leading to potential confounding by indication, partly adjusted for in the logistic regression analyses describe above. In addition, we also assessed confounding by indication by studying the associations within subgroups of pregnancies with high and low risk for adverse outcomes."

7. Methods: page 5, line 50, what was "postpartum bleeding"? Was it PPH? I don't see this outcome in Table 4, I saw only "bleeding".

Reply: *Thank you for your comment. We apologize for the imprecision and have changed this to "bleeding" in the revised manuscript (page 5).*

8. Results: Page 7, line 55-59, and Figure 1, what about the third or more pregnancies?

Reply: *The comment is well taken, However, we think including third and fourth pregnancy is likely to confuse the message, and we therefore a priori, decided to look at the consequences in the second pregnancy of a CD in the first. We have rephrased the title as suggested by the editor and the first reviewer to make this clearer.*

9. Discussion: page 12, line 48-57, the discussion about the adjustment for indication of CD in the first pregnancy was not very clear.

Reply: *Thank you for pointing this out. We have now made this clear in the method section* *and simplified the wording in the discussion to the following (page 13):* "*Moreover, the main findings persisted when adjusted for potential confounders in multivariable analyses, and when we assessed confounding by indication in analyses restricted to mothers with high and low risk of adverse outcomes. In these latter analyses, the main findings persisted in both groups, suggesting that confounding by indication was less likely."*

Reviewer: 3

Reviewer Name: Annette Regan

Institution and Country: Texas A&M University, United States Please state any competing

interests or state 'None declared': None declared

Thank you for the opportunity to review this interesting analysis of Norwegian health registry data to evaluate the risk of perinatal outcomes among births following a previous cesarean vs. a previous vaginal delivery. The study draws from a large, reliable register of births from a high-income country. However, I have a couple of concerns around the analytic approach, which I'm hoping the authors can address:

1. How were the primary study outcomes selected? No evidence was provided in the background to suggest we might expect increased risk of CP for cesarean and this seemed a little strange to me to include perinatal mortality and CP as main outcomes together. Some further background would be very helpful for the reader.

Reply*: Thank you for the comment., We have included information why we wanted to investigate if a previous cesarean delivery could be associated with increased risk for CP in the second, compared to vaginal delivery in the introduction (page 2, paragraph 2.) in the revised manuscript as follows:*

"Studies have also reported higher risk for placental complications and uterine rupture in pregnancies following a previous CD. These complications are also associated with higher risk for delayed neurodevelopment and cerebral palsy in the offspring."

2. I'm not sure the confounding by indication analysis really accomplishes what it intended to do. While I think it is helpful to categorize women into high and low risk pregnancies, it would also seem sensible to me to consider reasoning for cesarean section in analyses. ***Reply****: We agree with the reviewer that it would have been better had we known the reason for the first cesarean delivery (CD). However, this study is based on register data, and the Medical Birth Registry of Norway does not collect detailed information about the reasoning behind the CD. Nonetheless, the most likely indication of the first CD can be evaluated based on the registered complications in pregnancy and delivery, which is what we have done in this study.*

3. Did the authors factor for method of delivery in the second pregnancy? Sorry if I missed this – but this seems highly relevant as we know many of the study outcomes are associated with CD in

general and one possible explanation for results is that women with repeat CD are more prone to these issues (i.e., intrapartum stillbirth).

Reply: *Thank you for your comment. Although this comment is slightly different, we may refer to our response to comment 4 by reviewer 2. We consider that this research question needs to be addressed in a different study, which has partly been done in a recent Norwegian study.[2] These authors studied how the outcome of women with a previous CD differed depending on whether in the next labor, a trial of labor (TOLAC) was the mode of delivery or whether it was done as planned CD. Our aim was to study if outcome in the second delivery, differed by mode of delivery in the first, and we therefore did not find it appropriate to adjust for mediators, or choice of delivery mode in the second. We have assessed this important issue further in the discussion (page 15).*

4. Page 8 line 29-44: I think it would make more sense to adjust for IPI rather than exclude

women with more recent births, as IPI has been linked with the study outcomes and is known to be associated with the method of delivery in the preceding pregnancy.

Reply: *In our analyses we have considered IPI to be a potential mediator and therefore not adjusted for this variable in our analyses. The subgroup analyses were performed to explore if selection bias affected our results.*

5. I think the conclusion that CD should be avoided is potentially unfair, given a large portion of CDs are deemed necessary by clinician guidance. I assume the authors mean elective cesarean where no there is no clinician indication for CD should be avoided – and there are many other studies which have come to the same conclusion. It would be worth clarifying this.

Reply: *Thank you for your comment. We did not foresee that our conclusion could be misinterpreted in this way. It was not our intention. We have tried to clarify this in the revised text as follows:*

"Therefore, the main prevention of these severe complications in subsequent pregnancy may be to take individual plans for future pregnancies into account when considering CD without a clear medical indication".

Reference:

1. Ananth CV, Schisterman EF. Confounding, causality, and confusion: the role of intermediate variables in interpreting observational studies in obstetrics. *American journal of obstetrics and gynecology* 2017;217(2):167-75.

2. Lehmann S, Baghestan E, Børdahl PE, et al. Perinatal outcome in births after a previous cesarean section at high trial of labor rates. *Acta obstetricia et gynecologica Scandinavica* 2018

VERSION 2 – REVIEW

REVIEWER	Sohinee Bhattacharya University of Aberdeen United Kingdom
REVIEW RETURNED	25-May-2020

GENERAL COMMENTS	Many thanks for addressing all the issues raised in the revised manuscript. I have no further comments.

REVIEWER	Pisake Lumbiganon Department of Ob & Gyn Faculty of Medicine Khon Kaen University KHon Kaen Thailand 02-Jun-2020
REVIEW RETURNED	

GENERAL COMMENTS	1. The term “bleeding” in Table 4, was too vague, it has to be more specific e.g. postpartum haemorrhage that has a standard definition. 2. In the Flow chart of the study population, I do believe that there were some women who had both previous CD and VD, how were they classified?

VERSION 2 – AUTHOR RESPONSE

Reviewer: 1

Reviewer Name: Sohinee Bhattacharya

Institution and Country:

University of Aberdeen

United Kingdom

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

Many thanks for addressing all the issues raised in the revised manuscript. I have no further comments.

Reply: Thank you for the review.

Reviewer: 2

Reviewer Name: Pisake Lumbiganon

Institution and Country:

Department of Ob & Gyn

Faculty of Medicine

Khon Kaen University

KHon Kaen

Thailand

Please state any competing interests or state ‘None declared’: None declared

Please leave your comments for the authors below

1. The term “bleeding” in Table 4, was too vague, it has to be more specific e.g. postpartum haemorrhage that has a standard definition.

Reply: Thank you for the suggestion, we have changed the wording to postpartum haemorrhage in the table and in the text.

2. In the Flow chart of the study population, I do believe that there were some women who had both previous CD and VD, how were they classified?

Reply: Thank you for this comment. We agree that the flow chart was unclear and have revised it in order to make it more self-explanatory.