Dear Dr. Wim Weber,

We greatly appreciate the opportunity to revise our manuscript for further consideration. Please see our responses to the comments from the editors and reviewers below. We hope that you will find the manuscript improved and acceptable for publication.

Sincerely,

Maria C. Magnus (on behalf of the authors)
Centre for Fertility and Health
Norwegian Institute of Public Health
P.O. Box 222 Skøyen
0213 Oslo
Norway

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Members of the committee were: John Fletcher (chair), Jamie Kirkham (statistical advisor), Elizabeth Loder, José Merino, Wim Weber, Daoxin Yin.

Decision: Put points

Detailed comments from the meeting:

We thought your study addressed an interesting and important research question. We had the following concerns.

Comment 1: This is a straightforward analysis with no unexpected findings - miscarriage rates are in line with the literature. The J-shaped risk of miscarriage according to maternal age seems typical of what would be expected. The pattern observed for maternal ages 22-23 (Figure 2) may appear slightly distorted due to the differing y-axis scale (differences are quite minor despite the fluctuation observed).

Response comment 1: In the original version of the manuscript, we had included a panel b in figure 2 to better show the difference in risk across women who were 23-33 years of age. We did this to make it easier for the reader to see which age category was associated with the absolute lowest risk by "zooming-in" on the y-axis. However, we agree that some of the very modest differences were accentuated in this panel. Based on your comment, and the comment from one of the reviewers, we have now omitted panel b from figure 2.

Comment 2: Much of the statistical analysis focuses on the issue of calculating accurate miscarriage rates in the presence of induced abortions. A number of assumptions are made about including the relevant numerator/denominator in the miscarriage rate computations. The authors seem to come to a satisfactory solution around this and demonstrate their rates are largely unaffected by induced abortions and subsequently exclude these from the formal stats inference.

Response comment 2: We are glad that our description of how we accounted for the competing risk of induced abortions included a sufficient amount of detail for it to be interpretable for the reader.

Comment 3: Table 1 - We do not understand the 100% miscarriage rate when there is missing data.

Response comment 3: You're correct that this number was confusing. There were ten miscarriages in the patient register for which mother's age was missing (Table 1), and so this "missing" group had 100% miscarriage rate. We've revised the table to remove this confusion by replacing this to N/A.

Comment 4: First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Response comment 4: Please see our detailed responses to the comments from the reviewers below and marked revisions in the manuscript.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
In this manuscript, the authors present results from a large Norwegian birth registry specifically focused on reporting rates of miscarriage and risk factors associated with miscarriage in their population. This is a robust and well characterized data set that the authors do a nice job of explaining and utilizing. I have a few comments/questions.

Comment 1. In the "What this study adds" section 1st bullet- it would be helpful to clarify what the comparison is to for the "increased risk of miscarriage among both younter adn older mothers..."

Response comment 1: We have revised this bullet point as follows:

(p. 2):
"Careful adjustment for induced abortions had little effect on age trends. In particular, the modest increased risk among youngest mothers (<20 years) persisted."

Comment 2. Abstract Conclusion- recommend changing final phrase to "some adverse pregnancy outcomes."

Response comment 2: We have revised the final phrase in the conclusion of the abstract as follows:

Abstract (p. 3):
"Risk of miscarriage varies greatly with maternal age, shows a strong pattern of recurrence, and risk is also increased after some adverse pregnancy outcomes. Miscarriage and other pregnancy complications appear to share underlying causes, which could be biological conditions or unmeasured common risk factors."

Comment 3. Introduction- consider moving the 3rd paragraph above the 2nd one for flow.

Response comment 3: We agree that this change improves the readability of the introduction and have therefore switched the order of the two paragraphs.

Comment 4. There were several outcomes from prior pregnancies that were noted in the Methods that did not show up in the Results. These include post-term, SGA, and LGA. these need to show up in the results table.

Response comment 4: This discrepancy was because we were inconsistent in our use of abbreviations and terminology in the methods section and tables. For example, the tables described fetal growth as small, normal and large, when we were actually referring to small-for-gestational-age, normal-for-gestational-age, and large-for-gestational-age. For gestational age, the categories in the tables were also preterm, term and post-term. We have carefully revised the wording in all section of the manuscript to make sure that we are using consistent terminology throughout.

Comment 5. Figure 2 why is there a 2nd figure focusing in on age 23-33? What does it add that the first panel does not have?

Response comment 5: We had magnified the data in Figure 2 (panel B) to better show the age category with the absolute lowest risk of miscarriage. But this seems to have created some confusion, since the first panel in the figure shows all the relevant information. We have therefore excluded the second panel from Figure 2 in the revised version of the manuscript.

Additional Questions:
Please enter your name: David Haas

Job Title: Professor of OB/GYN

Institution: Indiana University School of Medicine

Reviewer: 2

Recommendation:

Comments:
This study examined the burden of miscarriage in the Norwegian population and evaluated the association between miscarriage and maternal age and pregnancy history.
The authors used national data from Norwegian registries to meet their objectives.
The study has major flaws including the following:

Comment 1.   The authors claimed that the data were collected prospectively which means that the registries were primarily designed to provide data to meet the objectives of this study among other objectives. However, the collected data were very deficient in many aspects including confounding factors for miscarriage such as paternal age, previous induced abortion, BMI, co-morbidity such as maternal diabetes, employment and the nature of maternal work if she is doing night shift, socioeconomic status in addition to ethnic origin of the mother and her immigration status. The latter condition is important considering that 16% of the Norwegians are immigrants some are from The Middle East where consanguineous marriages are recognized with increased possibility of congenital abnormalities. The deficient data on all proven factors associated with miscarriage makes the conclusion about the effect of maternal age and pregnancy history uncertain especially that the odds for these outcomes were small.

Response comment 1:

The reviewer is correct that our national data are limited in their detail. But we disagree about the issue of confounding.

Confounding is important when a study draws causal conclusions. For the analysis of pregnancy history in particular, we do not draw causal conclusions. The associations between miscarriage and pregnancy complications suggest that these outcomes are linked by unmeasured causal factors. This is not a "major flaw," but rather an opportunity to discover new underlying causes of both miscarriage and the related complications. Underlying factors may be diabetes or SES or BMI, as the reviewer suggests, or they may be genetics or environmental exposures. Our findings open research hypotheses that have not previously been apparent. We now try to make this opportunity more explicit in the Discussion and Conclusions.

Discussion (p. 12-13):
"The associations of miscarriage risk with complications in previous pregnancies point to the presence of causal factors that increase the risk of both. Information on potential causal factors is limited in the national registries. We are able to show that maternal smoking does not contribute to the associations, but we lack information on paternal age, maternal ethnicity, education and body-mass index. Ethnicity could be important since we know that 14% of Norwegians are immigrants (and ~25% of pregnancies in the current study were to women born outside of Norway).[1] Although the majority of immigrants are from other Nordic and eastern-European countries, there are immigrant groups that possibly have a greater underlying risk of miscarriage compared to ethnic Norwegians.[2-4] More focused studies with more detained information may be able to identify new underlying causes for both miscarriage and related pregnancy complications."

 We have also revised the conclusion accordingly (p. 14-15):

"In sum, population-based data from Norway provide precise estimates of miscarriage risk

related to mother's age, with the lowest risk at age 27. Risk of miscarriage increases as much as fourfold after three consecutive previous miscarriages, implying considerable variability in risk among couples. Exploratory associations suggest that miscarriage risk is linked to some previous pregnancy complications (stillbirth, preterm delivery and gestational diabetes). More focused studies of these associations may lead to new insights regarding the shared underlying causes of pregnancy complications and miscarriage"

Comment 2.   The results of this study showed another major issue which the missing data from each of the tables 2-5. The large number of missing data introduces the possibility of bias and threatens the validity of the conclusion reached by the authors especially that there are no comparisons in the main determinants between the missing group and the analyzed group.

Response comment 2: We appreciate the reviewer's concerns about missing data. We assume that this mostly refers to the pregnancies excluded from the analyses of prior pregnancy outcomes. The overwhelming majority of these excluded pregnancies were excluded because the current or prior pregnancy was an induced abortion. The additional excluded pregnancies were those to women with a registered parity at the time of that pregnancy greater than 0, or women whose two subsequent records indicated that they had experienced a pregnancy in between the two recorded pregnancies, but for whom we did not know the outcome of the prior (unregistered) pregnancy. We also had a proportion of women for whom we did not have their of birth record (i.e. whether they themselves had been born preterm or small-for-gestational age), because they were born outside of Norway. Both of these two reasons for missing data is a consequence of immigration and emigration. We have mentioned this as a limitation in the discussion. Based on your comment, we have also provided supplemental tables showing the distribution of the pregnancy outcome among: 1) included versus pregnancies that were excluded because we did not know the outcome of the prior pregnancy (eTable 1); and 2) pregnancies to women for whom we did and did not have information from their own birth record (eTable 5). We briefly describe this in the results.

Results (p. 7):
"Women with previous deliveries outside Norway, have missing records for these births in the birth register (3%). The registered parity reveals if a woman has any missing birth records. Information on prior pregnancies was most likely to be missing if the current pregnancy ended in live birth (eTable 1)."

Results (p. 10):
"The outcome of pregnancies of women for whom we had information from their own birth record was very similar to outcomes for women lacking this information (eTable 5)."

Discussion (p. 12):
"Births to Norwegians outside Norway are not registered in the birth register. For some women we therefore lacked information on the outcome of the woman's prior pregnancy. Also, for women born outside Norway, her own birth record was not in the register, and we did not know whether she herself was preterm, small-for-gestational-age etc. However, there was little difference in pregnancy outcomes in women with and without this information."

Additional Questions:
Please enter your name: Hayfaa Wahabi

Job Title: Associate professor Evidence-based healthcare and knowledge translation

Institution: King Saud University. Riyadh, Saudi Arabia

Reviewer: 3

Recommendation:

Main Comments:
This paper does not present many surprises but the risk estimates are solidly supported by a comprehensive, national database and reflect pregnancy outcomes for women in a high income country with good access to medical and reproductive health care. The inter-generational links between pregnancy complications are new to me. The persisting elevated burden of miscarriage borne by teenaged women is also interesting.

I attach a document listing some suggested revisions. I have asked the authors to check some suspected typographical errors, give more information in table and figure footnotes, provide supplementary information about gestation at miscarriage which allow comparison with other publications' definitions of first trimester or second trimester miscarriage and substantiate a few statements which currently lack numeric data and/or referenced source data.

Response to main comments:
We appreciate your time spent going through the manuscript in such detail. Please see our response to your comments below.

Title:
The role of maternal age and pregnancy history in risk of miscarriage. No suggested changes First author:
Magnus, Maria Christine
MS number
BMJ-2018-048089

**Comment 1: Dot points: What is already known, what this study adds These are clearly enunciated.
No changes suggested**

Comment 2: Abstract Well-structured. Main results expressed clearly. No changes suggested

Comment 3: Introduction The authors convince the reader that miscarriage is important but that ascertaining its incidence and associated risks is not as simple as first imagined. The aims of quantifying miscarriage risk and relating it to maternal age and previous pregnancy complications are convincingly stated. No changes suggested

Methods

Comment 4: 1st paragraph: Methods described well. Clear and repeatable information. No changes suggested

Comment 5: Pregnancy outcomes and identification of unique pregnancies: Uses a 42 day rule to determine if an ICD miscarriage related code was for a new pregnancy. I think this is reasonable and replicable. No changes suggested

Statistical analysis:

Comment 6: This is readable to the academic clinician reviewer who has some basis statistical training but does not claim to be a biostatistician.

Comment 7: The sensitivity analyses assessing according to inter-pregnancy interval, adjustment for smoking and sensitivity analysis for previous pregnancy complications are of clinical interest.

Results

Comment 8: This is generally well presented and complements the figures and tables. Please see comments below about figures and tables, including 1 possible typographical error and my request for more information about error bars, abbreviations and definitions.

Response comment 8: Thank you for suggesting improvements. Please see our responses to your comments on the various tables and figures.

Discussion and conclusions

Comment 10: Para 1   Confirm some observations with new precision, contemporary, comprehensive national data from a high income country

Response comment 10: Done.

Comment 11: Para 2 Strengths Page 12, line 27 Correct typographical error "recognizes" should be "recognize" to agree with the plural subject "most women".

Response comment 11: Thank you. We have changed this sentence in the second paragraph of the discussion accordingly.

Discussion (p. 12):

"However, in Norway, most women who recognize a miscarriage are likely to receive care from a specialist as these will be able to provide ultrasound confirmation on the pregnancy status. All prenatal care in Norway is free of charge and available to all women in the country."

Comment 12: Para 2 Weaknesses: under-ascertainment of miscarriage due to requirement for specialist medical attention. The statement ".. in Norway, most women who recognize (s) a miscarriage are likely to receive care from a specialist" is not substantiated.

Response comment 12: Please see our rewording in the response to your previous comment.

Comment 13: The authors' 3rd paragraph draws on other "prospective studies with full ascertainment of early miscarriages", stating that overall risk of miscarriage in such studies was similar to that found in the current study. The reader would be more convinced if
o   The numeric risks of miscarriage from REFS 5 -7, 2, 4, 8 were listed or tabulated so that the reader can judge for themselves if they agree with the authors' assertion that "… miscarriage in Norway was 12.8%.This risk is … similar… to reports…"

o   **Future research could estimate the extent of under-ascertainment of miscarriage due to omitting miscarriages which were managed in a non-specialist setting, e.g. by general medical practitioners, community nurses or midwives**

Response comment 13: Based on your recommendation, we have amended this paragraph in the discussion as follows.

Discussion (p. 13):
"Overall risk of miscarriage among recognized pregnancies in Norway was 12.8%. This risk is remarkably similar to reports from other Nordic countries (range between 13 and 14%).[5-7] Estimates from United States and Canada have been more variable (range between 9 and 20%).[8-10] This consistency with other Nordic studies, and with prospective studies with full ascertainment of early miscarriages, provides some reassurance that the Norwegian registries capture the majority of recognized miscarriages. Future research could estimate the extent of under-ascertainment of miscarriage due to omitting miscarriages that were managed in a non-specialist setting, e.g. by general medical practitioners, community nurses or midwives. "

Comment 14: Consider additional information (probably as supplementary material) for international comparisons of miscarriages at different gestational age bands or "trimesters": for example:
< 10 weeks: biological change from 1st trimester to mid-trimester as per Silver, RM. Nomenclature for Pregnancy Outcomes. Time for a Change Obstet Gynecol 2011;118:1402–8. DOI: 10.1097/AOG.0b013e3182392977 < 12 weeks: health services change to Norwegian pregnancy register < 14 weeks: ICD coding change to "midtrimester"
All <20 weeks: Norwegian definition of miscarriage All < 22 weeks: Some other countries' definition All < 24 weeks: UK and other international definition

Response comment 14: We made the assumption that all miscarraiges in the patient register occurred before 12 gestational weeks, since they would have been registered in the birth register if they occurred after this time. We have now included a supplementary table (eTable 1) showing the proportion of miscarriages among all pregnancies before 12 gestational weeks, 14 gestational weeks, 22 gestational weeks and 22 gestational weeks .

Results (p. 10):
"We show the proportion of miscarriages <12 gestational weeks, <14 gestational weeks, <20 gestational weeks, <22 gestational weeks and <24 gestational weeks in eTable 1."

Comment 15: References: <u>No suggested changes</u>

Comment 16: Figure 1 This flow diagram is generally presented clearly.
Please correct typographical errors where h and t are transposed in the word "Stillbirths" in the 2nd box to the right of the 4th row and in the lowermost box.
I recommend using a footnote to define abbreviations NPR and MBRN +/- ICD10. NPR and MBRN may not be immediately understood by an international reader, particularly a reader who reads this figure (or reproduces it with permission) separate from the main article.

Response comment 16: Done.

Comment 17: Figure 2 This pair of diagrams illustrate well the j-shaped curve or risk of miscarriage with age with part b expanding on the decade of age 23 to 33 years with detail including an indication of estimate uncertainty as vertical bars around a central point.
What do the vertical bars mean in 2(b)? Are they upper and lower limits those of a confidence interval?

Response comment 17: We have cut the second panel at the recommendation of the editor and another reviewer. The main information is provided in the new Fig 2. The bars in Fig 2 represents the confidence interval. This has been clarified in a footnote.

Comment 18: Table 1 Please check the lowermost, rightmost cell, corresponding to "Total" (age group) and "Proportion miscarriages including induced abortions that would have resulted in a miscarriage in the numerator and all induced abortions in the denominator % (N)". The figure is 1.28 but I wonder if this should be 12.8, that is, perhaps the decimal point is misplaced? Otherwise this table is useful and readable.

Response comment 18: Yes, the decimal point was misplaced. Thanks for such a careful inspection of our numbers. This error has now been corrected.

Comment 19: Table 2 This well illustrates the number and % of miscarriages for women sub-grouped by the registered outcome of the prior pregnancy. It also shows the age-adjusted odds ratio for miscarriage relative to the reference group of women with no previous registered pregnancy. <u>No changes suggested.</u>

Comment 20: Table 3 This table effectively illustrates the dose-association curve of previous miscarriage number 0 to 3 and the age-adjusted odds ratio for miscarriage. <u>No changes suggested.</u>

Comment 21: Table 4 This table well illustrates that previous pregnancy complications, other than previous post-term gestation, are associated with small but measurable increases in age-adjusted odds ratio for miscarriage.
The table would be more understandable as a stand-alone item if terms were defined in a footnote. In particular, I recommend that "Small" and "Large" fetal growth are defined as < 10th and > 90th centiles, citing birthweight or fetal weight standards so that the reader can find this. The footnote could include all other definitions +/- references for preterm, post-term, congenital malformations, pre-eclampsia, gestational diabetes.

Response comment 21: We made the requested changes to the figure and the corresponding footnote.

Comment 22: Table 5 This table illustrates inter-generational risks for pregnancy complications and miscarriage in the next pregnancy. Other than adding footnoted definitions to improve readability of the table as a stand-alone item of data (the same suggestions as for Table 4), I do not suggest changes.

Response comment 22: We have made the requested changes to the table.

Comment 23: Supplementary methods
This seems reasonable. I would also value a statistician to review

Response comment 23: We welcome a statistical review if deemed necessary by the editors.

Comment 24: Supplementary table: eTable 1 Risk of miscarriage according to the previous pregnancy ended in a live birth, stillbirth, miscarriage or a neonatal death (that is excluding induced abortion). This is readable and adjusted both for maternal age and for inter-pregnancy interval. <u>No changes suggested</u>

Comment 25: Supplementary table: eTable 2 Risk of miscarriages by whether the previous pregnancy was a live birth, with a pregnancy complication, adjusting for age, inter-pregnancy interval and smoking. <u>No changes suggested</u>

Additional Questions:
Please enter your name: Elizabeth A. McCarthy

Job Title: Senior Lecturer

Institution: University of Melbourne

References

1.   (SSB) SN. 14 prosent av befolkningen er innvandrere/ 14 percent of the population are immigrants. 2018; https://www.ssb.no/befolkning/artikler-og-publikasjoner/14-prosent-av-befolkningen-er-innvandrere. Accessed 28/01/2019, 2019.
2.   Oniya O, Neves K, Ahmed B, Konje JC. A review of the reproductive consequences of consanguinity. *Eur J Obstet Gynecol Reprod Biol.* 2019;232:87-96.
3.   Tanner LD, Tucker LY, Postlethwaite D, Greenberg M. Maternal race/ethnicity as a risk factor for cervical insufficiency. *Eur J Obstet Gynecol Reprod Biol.* 2018;221:156-9.
4.   Oliver-Williams CT, Steer PJ. Racial variation in the number of spontaneous abortions before a first successful pregnancy, and effects on subsequent pregnancies. *Int J Gynaecol Obstet.* 2015;129(3):207-12.
5.   Adolfsson A, Larsson PG. Cumulative incidence of previous spontaneous abortion in Sweden in 1983-2003: a register study. *Acta Obstet Gynecol Scand.* 2006;85(6):741-7.
6.   Hemminki E, Forssas E. Epidemiology of miscarriage and its relation to other reproductive events in Finland. *Am J Obstet Gynecol.* 1999;181(2):396-401.
7.   Nybo Andersen AM, Wohlfahrt J, Christens P, Olsen J, Melbye M. Maternal age and fetal loss: population based register linkage study. *Bmj.* 2000;320(7251):1708-12.
8.   Almeida ND, Basso O, Abrahamowicz M, Gagnon R, Tamblyn R. Risk of Miscarriage in Women Receiving Antidepressants in Early Pregnancy, Correcting for Induced Abortions. *Epidemiology.* 2016;27(4):538-46.
9.   Wilcox AJ, Weinberg CR, O'Connor JF, et al. Incidence of early loss of pregnancy. *N Engl J Med.* 1988;319(4):189-94.
10.   Rossen LM, Ahrens KA, Branum AM. Trends in Risk of Pregnancy Loss Among US Women, 1990-2011. *Paediatr Perinat Epidemiol.* 2018;32(1):19-29.