OBSTETRICS & GYNECOLOGY

**NOTICE:** This document contains correspondence generated during peer review and subsequent revisions but before transmittal to production for composition and copyediting:

- Comments from the reviewers and editors (email to author requesting revisions)
- Response from the author (cover letter submitted with revised manuscript)*

**The corresponding author has opted to make this information publicly available.*

Personal or nonessential information may be redacted at the editor's discretion.

Questions about these materials may be directed to the *Obstetrics & Gynecology* editorial office: obgyn@greenjournal.org.

**Date:** Apr 26, 2019
**To:** "Robert M. Silver" [redacted]
**From:** "The Green Journal" em@greenjournal.org
**Subject:** Your Submission ONG-19-569

RE: Manuscript Number ONG-19-569

Maternal Sleep Position through 30 weeks Gestation and Adverse Pregnancy Outcomes The NuMoM2b Prospective Cohort Study

Dear Dr. Silver:

Your manuscript has been reviewed by the Editorial Board and by special expert referees. Although it is judged not acceptable for publication in Obstetrics & Gynecology in its present form, we would be willing to give further consideration to a revised version.

If you wish to consider revising your manuscript, you will first need to study carefully the enclosed reports submitted by the referees and editors. Each point raised requires a response, by either revising your manuscript or making a clear and convincing argument as to why no revision is needed. To facilitate our review, we prefer that the cover letter include the comments made by the reviewers and the editor followed by your response. The revised manuscript should indicate the position of all changes made. We suggest that you use the "track changes" feature in your word processing software to do so (rather than strikethrough or underline formatting).

Your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 17, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: This is a secondary analysis of a prospective observational multicenter cohort student of nulliparous women with a singleton gestation. Study participants completed an in depth sleep questionnaire in the first and third trimesters. A subset of women also underwent a home sleep test. The primary outcome was a composite of adverse obstetrical outcomes including IUFD, SGA and HTN disorders of pregnancy. The study was undertaken to determine if sleep position was related to these outcomes. The study found no association of sleep position and adverse obstetrical outcomes except for an apparent protective effect of non-left lateral sleep position in the third trimester. The authors conclude that going to sleep in the supine or right lateral position through 30 weeks EGA is not associated with an increased risk of IUFD, SGA or gHTN disorders. Ways in which this manuscript could be improved include:

1. Lines 117-118: I would provide a little detail here for a more robust introduction.

2. Lines 122: What are some examples of campaign approaches? I think it would be helpful to give a little more detail.

3. Lines 125-127: I know you elaborate later, but I think a little more detail would be useful here.

4. Line 152-154: Is this questionnaire validated? My understanding is that sleep position changes multiple times throughout a night of sleep. I would provide a little more detail about the validity of this method.

5. Lines 236-245: Again, without a discussion of the validity in self reported sleep position, I am not sure how much credence to pay to the negative findings of this study.

6. Line 310: What fetal behavioral states? NST? BPP? Please elaborate.

7. Line 322: Can one ever control movement during sleep?

8. Line 327: Does anxiety really lead to iatrogenic preterm birth? I would remove this.

9. Lines 335-336: I think you need to provide some details of these two studies and contrast or compare them with your work.

Reviewer #2: The study is a secondary analysis of data obtained as part of prospective cohort study NuMom2b, correlating the sleep position with adverse events observed with pregnancy. The study results are significant as they provide a

different lens for analysis as the studies looking into sleep position and adverse pregnancy outcomes till date have been either retrospective analysis or case control studies.

Title: The title is appropriate and addresses the outcomes evaluated in context of pregnancy.

1. Abstract: A well defined summary of background, research question and outcomes has been presented.
a. Line 83: Please clarify V1 and V3 for the abstract purpose.
b. Background: Line 171- The abnormal placental function in correlation with sleep position has been provided as an explanation criteria for components of composite outcome in methods. A brief background of sleep position, expected influence on placental growth and association with adverse outcome will help anchor the selection of outcome criterias.
c. Methods: Placental insufficiency and its consequences has led the selection criteria for some of the outcomes reported such as Hypertension and renal abnormalities. Details of evaluation performed for preeclampsia and severe preeclampsia has been provided (180-182). Ophthalmological evaluation is noticeably missing from this structure. Could you please provide support for your decision?
d. Results: line 253- A secondary analysis of objective sleep position determination with adverse pregnancy outcome would have provided an objective outlook on effect of position on outcomes. Also, the analysis includes "going to sleep position" only for stillbirths, I am wondering about the correlation between waking up position and the effect observed.

2. Line 295- Thank you for a valuable insight.

3. Line 301: Can you please provide more details about the individuals studied and different ways of sleep assessments? This sentence raises more questions than provide answers.

4. Line 305-314- I was looking for this information in background to provide context for the selection of events included for composite outcome. A composite outcome is only as good as the components included and this will also inform the clinical practice and the citation of research as a guide to framing the future studies.

5. Line 332-334- A wonderful summary of study characteristics. I will also do a subgroup analysis of objective data to support the findings.

6. Line 339- Good recommendation

7. Line 34-344- An unbiased summary of limitations of the study

8. References: The references provided are adherent to the journal format and are reasonably current.

9. Figure 1- An important flowchart to walk readers through the scientific inquiry.

10. Tables- The tables are important to estimate the effect.

I commend the authors on an interesting scientific inquiry lending a new direction to the effect of sleep position in pregnancy. The evidence is a redirect from the previous information available and widely prescribed practice. This will provide framework for future research to relook at the available evidence.

Reviewer #3: This is a secondary analysis of a large prospective observational study examining the relationship between sleep position and adverse pregnancy outcomes in singleton gestations born to nulliparous women. Participants prospectively completed sleep questionnaires, including questions about sleep position in the previous week, between 6-14 weeks and 22-30 weeks gestation. Sleep position was then analyzed according to the occurrence of a composite outcome consisting of stillbirth, SGA and hypertensive disorders of pregnancy. The authors found that sleeping in the supine or right lateral position was not associated with an increased risk of the composite adverse outcome.

While this is a large, multicenter trial that offers compelling data, there are some fairly significant issues with the study design. Of primary concern is the timing of sleep position ascertainment. Sleep position was assessed for final time (V3) at 22 0/7 to 29 6/7. Since the biologic mechanism by which sleep position may lead to adverse pregnancy outcomes is caval compression leading to reduced venous return and a consequent decrement in placental blood flow, a larger uterus, as is typical of the third trimester, would be expected to produce a pronounced physiologic response. However, sleep position at this potentially more critical juncture is not assessed in the current study. Furthermore, the low number of stillbirths in the overall population precludes substantial interpretation. In studies that have demonstrated a difference in outcome based on sleep position, late stillbirth has been the specific outcome of interest. Although the timing of stillbirth is not fully elucidated here, 40% occurred prior to viability and only 25% after 37 weeks. Finally, there was only modest correlation of reported compared with objectively assessed sleep position, which tempers the findings and hinders the trial design. In V3, women who did NOT report a supine sleeping position still spent 48.4% of the time in the supine position, which is remarkably similar to the 51.6% with both subjectively reported back sleeping and objectively observed supine positioning. This further begs the question of whether subjectively reported sleeping position is an appropriate surrogate for actual sleeping position, which is critical to accurately ascertain in light of the underlying biologic mechanisms potentially driving adverse outcomes in the study.

In summary, although there are methodologic flaws, the findings presented are nonetheless notable and very relevant. The lack of association between sleep position <30 weeks and adverse outcome in this large and prospectively-assessed cohort is reassuring. Although the sample size is undoubtedly insufficient to detect differences in rare outcomes such as stillbirth, an adequately powered trial would be impractical and logistically prohibitive.

Specific Comments:

Abstract:

1* Line 94-96: Although this statement is technically true, I find it somewhat misleading. Is there really a difference between 51.6% and 48.4% (as assessed in V3), the relevant time point in this study?

2* Conclusion: A caveat should be added that the numbers for some rare outcomes were small and introduce the potential for type II error.

Methods:

3* Why were anomalous infants not excluded? Since stillbirth is the primary outcome of interest and there is a well know correlation between stillbirth and anomalies/genetic abnormalities, it would make sense to eliminate this group, since this clearly may confound the outcome of interest (stillbirth due to placental insufficiency).

4* How were hypertensive disorders of pregnancy defined? According to ACOG? What criteria were used for diagnosis?

Results:

5* What was the average GA for each of the questionnaire periods? This becomes particularly relevant for V3, since earlier average assessment would weaken any potential correlation with third trimester stillbirth.

6* What was the correlation between V1 and V3 sleep position? Did women tend to modify their sleeping behavior over time? Or was it constant throughout gestation?

7* The stillbirth numbers don't make sense. The text reports 40 stillbirths, but only 18 are included in table 4. What happened to the other 22?

8* What was the specific timing of the stillbirths between 24 and 37 weeks? Could any etiology be assigned to these cases? As previously stated, anomalous or chromosomally abnormal stillbirths should likely be excluded from analysis all together.

9* Do the authors have any data on severe or asymmetric FGR/SGA? Since most infant growth abnormalities are simply constitutional, it would be more interesting to try to hone in on an outcome that is more likely to be related to placental insufficiency.

Discussion:

10* Is there any basic science data i.e. in animal models about the physiologic changes that do or do not occur with caval compression in a pregnancy? If so, this data should be introduced and discussed to either support or refute the biologic mechanisms which are purported to cause adverse outcomes.

11* Do the authors have a potential interpretation or biologically plausible explanation for the protective effect of non-left lateral positioning on stillbirth? This unexpected finding definitely needs to be addressed in the discussion.

STATISTICAL EDITOR'S COMMENTS:

1. Tables 1 and 2: There are many baseline differences noted in Table 1, other than the covariates used as adjustors. For example, smoking, pre-gestational DM, kidney disease, race. The study population is large enough among the women without APOs that an additional analysis could potentially be done to augment the multivariable analyses, that is, using propensity matching.

2. Otherwise, Tables 2, 3 and 4 are carefully done. Since the number of stillbirths was small (n = 13 vs 5), the counts were too few to allow for multivariable adjustment. Those associations may be spurious and should be cited among the limitations of this analysis which predominantly demonstrated no association of sleep position with composite APOs. The more prudent conclusion is that an association of stillbirth risk vs sleep position is neither established nor disproved by these data.

3. lines 172-173: Although this is a secondary analysis and the power calculations would be post-hoc, since the findings

are not statistically significant, it would be useful for the reader to include a brief analysis of the statistical power associated with the sample sizes and frequency of adverse outcomes for some of the key conclusions. This would help to assure the reader that the negative conclusions are indeed generalizable.

4. lines 262-264: Should include this analysis as on-line supplemental.

5. General: Although the samples are generally large, there is no need to cite NS p-values to precision of .0001. Two significant figures is adequate.

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the Methods section.

4. Was this abstract presented at the 39th Annual SMFM meeting? If so, please disclose the name, dates, and location of the meeting on the title page.

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions at https://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

8. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology

also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

9. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

10. Provide a précis on the second page, for use in the Table of Contents. The précis is a single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

11. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

12. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here: http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

13. Only standard abbreviations and acronyms are allowed. A selected list is available online at http://edmgr.ovid.com /ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

14. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

15. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

16. The Journal's Production Editor had the following to say about the figures in your manuscript:

"-The tables and figures are uploaded in one document – all tables and figures should be uploaded as separate files into Editorial Manager"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

17. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and

publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

***

If you choose to revise your manuscript, please submit your revision via Editorial Manager for Obstetrics & Gynecology at http://ong.editorialmanager.com. It is essential that your cover letter list point-by-point the changes made in response to each criticism. Also, please save and submit your manuscript in a word processing format such as Microsoft Word.

If you submit a revision, we will assume that it has been developed in consultation with your co-authors and that each author has given approval to the final form of the revision.

Again, your paper will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by May 17, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

The Editors of Obstetrics & Gynecology

2017 IMPACT FACTOR: 4.982
2017 IMPACT FACTOR RANKING: 5th out of 82 ob/gyn journals

_____
In compliance with data protection regulations, you may request that we remove your personal registration details at any time. (Use the following URL: https://www.editorialmanager.com/ong/login.asp?a=r) Please contact the publication office if you have any questions.

Dear Drs. Chescheir and Rouse:

Thank you for considering our revised manuscript entitled "Maternal Sleep Position through 30 weeks Gestation and Adverse Pregnancy Outcomes The NuMoM2b Prospective Cohort Study" (ONG-19-569) for publication in Obstetrics and Gynecology. We have addressed each of the reviewers and editors points in hopes of improving our paper as follows:

REVIEWER COMMENTS:

Reviewer #1: This is a secondary analysis of a prospective observational multicenter cohort student of nulliparous women with a singleton gestation. Study participants completed an in depth sleep questionnaire in the first and third trimesters. A subset of women also underwent a home sleep test. The primary outcome was a composite of adverse obstetrical outcomes including IUFD, SGA and HTN disorders of pregnancy. The study was undertaken to determine if sleep position was related to these outcomes. The study found no association of sleep position and adverse obstetrical outcomes except for an apparent protective effect of non-left lateral sleep position in the third trimester. The authors conclude that going to sleep in the supine or right lateral position through 30 weeks EGA is not associated with an increased risk of IUFD, SGA or gHTN disorders. Ways in which this manuscript could be improved include:

1. Lines 117-118: I would provide a little detail here for a more robust introduction.

**This was done as suggested.**

2. Lines 122: What are some examples of campaign approaches? I think it would be helpful to give a little more detail.

**This was done as suggested.**

3. Lines 125-127: I know you elaborate later, but I think a little more detail would be useful here.

**We have now cited the studies mentioned in lines 125-127. In the current version we do not add further details since they are included extensively later in the paper. We hope to be mindful of the overall length of the article and journal space. However, we are happy to add more details to the introduction at the request of the reviewers and editors.**

4. Line 152-154: Is this questionnaire validated? My understanding is that sleep position changes multiple times throughout a night of sleep. I would provide a little more detail about the validity of this method.

**There is no way to 100% "validate" the questionnaire since there is no gold standard positive to validate against. Nonetheless, the questionnaire used was similar to the questionnaires used by others and it has been "validated" in one study that compared self-reported sleep position and correlation with video report (Warland and Dorrian 2014). As with other studies there was modest but imperfect correlation between the self-report and objectively assessed sleep position. This is now stated in the methods**

**and this additional reference is included in the paper.**

5. Lines 236-245: Again, without a discussion of the validity in self reported sleep position, I am not sure how much credence to pay to the negative findings of this study.

**Please see response to reviewer 1, #4. In addition, the potential for self reported sleep position to be inaccurate is clearly stated in the limitations section of the discussion.**

6. Line 310: What fetal behavioral states? NST? BPP? Please elaborate.

**This is done as suggested.**

7. Line 322: Can one ever control movement during sleep?

**The line was modified to reflect the reviewers concern and to clarify the statement.**

8. Line 327: Does anxiety really lead to iatrogenic preterm birth? I would remove this.

**It may if it leads to false positive results with antenatal testing. However, we agree with the reviewer that this may be a stretch and we have removed the statement as suggested.**

9. Lines 335-336: I think you need to provide some details of these two studies and contrast or compare them with your work.

**This was done as suggested.**

Reviewer #2: The study is a secondary analysis of data obtained as part of prospective cohort study NuMom2b, correlating the sleep position with adverse events observed with pregnancy. The study results are significant as they provide a different lens for analysis as the studies looking into sleep position and adverse pregnancy outcomes till date have been either retrospective analysis or case control studies.

Title: The title is appropriate and addresses the outcomes evaluated in context of pregnancy.

**N/A**

1. Abstract: A well defined summary of background, research question and outcomes has been presented.

**N/A**

a. Line 83: Please clarify V1 and V3 for the abstract purpose.

**Done as suggested and to stay within limitations of abstract length.**

b. Background: Line 171- The abnormal placental function in correlation with sleep position has been provided as an explanation criteria for components of composite outcome in

methods. A brief background of sleep position, expected influence on placental growth and association with adverse outcome will help anchor the selection of outcome criterias.

**Done as suggested.**

c. Methods: Placental insufficiency and its consequences has led the selection criteria for some of the outcomes reported such as Hypertension and renal abnormalities. Details of evaluation performed for preeclampsia and severe preeclampsia has been provided (180-182). Ophthalmological evaluation is noticeably missing from this structure. Could you please provide support for your decision?

**Ophthalmological evaluation is not part of generally accepted criteria for the definition of preeclampsia and other gestational hypertensive disorders. Accordingly we did not collect data regarding ophthalmological evaluation.**

d. Results: line 253- A secondary analysis of objective sleep position determination with adverse pregnancy outcome would have provided an objective outlook on effect of position on outcomes. Also, the analysis includes "going to sleep position" only for stillbirths, I am wondering about the correlation between waking up position and the effect observed.

**The relationship between objectively measured sleep position and adverse pregnancy outcomes is shown in table V. The correlation between waking up position and adverse pregnancy outcomes is depicted in table III. The trends were similar for the individual outcomes – hypertension disorders of pregnancy, SGA and SB using the waking up position. Using the results for position for waking up during the last week, we had an adjusted OR for SB of 0.39 (0.15, 0.97). This is now briefly stated in the results.**

2. Line 295- Thank you for a valuable insight.

**N/A**

3. Line 301: Can you please provide more details about the individuals studied and different ways of sleep assessments? This sentence raises more questions than provide answers.

**Done as suggested.**

4. Line 305-314- I was looking for this information in background to provide context for the selection of events included for composite outcome. A composite outcome is only as good as the components included and this will also inform the clinical practice and the citation of research as a guide to framing the future studies.

**We mention this information in lines 118 – 120, and then elaborate further in the discussion as noted by the reviewer. We propose leaving the bulk of the information in the discussion to preserve brevity. However, we are happy to include the additional information in the discussion in the background as well at the editors' discretion.**

5. Line 332-334- A wonderful summary of study characteristics. I will also do a subgroup analysis of objective data to support the findings.

**We agree that a subgroup analysis of objectively measured sleep and each adverse outcome is of interest. However, we did not include that analysis (showing no association between supine sleep and individual outcomes) owing to small numbers and limited power. This is now stated in the results section.**

6. Line 339- Good recommendation

**N/A**

7. Line 34-344- An unbiased summary of limitations of the study

**N/A**

8. References: The references provided are adherent to the journal format and are reasonably current.

**N/A**

9. Figure 1- An important flowchart to walk readers through the scientific inquiry.

**N/A**

10. Tables- The tables are important to estimate the effect.

**N/A**

I commend the authors on an interesting scientific inquiry lending a new direction to the effect of sleep position in pregnancy. The evidence is a redirect from the previous information available and widely prescribed practice. This will provide framework for future research to relook at the available evidence.

**N/A**

Reviewer #3: This is a secondary analysis of a large prospective observational study examining the relationship between sleep position and adverse pregnancy outcomes in singleton gestations born to nulliparous women. Participants prospectively completed sleep questionnaires, including questions about sleep position in the previous week, between 6-14 weeks and 22-30 weeks gestation. Sleep position was then analyzed according to the occurrence of a composite outcome consisting of stillbirth, SGA and hypertensive disorders of pregnancy. The authors found that sleeping in the supine or right lateral position was not associated with an increased risk of the composite adverse outcome.

While this is a large, multicenter trial that offers compelling data, there are some fairly significant issues with the study design. Of primary concern is the timing of sleep position ascertainment. Sleep position was assessed for final time (V3) at 22 0/7 to 29 6/7. Since the biologic mechanism by which sleep position may lead to adverse pregnancy outcomes is caval compression leading to reduced venous return and a consequent decrement in

placental blood flow, a larger uterus, as is typical of the third trimester, would be expected to produce a pronounced physiologic response. However, sleep position at this potentially more critical juncture is not assessed in the current study. Furthermore, the low number of stillbirths in the overall population precludes substantial interpretation. In studies that have demonstrated a difference in outcome based on sleep position, late stillbirth has been the specific outcome of interest. Although the timing of stillbirth is not fully elucidated here, 40% occurred prior to viability and only 25% after 37 weeks. Finally, there was only modest correlation of reported compared with objectively assessed sleep position, which tempers the findings and hinders the trial design. In V3, women who did NOT report a supine sleeping position still spent 48.4% of the time in the supine position, which is remarkably similar to the 51.6% with both subjectively reported back sleeping and objectively observed supine positioning. This further begs the question of whether subjectively reported sleeping position is an appropriate surrogate for actual sleeping position, which is critical to accurately ascertain in light of the underlying biologic mechanisms potentially driving adverse outcomes in the study.

In summary, although there are methodologic flaws, the findings presented are nonetheless notable and very relevant. The lack of association between sleep position <30 weeks and adverse outcome in this large and prospectively-assessed cohort is reassuring. Although the sample size is undoubtedly insufficient to detect differences in rare outcomes such as stillbirth, an adequately powered trial would be impractical and logistically prohibitive.

**Please see specific comments below**

Specific Comments:

Abstract:

1* Line 94-96: Although this statement is technically true, I find it somewhat misleading. Is there really a difference between 51.6% and 48.4% (as assessed in V3), the relevant time point in this study?

**We respectfully disagree. The numbers cited by the reviewer reflect the percentage of women who reported sleeping on heir back and who actually slept on their back and those who denied sleeping on their back and who slept on their back. The percentages do NOT reflect the percentage of people or time slept on the back. In addition, we used several thresholds to analyze objective sleep and we obtained similar results. We have now revised the text in the results in order to improve clarity and we apologize that the wording was unclear.**

**We also wholeheartedly agree with the reviewer (detailed comments above) that the fact that the imperfect correlation between self- report and actual sleep position is of concern! However, other investigators are using self-report alone to make strong conclusions about sleep and pregnancy. We believe this observation is of major importance and is an important message for readers, clinicians and researchers. It is a primary reason that we conclude that we need more studies rather than supine sleep is bad or good.**

2* Conclusion: A caveat should be added that the numbers for some rare outcomes were small and introduce the potential for type II error.

**Done as suggested**.

Methods:

3* Why were anomalous infants not excluded? Since stillbirth is the primary outcome of interest and there is a well know correlation between stillbirth and anomalies/genetic abnormalities, it would make sense to eliminate this group, since this clearly may confound the outcome of interest (stillbirth due to placental insufficiency).

**We agree with the reviewer that analysis of subsets of stillbirths would be of interest. However, there were simply too few stillbirths in the cohort to allow for meaningful subset analysis. Also, placental insufficiency may contribute to the pathophysiology of stillbirth in the setting of genetic abnormalities owing to genetically abnormal placentas. Accordingly, even this subset is of interest. It is noteworthy that there were few (if any) stillbirths due to solely to anomalies or genetic conditions. First, fetuses with known anomalies were excluded from NuMoM study enrollment, which decreased the overall rate. Second, there were no stillbirths with a known genetic abnormality. Thus, excluding such cases would not affect the results.**

4* How were hypertensive disorders of pregnancy defined? According to ACOG? What criteria were used for diagnosis?

**The definition of hypertensive disorders in pregnancy was rigorously defined using available criteria available at the time the study was conducted. The methods have previously been published in extensive detail and are cited in this paper. Moreover, cases were rigorously reviewed by MDs and unclear cases were adjudicated by the principle investigators. We are happy to include additional details in this paper (beyond the citation) at the discretion of the editors.**

Results:

5* What was the average GA for each of the questionnaire periods? This becomes particularly relevant for V3, since earlier average assessment would weaken any potential correlation with third trimester stillbirth.

**The average GA at visit 1 was 12.2 weeks; the average GA at visit 3 was 27.7 weeks.**

6* What was the correlation between V1 and V3 sleep position? Did women tend to modify their sleeping behavior over time? Or was it constant throughout gestation?

**Among the women who reported non-left lateral sleep at visit 1, 64.4% of them also reported non-left lateral sleep at visit 3. For the 4-category sleep position variable (left lateral, right lateral, supine, other), 46.2% of women reported sleeping in the same position at both visit 1 and visit 3, with women who slept in the left lateral or supine position at visit 1 most likely to report sleeping in the same position at visit 3 (64.4% and 43.8%, respectively).**

7* The stillbirth numbers don't make sense. The text reports 40 stillbirths, but only 18

are included in table 4. What happened to the other 22?

**Twelve stillbirths (N = 12) occurred prior to the start of the time window for the V3 mid-pregnancy sleep questionnaire (22 weeks). There were N=10 others without the V3 mid-pregnancy sleep questionnaire. Also note that of the 22 SBs that could not be included in the V3 mid-pregnancy analysis, 21 of them had a SB prior to 30 weeks GA and might have missed V3 sleep due to the visit being scheduled toward the end of the window after the SB had occurred. This is now clarified in the text.**

8* What was the specific timing of the stillbirths between 24 and 37 weeks? Could any etiology be assigned to these cases? As previously stated, anomalous or chromosomally abnormal stillbirths should likely be excluded from analysis all together.

**We agree with the reviewer that it would be valuable to assess subsets of stillbirth and focus on placental insufficiency. There were very few cases with malformations and there were none with abnormal karyotype (although systematic testing was not performed). Thus, excluding them would not change the results. Moreover, we think it is important to assess these cases since placental insufficiency is often a contributor to stillbirth in such cases owing to genetically abnormal placentas with insufficiency. We explored describing subsets of stillbirths but the numbers of each type are too small to do anything other than describe the cases. Thus, although we agree with the reviewer, there are simply too few cases to make any meaningful comments or conclusions. This is clearly stated in the paper.**

**The gestational age distributions among the 40 SBs included at V1 or V3 and among the 18 included at V3 are given below**

| Gestational Age In Completed Weeks | N(%) of SBs Included in Analysis | |
|---|---|---|
| | V1 or V3 | V3 |
| ≤24 weeks | 18 (45.0) | 0(0.0) |
| 25-29 weeks | 5(12.5) | 2(11.1) |
| 30-33 weeks | 1(2.5) | 1(5.6) |
| 34-36 weeks | 6(15.0) | 6(33.3) |
| 37+ weeks | 10(25.0) | 9(50.0) |
| Total | 40(100.0) | 18(100.0) |

9* Do the authors have any data on severe or asymmetric FGR/SGA? Since most infant growth abnormalities are simply constitutional, it would be more interesting to try to hone in on an outcome that is more likely to be related to placental insufficiency.

**We agree that this would be of interest. However, we cannot comment due to a lack of standardized data regarding umbilical artery Doppler studies in late pregnancy in FGR/SGA cases. However, we repeated the analysis using a more specific threshold for SGA (< 5%) and results were unchanged. This is now noted in the results.**

Discussion:

10* Is there any basic science data i.e. in animal models about the physiologic changes that do or do not occur with caval compression in a pregnancy? If so, this data should be introduced and discussed to either support or refute the biologic mechanisms which are purported to cause adverse outcomes.

**We included a thorough and comprehensive discussion of basic science data from humans about the physiology of caval compression. Animal data are not applicable to humans since anatomy varies dramatically among species. Accordingly, we have not been able to find appropriate data derived from animals to include.**

11* Do the authors have a potential interpretation or biologically plausible explanation for the protective effect of non-left lateral positioning on stillbirth? This unexpected finding definitely needs to be addressed in the discussion.

**We do not have a biologically plausible explanation for this result. With the small number of stillbirths available for study in this analysis, we are concerned that this is a spurious association. This is now stated in the paper.**

STATISTICAL EDITOR'S COMMENTS:

1. Tables 1 and 2: There are many baseline differences noted in Table 1, other than the covariates used as adjustors. For example, smoking, pre-gestational DM, kidney disease, race. The study population is large enough among the women without APOs that an additional analysis could potentially be done to augment the multivariable analyses, that is, using propensity matching.

**Based on your suggestion, we developed a propensity score for non-left lateral sleep position going to bed last week using the variables in Table 1. We then trimmed off the upper and lower tails (using <2.5th percentile "exposed" and >97.5th percentile "unexposed" as cutoffs), grouped the "trimmed" cohort participants by propensity score deciles, calculated odds ratios of the composite outcome for non-left lateral sleep position within these deciles, and summarized using a Mantel-Haenszel estimate. The adjusted odds ratios of the composite outcome for non-left lateral sleep using this approach was 0.97 (0.85, 1.10) at V1 and 1.01 (0.90, 1.13) at V3. We did the same for hypertensive disorders of pregnancy and SGA at V3. The adjusted odds ratios for these outcomes were 0.94 (0.82, 1.08) and 1.06 (0.91, 1.24), respectively. Finally, for SB we were able to group by propensity score tertiles. The adjusted odds ratio for this outcome was 0.28 (0.09, 0.90). We have briefly described this approach in the methods section and commented on the findings in the results section.**

2. Otherwise, Tables 2, 3 and 4 are carefully done. Since the number of stillbirths was (n = 13 vs 5), the counts were too few to allow for multivariable adjustment. Those associations may be spurious and should be cited among the limitations of this analysis which predominantly demonstrated no association of sleep position with composite APOs. The more prudent conclusion is that an association of stillbirth risk vs sleep position is neither established nor disproved by these data.

**We agree that the small number of stillbirths and the potential for confounding that cannot be explored carefully make the SB results tenuous. We agree with your suggestion and have added this to the discussion.**

3. lines 172-173: Although this is a secondary analysis and the power calculations would be post-hoc, since the findings are not statistically significant, it would be useful for the reader to include a brief analysis of the statistical power associated with the sample sizes and frequency of adverse outcomes for some of the key conclusions. This would help to assure the reader that the negative conclusions are indeed generalizable.

**We looked at detectible odds ratios given: a sample size of N=8000 participants; a significance level=0.05; power=0.80; probability of non-left lateral sleep=0.57; and the probability of APO given left lateral sleep = 13% for hypertensive disorders of pregnancy, 10% SGA, 0.4% SB, and 22% for the composite. We found that we could detect odds ratios of 1.201 for hypertensive disorders of pregnancy, 1.226 for SGA, 2.385 for SB, and 1.162 for the composite. The study was adequately powered to detect clinically meaningful odds ratios. We have added this information in the results section.**

4. lines 262-264: Should include this analysis as on-line supplemental.

**This analysis has been included as Supplemental Table 2 in the updated set of tables and the supplemental table has been referenced in the text of the paper.**

5. General: Although the samples are generally large, there is no need to cite NS p-values to precision of .0001. Two significant figures is adequate.

**Tables have been changed to include 2 decimals for p-values.**

EDITORIAL OFFICE COMMENTS:

1. The Editors of Obstetrics & Gynecology are seeking to increase transparency around its peer-review process, in line with efforts to do so in international biomedical peer review publishing. If your article is accepted, we will be posting this revision letter as supplemental digital content to the published article online. Additionally, unless you choose to opt out, we will also be including your point-by-point response to the revision letter, as well as subsequent author queries. If you opt out of including your response, only the revision letter will be posted. Please reply to this letter with one of two responses:
1. OPT-IN: Yes, please publish my response letter and subsequent email correspondence related to author queries.
2. OPT-OUT: No, please do not publish my response letter and subsequent email correspondence related to author queries.

**We elect to OPT-IN. Thank you.**

2. As of December 17, 2018, Obstetrics & Gynecology has implemented an "electronic Copyright Transfer Agreement" (eCTA) and will no longer be collecting author agreement

forms. When you are ready to revise your manuscript, you will be prompted in Editorial Manager (EM) to click on "Revise Submission." Doing so will launch the resubmission process, and you will be walked through the various questions that comprise the eCTA. Each of your coauthors will receive an email from the system requesting that they review and electronically sign the eCTA.

Any author agreement forms previously submitted will be superseded by the eCTA. During the resubmission process, you are welcome to remove these PDFs from EM. However, if you prefer, we can remove them for you after submission.

**N/A**

3. Clinical trials submitted to the journal as of July 1, 2018, must include a data sharing statement. The statement should indicate 1) whether individual deidentified participant data (including data dictionaries) will be shared; 2) what data in particular will be shared; 3) whether additional, related documents will be available (eg, study protocol, statistical analysis plan, etc.); 4) when the data will become available and for how long; and 5) by what access criteria data will be shared (including with whom, for what types of analyses, and by what mechanism). Responses to the five bullet points should be provided in a box at the end of the Methods section.

**N/A since this was not a clinical trial. However, all data are publically available in DASH.**

4. Was this abstract presented at the 39th Annual SMFM meeting? If so, please disclose the name, dates, and location of the meeting on the title page.

**Yes. Done as suggested.**

5. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines for reporting randomized controlled trials (ie, CONSORT), observational studies (ie, STROBE), meta-analyses and systematic reviews of randomized controlled trials (ie, PRISMA), harms in systematic reviews (ie, PRISMA for harms), studies of diagnostic accuracy (ie, STARD), meta-analyses and systematic reviews of observational studies (ie, MOOSE), economic evaluations of health interventions (ie, CHEERS), quality improvement in health care studies (ie, SQUIRE 2.0), and studies reporting results of Internet e-surveys (CHERRIES). Include the appropriate checklist for your
manuscript type upon submission. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at http://ong.editorialmanager.com. In your cover letter, be sure to indicate that you have followed the CONSORT, MOOSE, PRISMA, PRISMA for harms, STARD, STROBE, CHEERS, SQUIRE 2.0, or CHERRIES guidelines, as appropriate.

**This study adhered to STROBE guidelines. This has preciously been documented and submitted to Obstetric and Gynecology for this study. We are happy to do so again at the editors request.**

6. Standard obstetric and gynecology data definitions have been developed through the reVITALize initiative, which was convened by the American College of Obstetricians and Gynecologists and the members of the Women's Health Registry Alliance. Obstetrics & Gynecology has adopted the use of the reVITALize definitions. Please access the obstetric and gynecology data definitions athttps://www.acog.org/About-ACOG/ACOG-Departments/Patient-Safety-and-Quality-Improvement/reVITALize. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

**N/A**

7. Because of space limitations, it is important that your revised manuscript adhere to the following length restrictions by manuscript type: Original Research reports should not exceed 22 typed, double-spaced pages (5,500 words). Stated page limits include all numbered pages in a manuscript (i.e., title page, précis, abstract, text, references, tables, boxes, figure legends, and print appendixes) but exclude references.

**Done as suggested.**

8. Titles in Obstetrics & Gynecology are limited to 100 characters (including spaces). Do not structure the title as a declarative statement or a question. Introductory phrases such as "A study of..." or "Comprehensive investigations into..." or "A discussion of..." should be avoided in titles. Abbreviations, jargon, trade names, formulas, and obsolete terminology also should not be used in the title. Titles should include "A Randomized Controlled Trial," "A Meta-Analysis," or "A Systematic Review," as appropriate, in a subtitle. Otherwise, do not specify the type of manuscript in the title.

**Done as suggested.**

9. Specific rules govern the use of acknowledgments in the journal. Please note the following guidelines:

* All financial support of the study must be acknowledged.
* Any and all manuscript preparation assistance, including but not limited to topic development, data collection, analysis, writing, or editorial assistance, must be disclosed in the acknowledgments. Such acknowledgments must identify the entities that provided and paid for this assistance, whether directly or indirectly.
* All persons who contributed to the work reported in the manuscript, but not sufficiently to be authors, must be acknowledged. Written permission must be obtained from all individuals named in the acknowledgments, as readers may infer their endorsement of the data and conclusions. Please note that your response in the journal's electronic author form verifies that permission has been obtained from all named persons.
* If all or part of the paper was presented at the Annual Clinical and Scientific Meeting of the American College of Obstetricians and Gynecologists or at any other organizational meeting, that presentation should be noted (include the exact dates and location of the meeting).

**Done as suggested.**

10. Provide a précis on the second page, for use in the Table of Contents. The précis is a

single sentence of no more than 25 words that states the conclusion(s) of the report (ie, the bottom line). The précis should be similar to the abstract's conclusion. Do not use commercial names, abbreviations, or acronyms in the précis. Please avoid phrases like "This paper presents" or "This case presents."

**Done as suggested.**

11. The most common deficiency in revised manuscripts involves the abstract. Be sure there are no inconsistencies between the Abstract and the manuscript, and that the Abstract has a clear conclusion statement based on the results found in the paper. Make sure that the abstract does not contain information that does not appear in the body text. If you submit a revision, please check the abstract carefully.

In addition, the abstract length should follow journal guidelines. The word limits for different article types are as follows: Original Research articles, 300 words. Please provide a word count.

**Done as suggested.**

12. Abstracts for all randomized, controlled trials should be structured according to the journal's standard format. The Methods section should include the primary outcome and sample size justification. The Results section should begin with the dates of enrollment to the study, a description of demographics, and the primary outcome analysis. Please review the sample abstract that is located online here:http://edmgr.ovid.com/ong/accounts/sampleabstract_RCT.pdf. Please edit your abstract as needed.

**Done as suggested.**

13. Only standard abbreviations and acronyms are allowed. A selected list is available online athttp://edmgr.ovid.com/ong/accounts/abbreviations.pdf. Abbreviations and acronyms cannot be used in the title or précis. Abbreviations and acronyms must be spelled out the first time they are used in the abstract and again in the body of the manuscript.

**Done as suggested.**

14. The journal does not use the virgule symbol (/) in sentences with words. Please rephrase your text to avoid using "and/or," or similar constructions throughout the text. You may retain this symbol if you are using it to express data or a measurement.

**Done as suggested.**

15. Please review the journal's Table Checklist to make sure that your tables conform to journal style. The Table Checklist is available online here: http://edmgr.ovid.com/ong/accounts/table_checklist.pdf.

**Done as suggested.**

16. The Journal's Production Editor had the following to say about the figures in your manuscript:

"-The tables and figures are uploaded in one document – all tables and figures should be uploaded as separate files into Editorial Manager"

When you submit your revision, art saved in a digital format should accompany it. If your figure was created in Microsoft Word, Microsoft Excel, or Microsoft PowerPoint formats, please submit your original source file. Image files should not be copied and pasted into Microsoft Word or Microsoft PowerPoint.

When you submit your revision, art saved in a digital format should accompany it. Please upload each figure as a separate file to Editorial Manager (do not embed the figure in your manuscript file).

If the figures were created using a statistical program (eg, STATA, SPSS, SAS), please submit PDF or EPS files generated directly from the statistical program.

Figures should be saved as high-resolution TIFF files. The minimum requirements for resolution are 300 dpi for color or black and white photographs, and 600 dpi for images containing a photograph with text labeling or thin lines.

Art that is low resolution, digitized, adapted from slides, or downloaded from the Internet may not reproduce.

**Done as suggested.**

17. Authors whose manuscripts have been accepted for publication have the option to pay an article processing charge and publish open access. With this choice, articles are made freely available online immediately upon publication. An information sheet is available at http://links.lww.com/LWW-ES/A48. The cost for publishing an article as open access can be found at http://edmgr.ovid.com/acd/accounts/ifauth.htm.

Please note that if your article is accepted, you will receive an email from the editorial office asking you to choose a publication route (traditional or open access). Please keep an eye out for that future email and be sure to respond to it promptly.

**N/A**

Thanks again for considering this revised manuscript. Please do not hesitate to contact me if I can make further improvements in the paper.

Sincerely,

Bob Silver