OBSTETRICS & GYNECOLOGY

Date: Sep 30, 2019

To: "Ashish Premkumar" ████████████████████

From: "The Green Journal" em@greenjournal.org

Subject: Your Submission ONG-19-1599

RE: Manuscript Number ONG-19-1599

The association of acculturation with adverse pregnancy outcomes.

Dear Dr. Premkumar:

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 Oct 21, 2019, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1: Premkumar et al have performed a secondary analysis of the prospectively collected nuMoM2b cohort. They examined the effect of acculturation as defined by having a US vs. non-US birth place and preferred primary language proficiency. They observe that more acculturated women were more likely to have a higher rate of spontaneous preterm birth and preeclampsia.

This is an interesting and unique utilization of existing data. It is well written and thoughtfully analyzed. It will create interest in the OB community and likely to be well cited. Atypically, I have no substantive criticisms of the methodology or interpretation. However considering the experience of the collected authors, this is not surprising.

The authors are careful to note the limitations - however it seems likely that the effects they are documenting are particular to the Hispanic immigration experience in the US - given the large proportion of Hispanics in the low acculturation category. I realize that they do not find an effect after controlling for race, however a bivariate control variable for racial status is unlikely to capture the full exposure value of Hispanic acculturation. If I was to raise one criticism, I would like the authors to offer a bit more by way of interpretation of their findings. Do they feel that this is the immigration paradox? Is there any way to refer to or segregate by country of origin? I suspect that they authors have considered these issues, but this is likely to be a conversation if not controversy generating piece and a bit more subjective interpretation would be helpful.

Reviewer #2: The association of acculturation with adverse pregnancy outcomes

Perinatal adverse outcomes have multiple putative etiologies. Some of the acknowledged association between baseline characteristics and morbidity are extremes of maternal age, self-reported race/ethnicity, parity, body mass index, education, and insurance status.

This multi-center study professes to find a counterintuitive, direct proportionality between acculturation and pregnancy outcome. The novelty of this link, while puzzling, is undeniable and meritorious. The strength of the data—multicenter, geographically dispersed, prospectively collected, large sample size, trained research staff, and impeccably analyzed, subgroup analysis—make this manuscript one to remember.

In spite of its excellence, I would suggest the authors address the following:

1.   Was this a planned secondary analysis, or is it an unplanned analysis? If unplanned, why?

2.   In the abstract, it should be clarified that Spanish was the only other language "employed" during the study. Not all immigrants, including myself, speak/spoke Spanish. Reading this limitation in line 181 was somewhat disappointing.

3.   Clarification is needed regarding the exposure, and it's categorization into more vs. less acculturation: i) What time in pregnancy was it assessed; ii) Was it validated i.e. some Asians may not consider themselves proficient unless they got at least 750 on the SAT; iii) What adjustments were made during prenatal visits to accommodate less acculturated and could these adjustments have introduced bias?

4.   A minor, albeit personal, example, is illustrative of the weakness of the simplistic binary categorization. My younger daughter was born in Naples, Italy to parents whose English SAT scores were 780 and 360. Her score was "only 700," and thus she does not consider her to be proficient in language because it was less than the mother. To make the example more complicated, she was born at United States Naval Hospital, Naples, Italy, to parents in the military service and she considers herself a dual citizen. According to your definition, she would self-report herself to be less acculturated (born outside US), which exemplifies the weakness of the binary, non-validated exposure.

5.   In the abstract and at the outset of result section, please note that the rate of less acculturation was 18.2% (1,818/9,942), providing a needed perspective.

6.   Aside from stillbirth, there is lack of granularity with the severity of APO. Delivery at 34-36 weeks is different than at 24-26 weeks. Similarly, preeclampsia with and without severe features have different implications. Thus, at least in the supplemental Tables please provide the gradient of SPO e.g. PTB at 24-28, 29-34, 34-36; hypertensive with and without severe features.

7.   The symmetry between SGA and LGA—definition, rate, immediate and long term complications, reoccurrence rate—is undeniable. Hence, if small for gestational age is considered APO, large for gestational age should also be.

8.   Grimes DA and Schulz KF (Obstet Gynecol. 2012; 120:920-7) chastised the research community for creating false alarms and pseudo-epidemics. Please address their concerns, especially considering the aOR are less than 1.52 (Table 3).

9.   The claim made in lines 282-284 needs references, as does the wishful thinking in lines 288-290.

10.   Not to be thin skinned, the descriptor "women of color" should be deleted. Candidly, I find it borderline offensive, culturally insensitive, and inaccurate. Including albinos, we all have color. PLEASE remove it, even if the phrase is used by other well regarded authors. To offend one is to upset one too many.

11.   The Directed Acyclic Graph lacks evidence and is unnecessary, and following all the arrows is vertiginous. Please delete it.

Reviewer #3: This is an important article that contributes to the sociological literature on race and birth outcomes. I would encourage the authors to make sure their findings are accessible to a general ob-gyn audience and are clinically relevant.

Abstract
- Please describe your analysis methods and variables included in multivariate analysis in the methods section.
- The statistical relevancy of univariate analysis is unclear. I would suggest not including these in the abstract.

Introduction
- Acculuration and possible aspects are well-defined.

Methods
- Line 173, suggest making this two sentences for clarity.
- How did you adjust for parity when only nulliparous women were included? Does this adjust for prior pregnancy losses or terminations only?
- What is personal or income-based insurance?
- Appendix 1 and Breslow-Day test are likely outside the understanding of most readers. I would suggest adding more information on these or eliminating from your paper.

Results
- Line 243: Typo in increase

Discussion
- Did you have any data on residence? The ethnic enclave hypothesis is prominent in the discussion section.

- Good discussion of the strengths and weaknesses of the study, including power issues

Reviewer #4: This is a secondary analysis of the nuMoM2b study that included about 10,000 women with singleton gestations and was conducted from 2010 to 2013 at 8 academic centers. The authors evaluated the association between responses to 3 acculturation questions and 5 pregnancy outcomes. Comments and questions follow.

1. Abstract.
The abstract is a faithful summary of the manuscript, but a few more details would be helpful. The definition of acculturation includes the variables that the authors evaluated but not how to combine them to determine which study group to put the patient into (more acculturated vs less acculturated).

2. Introduction.
This is an interesting background discussion about acculturation. It would be helpful if the authors could include some numerical data about assessment of acculturation (because it is being used as a quantitative measure of risk) and also any references supporting association of acculturation with the study outcomes, just to give context for why these outcomes were selected.

3. Methods.
a. Line 162. It is reasonable to exclude pregnancies with fetal malformations, but why do so based on a 6- to 13 6/7-week ultrasound exam (prior to enrollment)?
b. Lines 175-184. Please provide more information about categorization of study participants as more acculturated or less acculturated. The description is not precise enough to allow readers to perform the determination.
c. Chronic hypertension is a risk factor for several of the outcomes studied. Did the authors adjust for it?
d. What was the purpose for including girls as young as 13? Some of the education and employment or insurance variables are not relevant in middle school-aged girls.

4. Results
a. Lines 230-234. The authors write in lines 230-231 that more acculturated women were likely to be between ages of 13 and 21 (actually the reverse - those less than 21 were more likely to be acculturated), and then they write in lines 233-234 that more acculturated women were less likely to have advanced degrees. Is that because they were too young to be in graduate school?
b. Here or in the discussion, please address heterogeneity of the population. Risks in immigrants who speak English poorly but have PhDs may differ from risks in immigrants who also speak English poorly but who have not had educational opportunities.
c. Lines 235-239. For each of these outcomes, the absolute difference in risk is approximately 2%. Please address magnitude of risk, because odds ratios below 3 are less likely to be clinically significant.

5. Discussion.
a. In the discussion, the authors explore the social epidemiology and cultural anthropology underpinnings of the study. The hypotheses discussed in lines 269-281 are appropriate background content, but they are not directly related to the study outcomes. In addition to presenting the association between survey responses and diagnoses, would try to establish a medical basis for that the differences.
b. Lines 318-323. If interviews were conducted in English or Spanish only, how did the authors address the needs of women from countries where other languages were spoken? One of 2 study variables was ability to speak English, and the rate of "other" ethnicity was nearly 3 times higher in the less acculturated group. Did the authors consider excluding women whose preferred language was neither English or Spanish?

STATISTICAL EDITOR COMMENTS:

The Statistical Editor makes the following points that need to be addressed:

Tables 1, 2, 3: In addition to the demographic factors identified, there are important variables not identified that could have influenced pre-eclampsia or eclampsia, namely baseline BMI, wgt gain during pregnancy, baseline BP. The counts of adverse outcomes among the less acculturated were too few to allow for adjustment with 6 variables for indicated PTB and for stillbirth.

Table 3: Need to include crude ORs to contrast with aORs.

Appendices: These data are a subset, with therefore lower samples, lower power and inability to generalize any NS findings. Also, the column headings have the same "n"s as in the main text, but should be lower values than the main

text.

EDITOR COMMENTS:

1. Thank you for your submission to Obstetrics & Gynecology. In addition to the comments from the reviewers above, you are being sent a notated PDF that contains the Editor's specific comments. Please review and consider the comments in this file prior to submitting your revised manuscript. These comments should be included in your point-by-point response cover letter.

The notated PDF is uploaded to this submission's record in Editorial Manager. If you cannot locate the file, contact Randi Zung and she will send it by email - rzung@greenjournal.org.

- We no longer require that authors adhere to the Green Journal format with the first submission of their papers. However, any revisions must do so. I strongly encourage you to read the instructions for authors (the general bits as well as those specific to the feature-type you are submitting). The instructions provide guidance regarding formatting, word and reference limits, authorship issues, and other things. Adherence to these requirements with your revision will avoid delays during the revision process, as well as avoid re-revisions on your part in order to comply with the formatting. Pay particular attention to use of abbreviations, please.

- acculturation can occur in other countries as well so its not just orienting toward the US culture--its towards the new or adopted culture.

- We have concerns about a number of confounders that have not been included in your study that are known contributors to risks for various perinatal complications. I suspect that the nuMOMs2B data set include these data. This would include maternal BMI, weight gain in pregnancy, baseline blood pressure as noted in the statistical reviewer's comments. In addition, cigarette smoking exposure would be important to include as well.   Without including this data, it is very difficult to ascribe the differences to acculturation alone.

- One of the critiques of your paper is that these 2 criteria (place of birth, language) are inadequate proxies for acculturation. In your discussion section, please comment on potential limitations of using just these 2 characteristics and other definitions used in other studies.

- In the appendix section, given that this analytic framework is unusual for our journal, please provide a brief explanation of the purpose of this approach, how its done, and what it tells a person.

- 13 and 21 years

- it looks like (by the eyeball test) that the degree of education is pretty similar between the groups, except at the advanced degree level, likely representing women who were immigrated for education purposes or for jobs. I think a fuller explanation of your data here would be (if statistical analysis confirms) that education status is similar except for at the highest level.

- Values vs Effect Size and Confidence Intervals: While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. This is true for the abstract as well as the manuscript.

- please report all of the primary outcomes: include SGA and stillbirth, for instance.

- Please note in discussion that effect sizes (RR, OR) within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA, Schulz KF. Ob Gyn 2012;120:920-7)

- its not clear in any data you have presented that you included others than US born and Latina women since you only did interviews in English and Spanish and I find no data showing you included women from countries for which other languages are the norm (such as African, Asian/Pacific, Arabic-speaking countries).

- Please state they you did this by the DAG analysis.

- able to evaluate previous findings?

- For each of the tables, please clarify definition of less acculturated. From the methods section, it seems to have included those born outside the US as well as those born in the US but with limited English proficiency. The table footnotes do not include those born outside the US.

2. 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. 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:
A.   OPT-IN: Yes, please publish my point-by-point response letter.
B.   OPT-OUT: No, please do not publish my point-by-point response letter.

3. 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.

Please check with your coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed on the manuscript's title page.

4. All studies should follow the principles set forth in the Helsinki Declaration of 1975, as revised in 2013, and manuscripts should be approved by the necessary authority before submission. Applicable original research studies should be reviewed by an institutional review board (IRB) or ethics committee. This review should be documented in your cover letter as well in the Materials and Methods section, with an explanation if the study was considered exempt. If your research is based on a publicly available data set approved by your IRB for exemption, please provide documentation of this in your cover letter by submitting the URL of the IRB website outlining the exempt data sets or a letter from a representative of the IRB. In addition, insert a sentence in the Materials and Methods section stating that the study was approved or exempt from approval. In all cases, the complete name of the IRB should be provided in the manuscript.

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. 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).

9. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.

10. 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.

11. 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.

12. 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.

13. In your Abstract, manuscript Results sections, and tables, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone.

If appropriate, please include number needed to treat for benefits (NNTb) or harm (NNTh). When comparing two procedures, please express the outcome of the comparison in U.S. dollar amounts.

Please standardize the presentation of your data throughout the manuscript submission. For P values, do not exceed three decimal places (for example, "P = .001"). For percentages, do not exceed one decimal place (for example, 11.1%").

14. 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.

15. The American College of Obstetricians and Gynecologists' (ACOG) documents are frequently updated. These documents may be withdrawn and replaced with newer, revised versions. If you cite ACOG documents in your manuscript, be sure the reference you are citing is still current and available. If the reference you are citing has been updated (ie, replaced by a newer version), please ensure that the new version supports whatever statement you are making in your manuscript and then update your reference list accordingly (exceptions could include manuscripts that address items of historical interest). If the reference you are citing has been withdrawn with no clear replacement, please contact the editorial office for assistance (obgyn@greenjournal.org). In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript (exceptions could include manuscripts that address items of historical interest). All ACOG documents (eg, Committee Opinions and Practice Bulletins) may be found via the Clinical Guidance & Publications page at https://www.acog.org/Clinical-Guidance-and-Publications/Search-Clinical-Guidance.

16. 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.

17. If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded in a word processing format such as Microsoft Word. Your revision's cover letter should include the following:
    * A confirmation that you have read the Instructions for Authors (http://edmgr.ovid.com/ong/accounts/authors.pdf), and
    * A point-by-point response to each of the received comments in this letter.

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 Oct 21, 2019, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Nancy C. Chescheir, MD
Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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if you have any questions.

[REDACTED]

Editor
Obstetrics & Gynecology

10/23/2019

Dear Editor,

Thank you for this opportunity to resubmit our manuscript entitled "**The association of acculturation with adverse pregnancy outcomes**." Authors include Ashish Premkumar, Michelle P. Debbink, Robert M. Silver, David M. Haas, Hyagriv N. Simhan, Deborah A. Wing, Samuel Parry, Brian M. Mercer, Jay Iams, Uma M. Reddy, George Saade, and William A. Grobman. The authors report no conflict of interest. All authors have approved this version of the manuscript for submission.

In response to the comments from the reviewers, we undertook a re-analysis of our data with updated tables and results. We have uploaded a tracked version of the manuscript and tables. Regarding the reviewers comments, we have responded to them below:

Reviewer #1
1. If I was to raise one criticism, I would like the authors to offer a bit more by way of interpretation of their findings. Do they feel that this is the immigration paradox? Is there any way to refer to or segregate by country of origin?
    a. We have clarified this in our Discussion. Please see page 13, lines 318-21.

Reviewer #2
1. Was this a planned secondary analysis, or is it an unplanned analysis?
    a. This was a planned secondary analysis. We have added language in the Methods section to illustrate this. Please see page 6, line 152.
2. In the abstract, it should be clarified that Spanish was the only other language "employed" during the study. Not all immigrants, including myself, speak/spoke Spanish. Reading this limitation in line 181 was somewhat disappointing.
    a. We have clarified this in the abstract. Please see page 3, lines 79-80.
3. Clarification is needed regarding the exposure, and it's categorization into more vs. less acculturation: i) What time in pregnancy was it assessed; ii) Was it validated i.e. some Asians may not consider themselves proficient unless they got at least 750 on the SAT; iii) What adjustments were made during prenatal visits to accommodate less acculturated and could these adjustments have introduced bias?

a. Timing of exposure assessment has been clarified in the text. Please see page 7, line 177. As the exposure assessment was part of study protocol, this data was not utilized for routine prenatal care. Furthermore, all assessment of language proficiency was self-reported, and was not subject to further testing. In the case the reviewer mentions regarding self-reported proficiency for someone who does not feel proficient without a very high SAT score, this is not something we can assess with the data available. However, we suspect that accounting for education may help to address some of this concern, since it is likely that individuals with a high SAT score in English who are not native speakers are likely to have significant years of education. Our models hold education constant, which should eliminate the portion of the coefficient for acculturation that is due to education, which may serve as a proxy for the phenomenon the reviewer describes.

4. In the abstract and at the outset of result section, please note that the rate of less acculturation was 18.2% (1,818/9,942), providing a needed perspective.
    a. This finding is already present in the Abstract (see page 3, lines 88-90) and was added in the Results (see page 10, lines 246-8).

5. A minor, albeit personal, example, is illustrative of the weakness of the simplistic binary categorization. My younger daughter was born in Naples, Italy to parents whose English SAT scores were 780 and 360. Her score was "only 700," and thus she does not consider her to be proficient in language because it was less than the mother. To make the example more complicated, she was born at United States Naval Hospital, Naples, Italy, to parents in the military service and she considers herself a dual citizen. According to your definition, she would self-report herself to be less acculturated (born outside US), which exemplifies the weakness of the binary, non-validated exposure.
    a. We have illustrated the limitations in a binary categorization of acculturation in the Discussion. Please see pages 15-16, lines 364-72.

6. Aside from stillbirth, there is lack of granularity with the severity of APO. Delivery at 34-36 weeks is different than at 24-26 weeks. Similarly, preeclampsia with and without severe features have different implications. Thus, at least in the supplemental Tables. Please provide the gradient of SPO e.g. PTB at 24-28, 29-34, 34-36; hypertensive with and without severe features.
    a. We have decided to perform an analysis focusing on multiple subtypes of hypertensive disorders of pregnancy, and discussed these as post-hoc analyses in our text. Given our concerns regarding multiple comparisons and overfitting of our data to less common outcomes, echoed by the statistical editor of *Obstetrics & Gynecology*, as well as our reluctance to pursue unplanned analyses due to risk of type I and type II errors, we have decided to forego analysis of subtypes of preterm birth.

7. Grimes DA and Schulz KF (Obstet Gynecol. 2012; 120:920-7) chastised the research community for creating false alarms and pseudo-epidemics. Please address their concerns, especially considering the aOR are less than 1.52 (Table 3).

a. We have added language regarding this concern, which was also echoed by the statistical editor. Please see page 16, lines 381-88. In general response, we do not feel this is a "pseudo-epidemic" or "false alarm." Rather, understanding the social determinants of health is difficult and can be statistically muddy (as the DAG shows). Though this analysis and other studies may have smaller odds ratios, they demonstrate relationships that are consistently reproducible throughout the literature in numerous settings. When results are consistently reproducible, even with smaller odds ratios, this should raise concerns about the impact acculturation may have. Furthermore, we are adding to this literature by attempting to understand which APOs might be most important, which can generate hypotheses regarding the etiology of the relationship between acculturation and APOs.

8. The claim made in lines 282-284 needs references, as does the wishful thinking in lines 288-290.
    a. We have clarified this with citations and removed the statement in question in lines 288-290 in the initial version of the manuscript.

9. Not to be thin skinned, the descriptor "women of color" should be deleted. Candidly, I find it borderline offensive, culturally insensitive, and inaccurate. Including albinos, we all have color. PLEASE remove it, even if the phrase is used by other well regarded authors. To offend one is to upset one too many.
    a. We respectfully disagree with the comment made by the reviewer, as women of color is a commonly-accepted term for discussion of minority groups within the United States. The lead author (AP) has written multiple pieces that have employed this term, most recently in *Obstetrics and Gynecology* last year (see **Premkumar A**, Whetstone S, Jackson AV. Beyond Silence and Inaction: Changing the Response to Experiences of Racism in the Care Workforce. Obstet Gynecol 2018;132:820-7). We hear the reviewer's concern over use of this phrase, and we acknowledge the lack of granularity in the phrase; however, it is also important to acknowledge the ways in which women of color have very different experiences due to structural racism. This remains important when discussing immigration, because immigration is also racialized, and migrants who are also women of color will have different experiences than white immigrants.

10. The Directed Acyclic Graph lacks evidence and is unnecessary, and following all the arrows is vertiginous. Please delete it.
    a. We respectfully disagree with the comment made by the reviewer. We have expanded the description in the methods of the utility of a DAG, which is a crucial component of the analysis. It is very commonly used in epidemiologic studies, in particular for social determinants of health work, because it helps to elucidate the proposed causal pathways and identify variables that should be included in our multivariable regression analysis. We have decided to keep the DAG as part of the appendix and to offer a short discussion in our Methods section regarding the utility of a DAG. Please see page 9, lines 223-30.

Reviewer #3
1. In the abstract, please describe your analysis methods and variables included in multivariate analysis in the methods section.
    a. We have added in a section on the methods and variables included in the analysis. Please see page 3, lines 84-87
2. The statistical relevancy of univariate analysis is unclear. I would suggest not including these in the abstract.
    a. We have removed the univariable analysis from the abstract
3. Line 173, suggest making this two sentences for clarity.
    a. We have completed this request.
4. How did you adjust for parity when only nulliparous women were included? Does this adjust for prior pregnancy losses or terminations only?
    a. We adjusted for gravidity, not parity. Please see page 3, lines 84-87.
5. What is personal or income-based insurance?
    a. Personal or income-based insurance are insurance payors that are purchased by individuals, independent of employers.
6. Appendix 1 and Breslow-Day test are likely outside the understanding of most readers. I would suggest adding more information on these or eliminating from your paper.
    b. We have added further information about DAGs and Breslow-Day tests of interaction. Please see page 9, lines 223-30.
7. Line 243: Typo in increase
    a. This has been corrected.
8. Did you have any data on residence? The ethnic enclave hypothesis is prominent in the discussion section.
    a. We did not have specific geospatial data on residence.

Reviewer #4
1. The abstract is a faithful summary of the manuscript, but a few more details would be helpful. The definition of acculturation includes the variables that the authors evaluated but not how to combine them to determine which study group to put the patient into (more acculturated vs less acculturated).
    a. We have added further information to clarify the categorization of the exposure. Please see page 3, lines 78-80.
2. This is an interesting background discussion about acculturation. It would be helpful if the authors could include some numerical data about assessment of acculturation (because it is being used as a quantitative measure of risk) and also any references supporting association of acculturation with the study outcomes, just to give context for why these outcomes were selected.
    a. Acculturation traditionally is not assessed through quantitative measurements (e.g. from a 0-10 scale), but is instead thought of as a categorical quality. In regards to data associating acculturation with study outcomes, please see page 5, lines 133-135.
3. Line 162. It is reasonable to exclude pregnancies with fetal malformations, but why do so based on a 6- to 13 6/7-week ultrasound exam (prior to enrollment)?

a. While the nuMoM2b protocol specified that women would be excluded if a fetal malformation were diagnosed between 6w0d to 13w6d, the protocol did not establish that women would be excluded if anomalies were discovered on ultrasounds performed later in gestation. We have chosen to adhere to the nuMoM2b protocol regarding this perspective.

4. Lines 175-184. Please provide more information about categorization of study participants as more acculturated or less acculturated. The description is not precise enough to allow readers to perform the determination.
    a. We disagree with the reviewer's comment, as we have outlined as clearly as possible the categorization of acculturation.

5. Chronic hypertension is a risk factor for several of the outcomes studied. Did the authors adjust for it?
    a. This was not adjusted for, as it would introduce collider stratification bias into the analysis given the likelihood that chronic hypertension is on a pathway between acculturation, stress, and hypertensive disorders of pregnancy. Please see page 9, lines 223-30. However, in response to reviewer 2, we post-hoc subdivided the preeclampsia or eclampsia outcome into subtypes of severity (e.g. (superimposed) preeclampsia with severe features OR (superimposed) preeclampsia without severe features) and added gestational hypertension.

6. What was the purpose for including girls as young as 13? Some of the education and employment or insurance variables are not relevant in middle school-aged girls.
    a. While we agree that employment is not necessarily relevant, and that education may be censored at the patient's current age, insurance is still relevant, as most minors are eligible to receive insurance except for undocumented migrants which is relevant as a potential confounder. In addition, the inclusion of the entire sample is important, as it improves generalizability. The exposure of interest is related to age only in the sense that it is time-dependent on length of exposure in the new country, but this is not necessarily related to a patient's age (e.g., a 13-year old pregnant migrant may have moved to the U.S. at age 1, been in U.S. schools since age 4, and therefore may actually be *more* acculturated than a 38 year old migrant also in her new country for 12 years). We therefore did not want to exclude these participants in the study in order to get a robust understanding of acculturation.

7. Lines 230-234. The authors write in lines 230-231 that more acculturated women were likely to be between ages of 13 and 21 (actually the reverse - those less than 21 were more likely to be acculturated), and then they write in lines 233-234 that more acculturated women were less likely to have advanced degrees. Is that because they were too young to be in graduate school?
    a. We respectfully feel the relationship the reviewer describes can be stated in either direction as this is a simple 2x3 descriptive table, with two acculturation and three age categories. The distributions are statistically different from what would be expected, and the order of stating this difference is generally irrelevant to a reader's understanding. If the editors

feel strongly, we will re-word the sentence. In response to the second portion of the question, over 78% of the more acculturated women were over 22, while 85% of the less acculturated were over 22. With an absolute difference of only 7%, it is unlikely that age alone explains the lack of advanced degrees among this population. It is more likely that this is related to the comments we and the reviewer make below about the relationship to education and advanced degrees and "allowed" immigration.

8. Here or in the discussion, please address heterogeneity of the population. Risks in immigrants who speak English poorly but have PhDs may differ from risks in immigrants who also speak English poorly but who have not had educational opportunities.

    a. The data do not permit us to assess that level of granularity with any statistical confidence. However, we do acknowledge generally in the discussion that lack of granularity limits our ability to understand acculturation and its relationship to APOs. In response to the reviewer, we have added this lack of granularity about education in the discussion – see page 16, line 369. However, as a point of clarification, data suggest that educational attainment is rife with complicated sociopolitical ramifications regarding ability of certain individuals to migrate (e.g. to engage in the acculturation process) (see Schwartz SJ et al. Rethinking the Concept of Acculturation: Implications for Theory and Research. Am Psychol 2010; 65(4):237-51). Furthermore, the relationship between language and education is complex, and has much to do with ethnic enclaves and living arrangements. Indeed, some data suggests that education is a moderator of health outcomes, rather than a confounder (see Fox M et al. Acculturation and Health: The Moderating Role of Sociocultural Context. Am Anthropol 2017;119(3):405-21).

9. Lines 235-239. For each of these outcomes, the absolute difference in risk is approximately 2%. Please address magnitude of risk, because odds ratios below 3 are less likely to be clinically significant.

    a. Please see our response to Reviewer #2, comment #7.

10. In the discussion, the authors explore the social epidemiology and cultural anthropology underpinnings of the study. The hypotheses discussed in lines 269-281 are appropriate background content, but they are not directly related to the study outcomes. In addition to presenting the association between survey responses and diagnoses, would try to establish a medical basis for that the differences.

    a. We disagree with the reviewers comments regarding lines 269-81, as these provide crucial context for ongoing debates within acculturation that contextualize the findings from our study. Furthermore, we described some of the medical basis for the differences in health outcomes based on acculturation in the introduction, specifically discussing the immigrant paradox and the healthy immigrant hypothesis (see page 5, lines 117-128). Please see the response to Reviewer #1, comment #1.

11. Lines 318-323. If interviews were conducted in English or Spanish only, how did the authors address the needs of women from countries where other languages were spoken? One of 2 study variables was ability to speak English, and the rate of "other" ethnicity was nearly 3 times higher in the less acculturated group. Did the authors consider excluding women whose preferred language was neither English or Spanish?

    a. Please see page 7, lines 175-184. While English or Spanish were the only two languages employed during study visits, individuals could participate in the study and be consented regardless of whether their primary language was English or Spanish.

Statistical editor

1. Acculturation can occur in other countries as well so its not just orienting toward the US culture--its towards the new or adopted culture.

    a. This study is specifically looking at the U.S., which drove the description we originally included. However, we have changed our wording to reflect the statistical editors concerned. See page 5, line 133.

2. We have concerns about a number of confounders that have not been included in your study that are known contributors to risks for various perinatal complications. I suspect that the nuMOMs2B data set include these data. This would include maternal BMI, weight gain in pregnancy, baseline blood pressure as noted in the statistical reviewer's comments. In addition, cigarette smoking exposure would be important to include as well. Without including this data, it is very difficult to ascribe the differences to acculturation alone.

    a. We disagree with these comments, as maternal BMI, baseline blood pressure, and cigarette smoking are noted markers of the acculturation process (see Fox M et al. Acculturation and Health: The Moderating Role of Sociocultural Context. Am Anthropol 2017;119(3):405-21). Therefore, to control for these variables would introduce collider stratification bias. Please see our discussion of our methods on page 9, lines 225-228.

3. One of the critiques of your paper is that these 2 criteria (place of birth, language) are inadequate proxies for acculturation. In your discussion section, please comment on potential limitations of using just these 2 characteristics and other definitions used in other studies.

    a. We have added language to discuss these limitations. See pages 15-16, lines 364-72.

4. In the appendix section, given that this analytic framework is unusual for our journal, please provide a brief explanation of the purpose of this approach, how its done, and what it tells a person.

    a. We have added language on DAGs. Please see page 9, lines 221-30.

5. It looks like (by the eyeball test) that the degree of education is pretty similar between the groups, except at the advanced degree level, likely representing women who were immigrated for education purposes or for jobs. I think a fuller explanation of your data here would be (if statistical analysis confirms) that education status is similar except for at the highest level.

a. Based on univariable analysis, there is a statistically higher incidence of "Some College" (20.0% v. 17.2%, p = 0.007) or "Technical or Associate's" (10.3% v. 8.7%, p = 0.031) among women with more acculturation; however, less acculturated women had a higher incidence of women with "Advanced degree work" (21.6% v. 29.3%, p < 0.001). This has been added on pages 10-11, lines 252-6

6. Values vs Effect Size and Confidence Intervals: While P values are a central part of inference testing in statistics, when cited alone, often the strength of the conclusion can be misunderstood. Whenever possible, the preferred citation should be in terms of an effect size, such as odds ratio or relative risk or the mean difference of a variable between two groups, expressed with appropriate confidence intervals. When such syntax is used, the P value has only secondary importance and often can be omitted or noted as footnotes in a Table format. Putting the results in the form of an effect size makes the result of the statistical test more clinically relevant and gives better context than citing P values alone. This is true for the abstract as well as the manuscript.
    a. We have performed this throughout the abstract and manuscript.

7. Please report all of the primary outcomes: include SGA and stillbirth, for instance.
    a. Please see page 11, lines 267-8.

8. Please note in discussion that effect sizes (RR, OR) within the zone of potential bias should be noted as weak. Those effect sizes in the zone of potential interest should be emphasized. (Ref: False alarms and pseudo-epidemics. The limitations of observational epidemiology. Grimes DA, Schulz KF. Ob Gyn 2012;120:920-7)
    a. Please see response to Reviewer #2, comment #7.

9. It's not clear in any data you have presented that you included others than US born and Latina women since you only did interviews in English and Spanish and I find no data showing you included women from countries for which other languages are the norm (such as African, Asian/Pacific, Arabic-speaking countries).
    a. We have clarified this on pages 11, lines 259-61.

10. For each of the tables, please clarify definition of less acculturated. From the methods section, it seems to have included those born outside the US as well as those born in the US but with limited English proficiency. The table footnotes do not include those born outside the US.
    a. This has been corrected in all of the attached tables and Appendices.

In the uploaded documents, please find the manuscript with 3 tables, 1 Supplementary Figure, and 3 Supplementary Tables. Please do not hesitate to reach out to us with any questions or concerns.

Best,

Ashish Premkumar, MD
On behalf of all authors

Date: Oct 28, 2019

To: "Ashish Premkumar" ████████████████████████████

From: "The Green Journal" em@greenjournal.org

Subject: Your Submission ONG-19-1599R1

RE: Manuscript Number ONG-19-1599R1

The association of acculturation with adverse pregnancy outcomes

Dear Dr. Premkumar:

Thanks so much for this revision. You will receive a notated PDF (uploaded to your EM Author account, under Attachments) with some queries I have after reading the revision and your rebuttal letter. We still have some concerns, however, regarding the differences in the baseline characteristics of the two groups.

The next version of your submission will be due by November 11, 2019. If you need an extension, or help locating the PDF, please contact Randi Zung (rzung@greenjournal.org).

The comments from the journal's Statistical Editor are as follows:

Table 1 clearly shows baseline differences in the cohorts due to BMI, DM, smoking, chronic HTN etc. To then show differences in frequency (Table 2) or crude odds (Table 3) without any adjustment for baseline differences assumes that any statistical difference is associated with acculturation status alone, may be one explanation, but it's not the only possible one.

Furthermore, the Authors need to increase the number of adjustors or match a subset of women in each cohort for the factors besides those they have included in the aOR model to adjust or match for important confounders. If, as the Authors argue, acculturation is linked to BMI, smoking, HTN etc, then the aORs with those additional variables may no longer show an association of acculturation vs the adverse outcomes. If so, then the Authors can argue in Discussion the reasons for how that outcome is explainable by the process of acculturation.

Also, regardless of the number of variables used as adjustors, as stated earlier and not addressed by the Authors, the counts for stillbirth (18) or indicated PTB (47) limit the potential for multivariable adjustment to a maximum of 2 or 5 confounders, so those aORs even in present form, are likely over fitted to the data.

My comments are:

Line 48: please state the direction of the association, not just that one exists.

Line 74: please state that this is a "planned" secondary analysis.

Line 89: Why did the study number change? I didn't note anything about that in your rebuttal letter.

Line 201: This definition is the one recommended for offering primary CS to women but identifies women with newborns significantly > 4.0 KG (one common definition of macrosomia) or > 10th percentile for birthweight. Why did you use this definition? Not using the weight percentile definition of course greatly reduces the chance of identifying macrosomia in any but late term pregnancies or those with poorly controlled diabetes earlier in pregnancy.

Line 228: please be very cautious about abbreviations--see instructions for authors. We limit abbreviations that are uncommon to make it easier on the reader.

Line 250: As noted by the statistical reviewer, we are still requesting a post-hoc analysis matching for some of these factors. These analysis can be included in supplemental digital content. While your hypothesis that these like on the causal pathway may be true, the differences in baseline between the groups should be addressed.

Line 420: I recommend strengthening this paragraph. The reproducibility of your data with other reports is significantly strengthens this association and I think you can make a stronger case for it. It would be great as well to make a suggestion in the closing paragraph about what a clinician is supposed to do with this information.

Sincerely,
Nancy C. Chescheir, MD

Editor-in-Chief

2018 IMPACT FACTOR: 4.965
2018 IMPACT FACTOR RANKING: 7th out of 83 ob/gyn journals

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Editor
Obstetrics & Gynecology

11/7/19

Dear Editor,

Thank you for this opportunity to resubmit our manuscript entitled "**The association of acculturation with adverse pregnancy outcomes**." Authors include Ashish Premkumar, Michelle P. Debbink, Robert M. Silver, David M. Haas, Hyagriv N. Simhan, Deborah A. Wing, Samuel Parry, Brian M. Mercer, Jay Iams, Uma M. Reddy, George Saade, and William A. Grobman. The authors report no conflict of interest. All authors have approved this version of the manuscript for submission.

In response to the comments from the statistical editor and the editor-in-chief, we have revised our manuscript. Please see our response to the comments from the staff below:

1. Table 1 clearly shows baseline differences in the cohorts due to BMI, DM, smoking, chronic HTN etc. To then show differences in frequency (Table 2) or crude odds (Table 3) without any adjustment for baseline differences assumes that any statistical difference is associated with acculturation status alone, may be one explanation, but it's not the only possible one. Furthermore, the Authors need to increase the number of adjustors or match a subset of women in each cohort for the factors besides those they have included in the aOR model to adjust or match for important confounders. If, as the Authors argue, acculturation is linked to BMI, smoking, HTN etc, then the aORs with those additional variables may no longer show an association of acculturation vs the adverse outcomes. If so, then the Authors can argue in Discussion the reasons for how that outcome is explainable by the process of acculturation.
   - We have created a separate model controlling for the aforementioned factors and have illustrated our findings in Table 3. We have also added to our discussion regarding our interpretation of these findings. Please see page 15, lines 349-57. Furthermore, we have removed the covariates included in the model from the abstract, as we feel like the complexity surrounding both models make it difficult to interpret in the abstract itself.
2. Also, regardless of the number of variables used as adjustors, as stated earlier and not addressed by the Authors, the counts for stillbirth (18) or indicated PTB (47) limit the potential for multivariable adjustment to a maximum of 2 or 5

confounders, so those aORs even in present form, are likely over fitted to the data.

- At this time, given the conflicting issue of overfitting of our model to indicated preterm birth and stillbirth and reviewer desires to have phenotypes of adverse pregnancy outcomes (i.e. subtype of preterm birth – see Reviewer #2, point #6), we have decided to leave these values in place. We have added wording in our discussion to highlight the issue of overfitting given the rarity of the outcome. Please see page 18, lines 414-16. However, if the editors do not find this acceptable and would prefer us to ultimately have these values removed from the manuscript, we would be happy to do so.

3. Line 48: please state the direction of the association, not just that one exists.
   - We have stated the direction of the association. Please see page 2, line 49.

4. Line 74: please state that this is a "planned" secondary analysis.
   - We have added this in the abstract. Please see page 3, line 74

5. Line 89: Why did the study number change? I didn't note anything about that in your rebuttal letter.
   - Apologies for the confusion. Because of reviewer comments regarding clarity surrounding the definition of acculturation, we re-analyzed the data and noted that approximately 90 subjects were recaptured after reconfirming our definition of acculturation within the dataset. Therefore, we have updated our sample size to include these individuals. We have also updated our findings to include the significant findings of preeclampsia without severe features, which was noted in Table 3 but mistakenly left out of discussion in the paper.

6. Line 201: This definition is the one recommended for offering primary CS to women but identifies women with newborns significantly > 4.0 KG (one common definition of macrosomia) or > 10th percentile for birthweight. Why did you use this definition? Not using the weight percentile definition of course greatly reduces the chance of identifying macrosomia in any but late term pregnancies or those with poorly controlled diabetes earlier in pregnancy.
   - We acknowledge this issue and have updated our analysis to include large for gestational age. The updated analysis, focusing on birthweight > 90%tile for gestational age, is included in the methods and tables.

7. Line 228: please be very cautious about abbreviations--see instructions for authors. We limit abbreviations that are uncommon to make it easier on the reader.
   - We have removed the abbreviation for DAG in the text

8. Line 250: As noted by the statistical reviewer, we are still requesting a post-hoc analysis matching for some of these factors. These analysis can be included in supplemental digital content. While your hypothesis that these like on the causal pathway may be true, the differences in baseline between the groups should be addressed.
   - Please see our response to #1 above

9. Line 420: I recommend strengthening this paragraph. The reproducibility of your data with other reports is significantly strengthens this association and I think you can make a stronger case for it. It would be great as well to make a suggestion

in the closing paragraph about what a clinician is supposed to do with this information.
- We have strengthened the paragraph in question. Please see page 16, lines 381-3. As this study is primarily epidemiological, we do not feel like we can confidently offer clinical guidance recommendations, particularly since acculturation is not routinely utilized as a clinical screening tool.

In the uploaded documents, please find the manuscript with 3 tables, 1 Supplementary Figure, and 3 Supplementary Tables. Please do not hesitate to reach out to us with any questions or concerns.

Best,

Ashish Premkumar, MD
On behalf of all authors