

# OBSTETRICS & GYNECOLOGY



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- 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](mailto:obgyn@greenjournal.org).

**Date:** Oct 17, 2019  
**To:** "Regan L. Bailey" [REDACTED]  
**From:** "The Green Journal" em@greenjournal.org  
**Subject:** Your Submission ONG-19-1723

RE: Manuscript Number ONG-19-1723

Dietary supplement use and its micronutrient contribution among pregnant and lactating U.S. women

Dear Dr. Bailey:

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 Nov 07, 2019, we will assume you wish to withdraw the manuscript from further consideration.

#### REVIEWER COMMENTS:

Reviewer #1: The authors present their work evaluating the micronutrient contribution of dietary supplements and their use in pregnant and lactating women in the US.

The following items should be addressed:

1. Abstract - results - it would be helpful to report here what percentage of the population who were invited to participate in the survey provided data.
2. Methods line 127-129 and line 137-139 - although NHANES does not publicly release the data for women outside this range, the authors should attempt to obtain at least the number of women who were pregnant and/or lactating and describe how many were excluded from participation due to this NHANES methodology. Also, the statement in line 137-139 explaining why women outside the 20-44 age range were excluded should be moved earlier, in order for readers to better understand the inclusion and exclusion criteria the authors used.
3. Methods line 145 - although 35 is a general cutoff utilized in pregnancy for advanced maternal age, none of the implications of age 35 in pregnancy are applicable to dietary intake or the objectives of this study. Why did the authors choose to evaluate the patients in this categorical fashion rather than keeping age as a continuous variable?
4. Methods line 190-192 - please clarify whether or not the authors utilized RDA specific to pregnancy/lactation given the altered nutritional requirements of these populations.
5. Results line 227 - here and elsewhere in the manuscript, the authors use the phrase "US pregnant women" however the data presented are only from those who participated in NHANES and met the authors' inclusion and exclusion criteria, n=9707; please rephrase as "study participants" or something similar in order to avoid confusing the reader.
6. Discussion line 361 - here and elsewhere, the authors report data but then do not provide the actual values and instead write in "data not shown." Why was this choice made? It would be beneficial for readers to see the actual numeric comparisons to be able to judge for themselves the magnitude of the association.
7. Figure 3 - the label "Based on the advice" should be renamed, maybe "Provider recommended"

Reviewer #2: This is a large national cross-sectional study focused on dietary supplement use in pregnant and lactating women, which fills a gap in the literature and also adds more timely and detailed information to complement the prior published study on the NHANES 1999-2006 analyses that was not further able to stratify by specific types of dietary supplements.

Methods: As questionnaires were used for data collection, were patient language-specific questionnaires used? If so, this might be helpful to note as there is a large portion (~47% of pregnant women and ~40% of lactating women) who were not non-hispanic white.

Methods: Under study participant exclusion criteria, multiple gestation pregnancies was not listed. As pregnancies with multiple gestations (i.e. twins, triplets) are recommended to take additional dietary supplements and make diet modifications compared to a singleton pregnancy, by including this population in the study (or not mentioning how many multiple gestational pregnancies were included in the analysis) it may confound the study findings.

Results: Although the family income level (i.e. PIR), marital status and education level were assessed for pregnant, lactating and NPNL women as a whole, were these categories further assessed by race/ethnicity to better understand if there's an association with the dietary supplement use within each race/ethnic category. As increased dietary supplement use/adherence is associated with women of increased PIR, married, and higher education level, this may suggest certain patient population groups that healthcare providers should pay closer attention to.

Discussion: It would be interesting for the authors to further discuss why there is a higher prevalence of dietary supplement intake in the second/third trimesters compared to the first. Is this because women in the first trimester have more difficulty with oral intake due to hyperemesis gravidarum or pregnancy related nausea/vomiting? Or, is it because ~50% of women do not recognize they are pregnant until at least 4-6 weeks gestation and do not establish prenatal care (which per this study, a large portion of dietary supplement use was because of provider recommendation) until later in the first trimester ~10-13 weeks.

Discussion: The mean intakes from dietary supplements of iodine, calcium, folic acid, niacin, and zinc exceeded the RDA in pregnant and lactating women. Is this because these values are higher in prenatal vitamins compared to multi-vitamin?

Discussion: Authors note that iron intake in pregnant women was only 72%. If there is trimester specific prevalence of iron intake, this might be of interest as most women with nausea/vomiting of pregnancy or hyperemesis gravidarum are unable to tolerate iron in the first trimester.

Discussion: Authors discuss that ~>40% of pregnant dietary supplement users exceeded the upper limit of folic acid intake from 2001-2014. As some women with a prior complicated pregnancy history (i.e. prior child with neural tube defect, cleft lip, or cardiac defect) are recommended to take additional folic acid (i.e. 1mg), women. Additionally, women with seizure disorders are recommended to take 4mg of folic acid daily, which is much higher than the usual recommended daily amount.

Discussion: Authors mention that with the daily mean intake of folic acid and iron some dietary supplement users may consume too high of doses that may lead to excessive intake. Although this is may be a waste of resources, excessive folic acid intake is not associated with any major adverse clinical outcomes and thus not of huge clinical significance. Additionally, many pregnant women are anemic or with low iron/ferritin levels in the third trimester and thus it is common to recommend higher iron intake than the daily recommended allowance to raise iron/ferritin (and thus hematocrit/hemoglobin) levels prior to delivery given the anticipated blood loss with childbirth. As this is likely difficult to assess within the scope of a questionnaire based study, it is worth mentioning in the discussion section.

Reviewer #3: This is a retrospective, descriptive review, which attempts to establish the degree of micronutrient and vitamin supplementation in women of reproductive age in the USA. pregnant, breastfeeding women, and no pregnant no breastfeeding women, Stratified by demographic, ethnic and economic characteristics as compared with the recommended doses of supplementation.

Reading the introduction one can realize that is an ambitious project, with the supportive data of the National Health and nutrition examination surveys.

The conclusion establishes that women who take dietary supplements frequently consume higher amounts of nutrients than recommended, it also states that those who do not take supplements consume inadequate doses of iron and folate.

It is important to establish that the study design does not allow to establish consumption, rather the availability of nutrients for consumption, since it is based on a report in the surveys by the users and on the review of the labels of the nutritional supplements available in the patient addresses.

Resumen concise and precise.  
introduction, states antecedents and related the main objective

#### Methods:

The majority of the sample studied were non-pregnant patients, not breastfeeding, it is important to establish the extrapolability of data to other populations, the criteria used by the NCSH for patient selection.

The authors state that is a nationally representative, cross sectional sample of US civilian, non institutionalized population. But there are no clear criteria of selection that surely the NCSH have take care on the representativity of the sample. More over the bias reported by the authors of overrepresentation of pregnant women in the 2000-2006 period, prompt interest in the selection criteria.

It's not clear enough the time o follow of the patients enrolled, they described a 30 day questionnaire, and the labels of the supplements were registered.

It's not clear in the methods if all the women of the questionnaire enrolled in the MEC.

The rest of the methodology is detailed and clear, in an ambitious project with multiple variables.

In the line 250 to 256, it's not clear that the percentages of motivation are part of the percentage of women that take the supplementation, one have to go to the figure for realize it, which is confuse.

The result are hard to understand due to the complexity of the data, maybe the explanation should be simplified to the facts that are of interest.

In the discussion there is stated that de nutrients are consumed when these study does not establish consume, otherwise supplements that the patients have in their houses. maybe the precise term should be the patients have access to a polivitamin with high levels of micronutrients.

The conclusion is of interest and alert in behalf the possibility of inadequate ingest of micronutrients in this susceptible population.

Maybe the recommendation of a study measuring the actual levels of these essential nutrients, in a representative sample of patients would be a useful final suggestion.

Reviewer #4: Overall this is a very interesting topic. Your data gets lost in the writing. Try and be more efficient in your language. Streamline your writing. You want the reader to be able to walk away with a conclusion

#### Background

It might be good include the potential negative effects of exceeding the upper limit. Providers may be less familiar with these.

#### Methods

Paragraph one - be consistent with your tenses

Throughout the methods section, do not include the numbers of women here. The numbers belong in your results section

Your methods section is far too long. You need to summarize

Be clear about where in your analysis you controlled for confounding factors

Line 121 - I would either be more specific with "Clinical, anthropometric, and biochemical data" or not include it given that you are more specific later on

Line 122 - is the protocol published or better described in other publications? If so, include reference.

Line 127 - why over sampled? How is that defined?

Line 128 - why the age restrictions? ( perhaps explained in line 139?)

Line 145 - why these age categories

#### Results

Consider spelling out some of your acronyms to help the reader.

P-values should be included in your text as you talk about differences or lack there of between categories.

Be clear about where in your analysis you controlled for confounding factors  
Readers will want to know by how much intake exceeded RDA and whether this is clinically significant. You have not provided enough information in this section for them to arrive at this conclusion

Line 239 - (data not shown) ?

\*\*\*Line 240 - consider showing use using age as the continuous variable that it is, rather than arbitrary categories  
Line 270 - discussion of means and medians does not seem to be especially relevant given that both exceed the RDA except Vit C. Also, use of mean and median should be determined by the type of variable.

#### Discussion

Given the importance of Bailey et al's findings, you may want to briefly mention their methods. A one liner even would help orient your reader.

I suggest starting your discussion with a clear statement of strengths and weakness of the paper

Line 302 - consolidate discussion of consequences/findings re: low folate

Line 316 - this entire paragraph is clunky. Imagine summarizing the entire paragraph into 1-2 sentences, then cut to make your writing more efficient.

Line 333- again, briefly mention methods in this study

Line 347 - taken in context with your prior sentence, this is oddly low considering the rate of insurance coverage of pregnant women private or public. Also, this seems to conflict with the cited data in line 365

Line 365 - there is also a potential for bias that could be causing the difference

Line 363 - it is unclear why you discuss WIC here. Also, you are missing other potential explanations for this finding

Line 369/372 - it is unclear if this is a decade of data or years of collected data a decade apart. Again, efficiency in your writing may help clarify that

Line 380 - have you understated that what is in the DS may be different than what the label suggests?

#### STATISTICAL EDITOR COMMENTS:

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

lines 129-130: The response rate of 69-81%, particularly since it varied by year 1999-2014 should be included as a potential limitation to generalizing these results.

General: The NHANES cohort is a nationally representative sample, but is it representative of all pregnant US women? Also, since these data were from aggregated years, there is likely insufficient data, but was there evidence of changing DS intake vs year?

lines 205-206: Why was it assumed that all DS were consumed with food, since with/without food intake can affect the absorption of folic acid?

Table 1: The small cohort of lactating women limits generalization.

Table 2: The missing data re: dates ( $461/1314 = \sim 35\%$ ), limits generalization re: analysis by trimester

Table 4: The RDAs for folic acid for pregnant and lactating women are 600 and 500, respectively, so the RDA in the Table have been adjusted by a factor of 0.6x, assuming that all DS were taken with food. Are the mean values (787, 718), the actual mean daily intakes, or have they been adjusted by the 0.6x factor, as well? Should be made clear to the reader.

The MTHFR polymorphism and its relation to folic acid metabolism is not mentioned and apparently not measured in this study. Since  $\sim 25\%$  of Hispanics and  $\sim 10\%$  of Caucasians have an impaired ability to convert folate to its active form, those individuals would not have the same RDA requirement, but would require more folic acid.

## 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.\*\*\*

- Please provide absolute values for variables, in addition to assessment of statistical significance. We ask that you provide crude OR's followed by adjusted OR's for all variables.

#### P 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.

- 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. For instance, DS would not be an acceptable abbreviation and will need to be spelled out through out the abstract and manuscript.

- How many women in each group were included?

- By counterparts are you referencing only other pregnant women, or do you mean for lactating and nonpregnant or lactating women as well as part of "counterparts"?

- "too high" implies some danger. Certainly for some of these nutrients, the safety threshold above the RDA is quite high so there wouldn't be a safety issue. Did you use the general RDA's for adults or did you use the RDA's for pregnant and lactating women? This needs to be explicitly stated in the methods section.

- Its a reach to ask health care providers to "monitor DS intake and dosing to compensate for under consumed nutrients". Pregnant women do not typically undergo dietary analyses for assessment of the broad group of nutrients you discuss. I can certainly endorse a comment about discussing nutrition and need, or lack thereof, for supplementation.

- I agree w/ one reviewer. Your methods section is too long. If the NHANES methodology for identifying pregnant and lactating women is published elsewhere, you can reference it and then briefly describe it. Otherwise, please put some of your methods section into supplemental digital content. (particularly that which references how pregnancy status ascertained. Important to include in methods why 20-44 is age range however.

- Did you use the RDA's for pregnant and lactating women? These are different, as I'm sure you know. Why wouldn't you use these?

- I've had to read the two sentences lines 235-238 a few times to understand so please edit. What do you mean by the prevalence of any DS use vs prenatal DS use in pregnant women? What's the difference you are trying to make here? Also, lactating women can not Currently be using prenatal vitamins (as they are not PRE natal any more unless they are also pregnant-a low frequency event in your study).

- folate is really only important for neural tube closure preconceptionally and in first 21 days post menstrual when the neural tube closes. Thereafter, it has other important needs such as RBC production, but please don't perpetuate the myth that its needed throughout pregnancy for neural tube issues.

- in the preconception period

- Does this 38 include DS + diet?

2. There is a second attachment called "Nutrients" that is uploaded for you to look at. It is taken from the Guidelines for Perinatal Care published by ACOG which articulates the nutrient needs for pregnant and lactating women that is recommended. Please address whether these were used in your paper as the standard and if not, why not.
3. 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.
4. 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.

5. 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.
6. 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.
7. 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).
8. Provide a short title of no more than 45 characters, including spaces, for use as a running foot.
9. 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.

10. 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.
11. 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.
12. 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%).

13. 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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

14. 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](mailto: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>.

15. Figures 1-3: Please upload as a separate figure file on Editorial Manager.

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 Nov 07, 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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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 Dr. Chescheir,

We appreciate the reviewers' and editor's thoughtful comments and insights. Individual responses to each of the comments are listed below, and changes to the manuscript are denoted with the "track change" function in Word. These changes greatly improved this manuscript.

The majority of the reviewer comments surrounded the study design features and interpretability of the NHANES data that are collected by the CDC, not the authors. We have provided much detail below and within the updated text to clarify these comments. The remainder of the comments focused on limitations of the data, for which we expanded the limitations section of the discussion. We believe that in this resubmission we have made all possible changes to the best of our ability.

We confirm that all authors have read the Instructions for Authors. Thank you for your time and consideration of this work for publication in Obstetrics & Gynecology.

Sincerely,

Regan Bailey

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**Reviewer #1: The authors present their work evaluating the micronutrient contribution of dietary supplements and their use in pregnant and lactating women in the US. The following items should be addressed:**

Authors' response: Thank you very much for these helpful comments.

1. Abstract - results - it would be helpful to report here what percentage of the population who were invited to participate in the survey provided data.

Authors' response: The CDC National Center for Health Statistics employs a targeted sampling framework to ensure the NHANES is nationally representative. We included the response rates in the Methods section and provided more explanation as described below. Unfortunately, the word limit for the abstract precluded adding more details in the abstract.

Line 207: "All analyses used survey procedures that account for the complex survey design, incorporating the 16-year examination weights constructed for the combined survey period. Weighting takes into account of the differential probabilities of selection (including oversampling), survey nonresponse, and differences in distributions between final sample and the target population; therefore, using the sampling weights produces nationally representative estimates (12)."

2. Methods line 127-129 and line 137-139 - although NHANES does not publicly release the data for women outside this range, the authors should attempt to obtain at least the number of women who were pregnant and/or lactating and describe how many were excluded from participation due to this NHANES methodology. Also, the statement in line 137-139 explaining why women outside the 20-44 age range were excluded should be moved earlier, in order for readers to better understand the inclusion and exclusion criteria the authors used.

Authors' response: We rearranged the section on inclusion and exclusion as requested.

We identified 201 pregnant women aged 13-19 years, 35 lactating women 15-19y, 4 pregnant women aged over 44 years, and no lactating women over 44y in the 1999-2006 NHANES data. We couldn't identify any pregnant and lactating women outside the 20-44 age range from the 2007-2014

NHANES data due to confidentiality issues. In order to keep the Methods section concise, we cited the NHANES sampling scheme for readers who are interested: The National Health and Nutrition Examination Survey: Sample design, 1999–2006. National Center for Health Statistics. Vital Health Stat 2(155). 2012 (Ref 11). In addition, we reported the number of women aged 12-19y and 50-59y separately when we describe the exclusion criteria.

3. Methods line 145 - although 35 is a general cutoff utilized in pregnancy for advanced maternal age, none of the implications of age 35 in pregnancy are applicable to dietary intake or the objectives of this study. Why did the authors choose to evaluate the patients in this categorical fashion rather than keeping age as a continuous variable?

Authors' response: Based on these comments, we presented age as a continuous variable (i.e., mean age of pregnant, lactating, and non-pregnant and non-lactating women) in Table 1. We categorized women into two age groups (20-34y and 35-44y) because we were interested in subgroup analyses. We hypothesized women who consider themselves to be or are considered by others to be of "advanced maternal age" may have different patterns of dietary supplement use, which is supported by our findings.

4. Methods line 190-192 - please clarify whether or not the authors utilized RDA specific to pregnancy/lactation given the altered nutritional requirements of these populations.

Authors' response: We presented RDAs specific to each life stage, including pregnancy/lactation, in Table 4 and Appendix 1. We clarified the sentence as follows: "The RDA is the average daily intake level sufficient to meet the nutrient requirement of nearly all healthy individuals in a particular life stage group (i.e., pregnant women, lactating women, women aged 19-30 years, and women aged 31-50 years)."

5. Results line 227 - here and elsewhere in the manuscript, the authors use the phrase "US pregnant women" however the data presented are only from those who participated in NHANES and met the authors' inclusion and exclusion criteria, n=9707; please rephrase as "study participants" or something similar in order to avoid confusing the reader.

Authors' response: Because NHANES sample is selected by using a complex, multistage probability design, the estimates are representative of the U.S. noninstitutionalized civilian population when appropriate sampling weights are applied as is the case in our analyses. Nonetheless, our estimates only provide a snapshot of all women who were pregnant on a given day during the survey, not a yearly estimate. Therefore, we specified the use of NHANES data wherever relevant and rephrased "U.S. pregnant women" to "pregnant women in the U.S."

6. Discussion line 361 - here and elsewhere, the authors report data but then do not provide the actual values and instead write in "data not shown." Why was this choice made? It would be beneficial for readers to see the actual numeric comparisons to be able to judge for themselves the magnitude of the association.

Authors' response: As suggested, we added the actual values (please see Figure 3 and Appendix 3) instead of writing "data not shown."

7. Figure 3 - the label "Based on the advice" should be renamed, maybe "Provider recommended"

Authors' response: We renamed it to "recommended by a healthcare provider"

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**Reviewer #2: This is a large national cross-sectional study focused on dietary supplement use in**

**pregnant and lactating women, which fills a gap in the literature and also adds more timely and detailed information to complement the prior published study on the NHANES 1999-2006 analyses that was not further able to stratify by specific types of dietary supplements.**

Authors' response: Thank you very much for this comment and for the thoughtful comments below.

1. Methods: As questionnaires were used for data collection, were patient language-specific questionnaires used? If so, this might be helpful to note as there is a large portion (~47% of pregnant women and ~40% of lactating women) who were not non-hispanic white.

Authors' response: Thank you for the insightful comment. The survey participants were able to select English or Spanish as the language of interview, or they could request a translator. We added this to the Methods section as follows: "The survey participants could select English or Spanish as the language of interview or could request a translator."

2. Methods: Under study participant exclusion criteria, multiple gestation pregnancies was not listed. As pregnancies with multiple gestations (i.e. twins, triplets) are recommended to take additional dietary supplements and make diet modifications compared to a singleton pregnancy, by including this population in the study (or not mentioning how many multiple gestational pregnancies were included in the analysis) it may confound the study findings.

Authors' response: We agree that women pregnant with multiple gestations need more intense care; but, unfortunately, NHANES does not collect information about multiple gestational pregnancies. Moreover, the Dietary Reference Intakes set by the National Academies of Science, Engineering, and Medicine do not consider multiple gestational pregnancies. We noted this as a limitation of our analysis in the Discussion as follows: "Lastly, NHANES did not collect information about multiple gestational pregnancies or specific risk factors (e.g., history of neural tube defects and MTHFR gene polymorphism), which should be considered when assessing individual's nutritional needs."

3. Results: Although the family income level (i.e. PIR), marital status and education level were assessed for pregnant, lactating and NPNL women as a whole, were these categories further assessed by race/ethnicity to better understand if there's an association with the dietary supplement use within each race/ethnic category. As increased dietary supplement use/adherence is associated with women of increased PIR, married, and higher education level, this may suggest certain patient population groups that healthcare providers should pay closer attention to.

Authors' response: We agree that race/ethnicity is a very important factor, but our sample size does not allow further stratification by race/ethnicity. We hope future studies with larger sample sizes can look into this interesting research question.

4. Discussion: It would be interesting for the authors to further discuss why there is a higher prevalence of dietary supplement intake in the second/third trimesters compared to the first. Is this because women in the first trimester have more difficulty with oral intake due to hyperemesis gravidarum or pregnancy related nausea/vomiting? Or, is it because ~50% of women do not recognize they are pregnant until at least 4-6 weeks gestation and do not establish prenatal care (which per this study, a large portion of dietary supplement use was because of provider recommendation) until later in the first trimester ~10-13 weeks.

Authors' response: Thank you for your insights. NHANES does not collect information about the reason for *not* taking dietary supplements, so we could not determine the reason for the lowest prevalence of dietary supplement use among women in their first trimester. We originally mentioned about women in their early pregnancy not being aware of pregnancy and/or associated recommendations. Prompted by

your comment, we added difficulties with oral intake during pregnancy as a potential barrier in the Discussion: “Women in their second and third trimesters were more likely to consume any supplement than those in their first trimester, confirming earlier findings by others (5); it is possible that women in their early pregnancy may not be aware of their pregnancy or associated recommendations (23) or have difficulties with oral intake due to pregnancy-related nausea and vomiting (24).”

5. Discussion: The mean intakes from dietary supplements of iodine, calcium, folic acid, niacin, and zinc exceeded the RDA in pregnant and lactating women. Is this because these values are higher in prenatal vitamins compared to multi-vitamin?

Authors' response: As mentioned in the Discussion, “the number and amount of nutrients included in prenatal supplements are not standardized, but almost all products contain one or more nutrients at levels that are as much as the RDA or more (20)”. Although we didn't formally compare the formulations by product types, our results suggest that prenatal supplements that most of pregnant and lactating women consume may provide higher amounts of nutrients compared to general multi-vitamin-minerals that non-pregnant and non-lactating women consume. This type of analysis is part of an ongoing NIH Office of Dietary Supplements project.

6. Discussion: Authors note that iron intake in pregnant women was only 72%. If there is trimester specific prevalence of iron intake, this might be of interest as most women with nausea/vomiting of pregnancy or hyperemesis gravidarum are unable to tolerate iron in the first trimester.

Authors' response: We have presented the prevalence of iron-containing dietary supplements on Table 2 (66.1% in the first trimester, 81.9% in the second trimester, and 89.3% in the third trimester) for readers who are interested. We couldn't speculate on nausea/vomiting because data are not available to address this question.

7. Discussion: Authors discuss that ~>40% of pregnant dietary supplement users exceeded the upper limit of folic acid intake from 2001-2014. As some women with a prior complicated pregnancy history (i.e. prior child with neural tube defect, cleft lip, or cardiac defect) are recommended to take additional folic acid (i.e. 1mg), women. Additionally, women with seizure disorders are recommended to take 4mg of folic acid daily, which is much higher than the usual recommended daily amount.

Authors' response: Thank you for raising this point. We emphasized that there may be cases demanding very high doses of supplementation of certain nutrients as “Lastly, NHANES did not collect information about multiple gestational pregnancies or some risk factors (e.g., history of neural tube defects and MTHFR gene polymorphism), which should be considered when assessing individual's nutritional needs,” and “While folic acid and iron supplementation is recommended during pregnancy, some supplement users may consume high doses that lead to excessive intakes. However, some of these high doses may be appropriate because they were recommended by healthcare providers due to special medical conditions.”

8. Discussion: Authors mention that with the daily mean intake of folic acid and iron some dietary supplement users may consume too high of doses that may lead to excessive intake. Although this is may be a waste of resources, excessive folic acid intake is not associated with any major adverse clinical outcomes and thus not of huge clinical significance. Additionally, many pregnant women are anemic or with low iron/ferritin levels in the third trimester and thus it is common to recommend higher iron intake than the daily recommended allowance to raise iron/ferritin (and thus hematocrit/hemoglobin) levels prior to delivery given the anticipated blood loss with childbirth. As this is likely difficult to assess within the scope of a questionnaire based study, it is worth mentioning in the discussion section.

Authors' response: Thank you for the insightful comments. We emphasized that there may be cases demanding very high doses of supplementation of certain nutrients as “While folic acid and iron supplementation is recommended during pregnancy, some supplement users may consume high doses that lead to excessive intakes. However, some of these high doses may be appropriate because they were recommended by healthcare providers due to special medical conditions.”

The National Academies of Sciences, Engineering, and Medicine set the Tolerable Upper Intake Level (UL) for folic acid based on hematological remission and neurological progression in the vitamin B12-deficient population and for iron based on gastrointestinal distress. Moreover, the health impact of high folic acid intake remains controversial and has been the topic of two recent NIH meetings (Boyles, Abee L., et al. "Safe use of high intakes of folic acid: research challenges and paths forward." Nutrition Reviews 74.7 (2016): 469-474.; <https://www.niddk.nih.gov/news/meetings-workshops/2019/metabolic-interaction-folates-folic-acid-vitamin-b12-deficiency>).

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**Reviewer #3: This is a retrospective, descriptive review, which attempts to establish the degree of micronutrient and vitamin supplementation in women of reproductive age in the USA pregnant, breastfeeding women, and no pregnant no breastfeeding women, Stratified by demographic, ethnic and economic characteristics as compared with the recommended doses of supplementation.**

**Reading the introduction one can realize that is an ambitious project, with the supportive data of the National Health and nutrition examination surveys.**

**The conclusion establishes that women who take dietary supplements frequently consume higher amounts of nutrients than recommended, it also states that those who do not take supplements consume inadequate doses of iron and folate.**

**It is important to establish that the study design does not allow to establish consumption, rather the availability of nutrients for consumption, since it is based on a report in the surveys by the users and on the review of the labels of the nutritional supplements available in the patient addresses.**

Authors' response: Thank you for your careful and insightful review. We believe we have addressed your comments, which were very helpful.

1. Resumen concise and precise.

Authors' response: Thank you for your comment. Our revised abstract is more concise.

2. introduction, states antecedents and related the main objective

Authors' response: Thank you. We described background, previous studies, remaining research questions, and our objectives in the Introduction as recommended.

3. Methods:

The majority of the sample studied were non-pregnant patients, not breastfeeding, it is important to establish the extrapolability of data to other populations, the criteria used by the NCSH for patient selection.

Authors' response: Thank you. The NCHS used a complex, multistage probability design to make sure that the weighted NHANES sample represents the U.S. civilian, noninstitutionalized population. We clarified the first sentence of the Methods section and cited “National Health and Nutrition Examination

Survey: Sample Design, 1999-2006” by National Center for Health Statistics (Ref 11) for readers who would be interested in the details of the sampling scheme. In addition, we added the following to the statistical analysis section: “All analyses used survey procedures that account for the complex survey design, incorporating the 16-year examination weights constructed for the combined survey period. Weighting takes into account of the differential probabilities of selection (including oversampling), survey nonresponse, and differences in distributions between final sample and the target population; therefore, using the sampling weights produces nationally representative estimates (12).” Accordingly, the oversampled pregnant women were assigned appropriate sample weights by NCHS to minimize any biases.

4. The authors state that is a nationally representative, cross sectional sample of US civilian, non institutionalized population. But there are no clear criteria of selection that surely the NCSH have take care on the representativity of the sample. More over the bias reported by the authors of overrepresentation of pregnant women in the 2000-2006 period, prompt interest in the selection criteria. Authors’ response: Please refer to our response to the preceding reviewer comment.

5. It's not clear enough the time o follow of the patients enrolled, they described a 30 day questionnaire, and the labels of the supplements were registered.

Authors’ response: Thank you. We added more details about the time line of the survey proedures throughout the Methods section. For example, “Since 1999, NHANES has operated as a continuous survey and includes an in-home interview where sociodemographic and dietary supplement use information is collected, followed by a health examination conducted in a mobile examination center within 1 to 3 weeks at which pregnancy and lactating information is collected,” “Dietary supplement information was collected via a 30-day questionnaire in conjunction with a product inventory in the participants’ homes,” and “After data collection, trained nutritionists at NCHS matched the products reported to the NHANES Dietary Supplement Database that contains information on the serving sizes and nutrient contents (per the product label’s supplement facts panel).”

6. It's not clear in the methods if all the women of the questionnaire enrolled in the MEC.

Authors’ response: Thank you. Not all women who responded to the in-home interview participated in the health examination in the Mobile Examination Center. We originally didn’t report how many women only participated in the interview because we only included those who participated in the health examination and, consequently, didn’t have pregnancy and lactation data. Because we weighted all analyses with the weight that accounts for non-response to the health examination, attrition between the in-home interview and the health examination does not bias our results. For readers who are interested, we cited the webpage listing survey response rates for all survey cycles (Ref 13).

7. The rest of the methodology is detailed and clear, in an ambitious project with multiple variables.

Authors’ response: Thank you. We appreciate your careful review.

8. In the line 250 to 256, it's not clear that the percentages of motivation are part of the percentage of women that take the supplementation, one have to go to the figure for realize it, which is confuse.

Authors’ response: Thank you for the comment. Figure 3 presents the data for all women. We revised the title of Figure 3 to mitigate possible confusion as follows: “Figure 3. Prevalence of reasons for dietary supplement use among pregnant and lactating women in the United States, NHANES 1999-2014”

9. The result are hard to understand due to the complexity of the data, maybe the explanation should be simplified to the facts that are of interest.

Authors' response: Thank you. We streamlined our Results section to aid the readers as recommended.

10. In the discussion there is stated that de nutrients are consumed when these study does not establish consume, otherwise supplements that the patients have in their houses. maybe the precise term should be the patients have access to a polivitamin with high levels of micronutrients.

Authors' response: Thank you for raising this important point. NHANES did measure consumption of dietary supplement products as well as nutrients from dietary supplements by collecting unusually detailed information about products, frequency, duration, and amount taken; therefore, we believe the use of the term "consumed" is correct. We agree that self-reported data are subject to reporting bias, which we addressed as a limitation of our data in the Discussion session as follows: "Little is known about the reporting bias and measurement error structure of dietary supplements (17)."

11. The conclusion is of interest and alert in behalf the possibility of inadequate ingest of micronutrients in this susceptible population.

Authors' response: Thank you.

12. Maybe the recommendation of a study measuring the actual levels of these essential nutrients, in a representative sample of patients would be a useful final suggestion.

Authors' response: We suggested possible future steps to improve the accuracy of nutrient intake estimation as follows: "Another limitation is that the NHANES database relies on manufacturer's label declarations, which may exceed the label declarations >20% (38). The Dietary Supplement Ingredient Database has been evaluating the analytical nutrient contents of dietary supplements, including prenatal supplements, which should be used to adjust label claims in future studies once it's completely developed (38). Future studies may also examine biomarkers in relation to supplement use (5, 10)." Currently, there are very few biomarkers available in NHANES.

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**Reviewer #4: Overall this is a very interesting topic. Your data gets lost in the writing. Try and be more efficient in your language. Streamline your writing. You want the reader to be able to walk away with a conclusion**

Authors' response: Thank you so much for your careful review and helpful comments. We streamlined the writing as recommended.

#### Background

1. It might be good include the potential negative effects of exceeding the upper limit. Providers may be less familiar with these.

Authors' response: As suggested, we described the potential negative effects in the Discussion as follows: "The UL was set based on neurological disorder and hematological remission in patients with vitamin B12 deficiency (19)." "The UL for iron was primarily based on gastrointestinal distress as an adverse effect (27)."

As the negative effects vary by nutrients, we provided the definition of the tolerable upper intake level in the Introduction as follows: "While almost no pregnant women had intakes above the tolerable upper intake level (UL) from food sources alone, dietary supplement use increased the proportion of

those exceeding the UL (i.e., potentially at risk of adverse effects due to excessive intakes) of some nutrients, especially iron and folic acid (8), prompting this analysis of nutrients contributed by supplements.”

## Methods

2. Paragraph one - be consistent with your tenses

Authors' response: As requested, we used the past tense when describing our data, analyses, and results consistently.

3. Throughout the methods section, do not include the numbers of women here. The numbers belong in your results section

Authors' response: NHANES analyses have conventionally reported the sample description, including the final analytic sample size, in the Methods section. As other reviewers have suggested, we moved the descriptions on our sample to the earlier section.

4. Your methods section is far too long. You need to summarize

Authors' response: We streamlined our Methods section as requested.

5. Be clear about where in your analysis you controlled for confounding factors

Authors' response: Because of descriptive nature of our analyses, we presented estimates for subgroups by important characteristics (e.g., age group, family income level, trimester, and race/ethnicity) rather than adjusting for these.

6. Line 121 - I would either be more specific with "Clinical, anthropometric, and biochemical data" or not include it given that you are more specific later on

Authors' response: We deleted the phrase as suggested.

7. Line 122 - is the protocol published or better described in other publications? If so, include reference.

Authors' response: As requested, we added references regarding NHANES sampling plan and estimation procedures wherever relevant to the Methods section.

8. Line 127 - why over sampled? How is that defined?

Authors' response: During 2000-2006, pregnant women were purposefully oversampled to produce stable and precise estimates. For that sample, a sampling rate of 1 was applied, meaning that if a field interviewer contacted a household with a pregnant woman, that woman would have a probability of 1 for inclusion in the study. We cited the NHANES sampling scheme for readers who are interested: The National Health and Nutrition Examination Survey: Sample design, 1999–2006. National Center for Health Statistics. Vital Health Stat 2(155). 2012 (Ref 11). In addition, as described under the statistical analysis section, “All analyses used survey procedures that account for the complex survey design, incorporating the 16-year examination weights constructed for the combined survey period. Weighting takes into account of the differential probabilities of selection (including oversampling), survey nonresponse, and differences in distributions between final sample and the target population; therefore, using the sampling weights produces nationally representative estimates (12).” Accordingly, the oversampled pregnant women were assigned appropriate sample weights by NCHS to minimize any biases.

9. Line 128 - why the age restrictions? ( perhaps explained in line 139?)

Authors' response: Data were not publicly released for ages outside of 20-44y since 2007. We moved the inclusion/exclusion criteria to earlier in the section.

10. Line 145 - why these age categories

Authors' response: We categorized women into two age groups (20-34y and 35-44y) because we were interested in subgroup analyses. We hypothesized women who consider themselves to be or are considered by others to be of "advanced maternal age" may have different patterns of dietary supplement use, which was supported by our findings.

## Results

11. Consider spelling out some of your acronyms to help the reader.

Authors' response: As suggested, we spelled out dietary supplement, non-pregnant and non-lactating women, multivitamin-minerals, instead of using DS, NPML, and MVM, respectively.

12. P-values should be included in your text as you talk about differences or lack there of between categories.

Authors' response: We conducted pairwise comparisons for main analyses and considered a conservative, Bonferroni-corrected  $P < 0.0167$  as statistically significant. To present the differences in concise way, we didn't present the actual P-values in the text.

13. Be clear about where in your analysis you controlled for confounding factors

Authors' response: This descriptive paper does not examine the association between exposure and outcomes, so confounding factors were not controlled. We presented estimates for subgroups by important characteristics (e.g., age group, family income level, trimester, and race/ethnicity) rather than adjusting for these.

14. Readers will want to know by how much intake exceeded RDA and whether this is clinically significant. You have not provided enough information in this section for them to arrive at this conclusion

Authors' response: The RDA is average daily level of intake sufficient to meet the nutrient requirements of ~97.5% of healthy population and is supposed to be met by nutrient intakes from foods and dietary supplements. Therefore, our finding that nutrient intakes from dietary supplement alone can exceed the RDA suggest that the nutrient contents of some supplements is very high. However, the consequences of consuming supplements that exceed the RDAs is not well documented, and is a very important research question. We hope our findings prompt research to answer this question. Nonetheless, we also presented the Tolerable Upper Intake Level (UL), which is linked to adverse health effects.

15. Line 239 - (data not shown)?

Authors' response: Because there's no regulatory definition of prenatal dietary supplements, their nutrient composition varies. We examined the nutrient composition of prenatal dietary supplements and found that almost all prenatal dietary supplements are multivitamin-minerals ( $\geq 3$  vitamins and  $\geq 1$  mineral).

16. \*\*\*Line 240 - consider showing use using age as the continuous variable that it is, rather than arbitrary categories

Authors' response: We presented age as a continuous variable (i.e., mean age of pregnant, lactating, and non-pregnant and non-lactating women) in Table 1, while keeping a subgroup analysis by age groups. We hypothesized women who consider themselves to be or are considered by others to be of “advanced maternal age” may have different patterns of dietary supplement use, which is supported by our findings.

16. Line 270 - discussion of means and medians does not seem to be especially relevant given that both exceed the RDA except Vit C. Also, use of mean and median should be determined by the type of variable.

Authors' response: The distributions of supplemental nutrient intakes were almost always non-normal. Therefore, we presented median as Appendix for readers who would be interested. We streamlined description and discussion of medians based on your comment.

#### Discussion

17. Given the importance of Bailey et al's findings, you may want to briefly mention their methods. A one liner even would help orient your reader.

Authors' response: Thank you for this suggestion. We described Bailey et al.'s methods in more detail as follows: “Recently, Bailey et al. (8) estimated the total usual nutrient intakes adjusting for within-person variation from the two 24-hour dietary recalls (including supplements) among pregnant women in the NHANES 2001-2014 and compared those to the Dietary Reference Intakes. A significant number of pregnant women had usual intakes below the Estimated Average Requirements (i.e., were at risk of inadequacy) for vitamins A (16%), B6 (11%), C (12%), D (46%), and E (43%), folate (16%), iron (36%), calcium (13%), magnesium (48%), and zinc (11%), and very few met or exceeded the AI for choline (8%).”

Bailey et al. data were also described in the Introduction as follows: “Yet, a recent report on total usual nutrient intakes (from both foods and supplements) among U.S. pregnant women using data from the National Health and Nutrition Examination Survey (NHANES) 2001-2014 concluded that a significant proportion (>10%) of pregnant women are not consuming enough of some nutrients (e.g., vitamins A, B6, C, D, and E, folate, calcium, iron, magnesium, and zinc) even with the use of supplements (8). While almost no pregnant women had intakes above the tolerable upper intake level (UL) from food sources alone, dietary supplement use increased the proportion of those exceeding the UL (i.e., potentially at risk of adverse effects due to excessive intakes) of some nutrients, especially iron and folic acid (8), prompting this analysis of nutrients contributed by dietary supplements.”

18. I suggest starting your discussion with a clear statement of strengths and weakness of the paper

Authors' response: Authors' instruction recommends starting the Discussion with a description of the primary findings. We kept the strengths and weaknesses at the end of the Discussion, but did add some clarity.

19. Line 302 - consolidate discussion of consequences/findings re: low folate

Authors' response: We revised the Discussion as requested (Line 291).

20. Line 316 - this entire paragraph is clunky. Imagine summarizing the entire paragraph into 1-2 sentences, then cut to make your writing more efficient.

Authors' response: We streamlined this paragraph as follows:

“For iron, the World Health Organization recommends daily supplementation with 30 to 60 mg of iron for pregnant women to prevent maternal anemia, puerperal sepsis, preterm birth, and low birth weight throughout pregnancy (25). Specifically for the U.S. population, the Centers for Disease Control and Prevention recommends 30 mg/day of iron supplementation for all pregnant women (26). We found that 72.3% of pregnant women were using iron-containing supplements, which contributed 38.4 mg/d on average among users. This explains the earlier findings of Bailey et al. (8) that, among pregnant women who took supplements, the prevalence of inadequate iron intake was 80.3% when only food sources were considered, but decreased to 13.9% when dietary supplements were included; at the same time, the prevalence of intakes above the UL increased from 0% to 40.2% when including supplements. The UL for iron was primarily based on gastrointestinal distress as an adverse effect (27). Among pregnant women not using supplements, almost all (95.3%) were at risk of iron inadequacy. Lactating women had a similar pattern of iron-containing supplement use as pregnant women.”

21. Line 333- again, briefly mention methods in this study

Authors' response: We briefly mentioned the methods of Perrine et al. as follows: “Information on iodine intake from food sources is not available in NHANES; but an analysis of urinary iodine concentration data from the 2001-2006 NHANES concluded that the iodine status of pregnant women was borderline sufficient; that of lactating women was generally sufficient; and some women, especially those who did not consume dairy products, were at risk for iodine insufficiency based on the WHO criteria (28).”

22. Line 347 - taken in context with your prior sentence, this is oddly low considering the rate of insurance coverage of pregnant women private or public. Also, this seems to conflict with the cited data in line 365

Authors' response: We only presented those who use prescribed prenatal before. We revised the sentence to minimize confusion as follows: “In 1999-2006, 37% and 28% of pregnant women (15-39 years) used prescription and over-the-counter prenatal supplements, respectively.”

23. Line 365 - there is also a potential for bias that could be causing the difference

Authors' response: Our original intention had been to suggest possible policy/clinic interventions, rather than explaining the income difference by WIC. Based on your comments, we deleted the discussion of WIC to minimize confusion.

24. Line 363 - it is unclear why you discuss WIC here. Also, you are missing other potential explanations for this finding

Authors' response: Please see our response to the preceding comment (Reviewer #4 comment #23).

25. Line 369/372 - it is unclear if this is a decade of data or years of collected data a decade apart. Again, efficiency in your writing may help clarify that

Authors' response: Thank you for the comment. We revised the phrase as follows: “Although we combined 16 years of data...”

26. Line 380 - have you understated that what is in the DS may be different than what the label suggests?

Authors' response: We agree that this is an important point. We addressed this in more detail as follows: “Another limitation is that the NHANES database relies on manufacturer's label declarations, which may exceed the label declarations 20% or more (38). Studies supporting the Dietary Supplement Ingredient

Database have been chemically analyzing the nutrient contents of dietary supplements, including prenatal supplements. This database should be used to adjust labeled amounts in future research once it's completely developed (38) ." A pilot study measuring prescription prenatal supplements is underway.

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**STATISTICAL EDITOR COMMENTS: The Statistical Editor makes the following points that need to be addressed.**

Authors' response: We appreciate and are grateful for these comments.

1. lines 129-130: The response rate of 69-81%, particularly since it varied by year 1999-2014 should be included as a potential limitation to generalizing these results.

Authors' response: Because we used survey weights that account for nonresponse, our estimates are not limited to only those who responded to the survey interviews as stated in the Methods section as follows: "All analyses used survey procedures that account for the complex survey design, incorporating the 16-year examination weights constructed for the combined survey period. Weighting takes into account of the differential probabilities of selection (including oversampling), survey nonresponse, and differences in distributions between final sample and the target population; therefore, using the sampling weights produces nationally representative estimates (12)."

2. General: The NHANES cohort is a nationally representative sample, but is it representative of all pregnant US women? Also, since these data were from aggregated years, there is likely insufficient data, but was there evidence of changing DS intake vs year?

Authors' response: Because the NHANES sample is selected by using a complex, multistage probability design, the estimates are representative of the U.S. noninstitutionalized civilian population when the appropriate sampling weights are applied as is the case with our analyses. However, our estimates only provide a snapshot of all women who were pregnant on a given day during the survey. Therefore, we described that our sample is from the NHANES wherever relevant and rephrased "U.S. pregnant women" to "pregnant women in the U.S."

As presented in Appendix 2 and described in the Results section, "Between 1999-2002 and 2011-2014, the prevalence of DS use remained stable among pregnant and lactating women not only in terms of any DS use, but also in specific product categories, and specific nutrient-containing DS used (Appendix 2)." We also highlighted this in the Discussion as follows: "Nonetheless, it should be noted that the number of pregnant women was much smaller in 2007-2014 cycles compared to 2000-2006 cycles when pregnant women were oversampled, which may have impacted the precision of the trend analyses".

3. lines 205-206: Why was it assumed that all DS were consumed with food, since with/without food intake can affect the absorption of folic acid?

Authors' response: Two different conversion factors are available based on folic acid with or without food as described below. We had to make assumptions here because data are not available on timing of taking dietary supplements relative to food intake.

Folate is consumed as natural forms of folate from foods (i.e., food folate) and the synthetic form from fortified foods and dietary supplements (i.e., folic acid). Because the bioavailability of these two major folate forms differs, the RDA is defined in  $\mu\text{g}$  dietary folate equivalents (DFE), which takes account of different bioavailability of different folate sources:  $1 \mu\text{g}$  of dietary folate equivalent =  $0.6 \mu\text{g}$  of folic acid from fortified food or as a supplement taken with foods =  $1 \mu\text{g}$  of food folate =  $0.5 \mu\text{g}$  of a supplement taken on an empty stomach. NHANES does not collect whether a person consumed DS with foods or on

an empty stomach, so we made the assumption that all dietary supplements were consumed with food based on previous studies as well as the recent FDA guidelines for manufacturers; this is described in the Methods section as follows: “Because we only examined folic acid consumed as supplements, we presented the RDA in  $\mu\text{g}$  folic acid using the conversion factor of  $1 \mu\text{g DFE} = 0.6 \mu\text{g folic acid}$  (19), assuming supplements were consumed with food. This assumption has been made in the most recent Food and Drug Administration guideline for labeling (21).”

4. Table 1: The small cohort of lactating women limits generalization.

Authors' response: We agree with this comment. The sample size of lactating women has been very small in NHANES, so there has been very little data available from a national perspective. Therefore, we combined 8 cycles of survey reflecting 16 years to ensure the sample size, 297 lactating women, is large enough to produce stable estimates. We carefully revised the manuscript to minimize possible misinterpretation regarding generalization and further highlighted this as a limitation in the Discussion as follows: “In addition, the number of lactating women was small even after combining multiple cycles, which contributed to the large SEs and imprecision of estimates. There is a need to further examine dietary supplement use during lactation with larger sample.”

5. Table 2: The missing data re: dates (461/1314 = ~ 35%), limits generalization re: analysis by trimester

Authors' response: Thank you for pointing this out. We highlighted the large number of missing for readers not to over-generalize as follows: “In addition, the trimester of pregnancy (first, second, or third trimester) was coded based on the self-reported month of pregnancy on the reproductive health questionnaire but was only available during 1999-2012. Out of 1,314 pregnant women in these survey cycles, 461 women were missing this information, mostly because they did not self-report pregnancy during the questionnaire interview but were identified as pregnant based on positive urinary pregnancy test results.”

6. Table 4: The RDAs for folic acid for pregnant and lactating women are 600 and 500, respectively, so the RDA in the Table have been adjusted by a factor of 0.6x, assuming that all DS were taken with food. Are the mean values (787, 718), the actual mean daily intakes, or have they been adjusted by the 0.6x factor, as well? Should be made clear to the reader.

Authors' response: Because dietary supplements contain folic acid, a synthetic form of folate, we only calculated folic acid intakes consumed as dietary supplements. We used “folic acid” throughout the manuscript and labeled the relevant table rows as “folic acid”. We also clarified this in the footnotes of Table 4 and Appendix 1 as follows: “In  $\mu\text{g}$  folic acid. The RDAs that were presented as  $\mu\text{g}$  of dietary folate equivalents were converted to  $\mu\text{g}$  of folic acid based on the equation set by the National Academies of Sciences, Engineering, and Medicine,  $1 \mu\text{g}$  of dietary folate equivalents =  $0.6 \mu\text{g}$  of folic acid with meals. The UL only applies to folic acid consumed via fortified food or dietary supplements.” Please refer to our response to #3 for further details.

7. The MTHFR polymorphism and its relation to folic acid metabolism is not mentioned and apparently not measured in this study. Since ~ 25% of Hispanics and ~ 10% of Caucasians have an impaired ability to convert folate to its active form, those individuals would not have the same RDA requirement, but would require more folic acid.

Authors' response: We appreciate this comment. Indeed, the folate requirements may vary by genetic compositions, but the RDA does not take into account of the MTHFR polymorphism. This is beyond the scope of our study, but is definitely an important topic and should be addressed in future studies. We

mentioned that folate requirements can vary by an individual's genetic composition, health status, history of miscarriage etc. as follows: "Lastly, NHANES did not collect information about multiple gestational pregnancies or risk factors, such as history of neural tube defects and MTHFR gene polymorphism, which should be considered when assessing individual's nutritional needs."

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## 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](mailto:rzung@greenjournal.org).\*\*\*

Authors' response: Thank you very much for your careful review of this manuscript and for providing detailed, helpful instructions.

1.1. Please provide absolute values for variables, in addition to assessment of statistical significance. We ask that you provide crude OR's followed by adjusted OR's for all variables.

P 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.

Authors' Response: We completely agree on emphasizing absolute values for variables and effect sizes, which is reflected throughout our manuscript.

1.2. 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. For instance, DS would not be an acceptable abbreviation and will need to be spelled out through out the abstract and manuscript.

Authors' Response: We spelled out the unlisted abbreviations, including dietary supplements (DS), multi-vitamin-mineral (MVM), and non-pregnant and non-lactating (NPNL). We carefully read the instructions for authors and followed those.

1.3. How many women in each group were included?

Authors' response: We added the number of women in each group as follows: "Cross-sectional data from 1,314 pregnant, 297 lactating, and 8,096 non-pregnant and non-lactating women (20-44 years) in the 1999-2014 National Health and Nutrition Examination Surveys were combined to produce statistically reliable, nationally representative estimates."

1.4. By counterparts are you referencing only other pregnant women, or do you mean for lactating and nonpregnant or lactating women as well as part of "counterparts"?

Authors' response: We clarified the sentence as follows: "Among pregnant women, those in their first trimester, aged 20-34 years, or living in a lower-income family were less likely to use dietary supplements compared to their counterparts."

1.5. "too high" implies some danger. Certainly for some of these nutrients, the safety threshold above the RDA is quite high so there wouldn't be a safety issue. Did you use the general RDA's for adults or did you use the RDA's for pregnant and lactating women? This needs to be explicitly stated in the methods section.

Authors' response: We deleted the word "too" based on comments from you and reviewers. We did present the current RDAs for pregnant, lactating, and general women of 19-30 years and 31-50 years to encompass our participants' age range (i.e., 20-44 years) in the tables and cited appropriate Dietary Reference Intakes reports in the Methods. To add more clarity, we revised the Methods section as follows: "The RDA is the average daily intake level sufficient to meet the nutrient requirement of nearly all healthy individuals in a particular life stage group (i.e., pregnant women, lactating women, women aged 19-30 years, and women aged 31-50 years)."

1.6. Its a reach to ask health care providers to "monitor DS intake and dosing to compensate for under consumed nutrients". Pregnant women do not typically undergo dietary analyses for assessment of the broad group of nutrients you discuss. I can certainly endorse a comment about discussing nutrition and need, or lack thereof, for supplementation.

Authors' response: We appreciate your comment. As suggested, we changed "monitor" to "discuss" and revised our Conclusion as follows: "Healthcare professionals should be aware of and communicate information about nutrition and dietary supplement use, especially for folic acid and iron. The American College of Obstetricians and Gynecologists and the American Society for Reproductive Medicine recommend that women who present for pre-pregnancy counseling should be screened for their diet and supplements to ensure they are meeting the RDAs for essential nutrients (19)."

1.7. I agree w/ one reviewer. Your methods section is too long. If the NHANES methodology for identifying pregnant and lactating women is published elsewhere, you can reference it and then briefly describe it. Otherwise, please put some of your methods section into supplemental digital content. (particularly that which references how pregnancy status ascertained. Important to include in methods why 20-44 is age range however.

Authors' response: As requested, we shortened the Methods section and cited NHANES documents and previous studies for readers who would be interested in more details. We did, however, keep the rationale for the 20-44 age range as requested.

1.8. Did you use the RDA's for pregnant and lactating women? These are different, as I'm sure you know. Why wouldn't you use these?

Authors' response: Yes, we used RDAs for pregnant and lactation women. Please refer to our response to the editor's comment #1.5.

1.9. I've had to read the two sentences lines 235-238 a few times to understand so please edit. What do you mean by the prevalence of any DS use vs prenatal DS use in pregnant women? What's the difference you are trying to make here? Also, lactating women can not Currently be using prenatal vitamins (as they are not PRE natal any more unless they are also pregnant-a low frequency event in your study).

Authors' response: We edited the paragraph for clarity: "Seventy-seven percent of pregnant women and 70.3% of lactating women used one or more dietary supplements, significantly higher than 44.8% of non-pregnant and non-lactating women. In particular, 64.4% of pregnant and 54.2% of lactating women used a prenatal product. Prenatal supplements were primarily multi-vitamin-minerals, which were defined as having  $\geq 3$  vitamins and at least 1 mineral."

As described in the Methods section, prenatal products are those that are labeled as "prenatal." Interestingly, our results show that more than half of lactating women consumed prenatal products. This is very important to note because prenatal products are not specifically formulated for lactating women and contain high amounts of nutrients; therefore, this was described in the Results section.

1.10. folate is really only important for neural tube closure preconceptionally and in first 21 days post menstrual when the neural tube closes. Thereafter, it has other important needs such as RBC production, but please don't perpetuate the myth that its needed throughout pregnancy for neural tube issues.

Authors' response: We totally agree. We revised the discussion to make our message clear as follows: "Folate is an especially important nutrient during the periconceptional period as it helps the fetus form the neural tube, but may not be consumed enough from food sources alone (23)." We also added information about the critical time period associated with the recommendation as follows: "Therefore, to help prevent neural tube defects, the U.S. Preventive Services Task Force recommends all women planning to become pregnant to take a supplement containing 400 to 800  $\mu\text{g}$  of folic acid each day, emphasizing a month before conception through 2 to 3 months of pregnancy as the critical period (2)."

1.11. in the preconception period

Authors' response: Please see our response to the preceding comment (editor's comment #1.10).

1.12. Does this 38 include DS + diet?

Authors' response: No, this only includes nutrients from dietary supplements. We clarified the sentence as follows: "Seventy-two percent of pregnant women were using iron-containing DS, which contributed 38 mg/d on average among users."

2. There is a second attachment called "Nutrients" that is uploaded for you to look at. It is taken from the Guidelines for Perinatal Care published by ACOG which articulates the nutrient needs for pregnant and lactating women that is recommended. Please address whether these were used in your paper as the standard and if not, why not.

Authors' response: Thank you for providing this document. Yes, we used the Recommended Dietary Allowances (RDA), set by the Food and Nutrition Board of the National Academies of Sciences, Engineering, and Medicine (NASEM), which is what the ACOG Guidelines for Perinatal Care recommend

(Ref 4). We also double-checked whether the numbers match. The only difference is that we presented the RDA of folate in  $\mu\text{g}$  folic acid, not  $\mu\text{g}$  DFE because we only report folic acid intake (i.e., a synthetic form of folate from fortified foods and dietary supplements). We described this in detail in the Methods section as well as in the footnotes of Table 4 and Appendix 1.

3. 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.

Authors' response: OPT-IN: Yes, please publish my point-by-point response letter.

4. 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.

Author's response: I have checked with all coauthors to confirm that the disclosures listed in their eCTA forms are correctly disclosed.

5. 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.

Authors' response: We have checked and confirm that our terminology conforms to these definitions.

6. 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.

Authors' response: We have 4,909 words, including title page, précis, abstract, text, and figure legends.

7. 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).

Authors' response: We confirm that we have followed these guidelines.

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

Authors' response: The short title is "Dietary supplements during pregnancy and lactation."

9. 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.

Authors' response: We double-checked the contents of the abstract and provided a word count.

10. 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.

Authors' response: We removed the non-standard abbreviations and acronyms and checked that those we do use are spelled out at first mention.

11. 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.

Authors' response: We removed the virgule symbol throughout the manuscript.

12. 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%).

Authors' response: we presented the estimates for the prevalence and group means with standard errors as is appropriate with survey statistics. We presented our results as group means of variables with standard errors of the means as is appropriate with survey statistics.

13. 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](http://edmgr.ovid.com/ong/accounts/table_checklist.pdf).

Authors' response: We reformatted the tables to conform to journal style.

14. 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](mailto: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>.

Authors' response: We believe the ACOG documents we cited are current and available.

15. Figures 1-3: Please upload as a separate figure file on Editorial Manager.

Authors' response: We uploaded separate figure files.

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.

Authors' response: We will look for that message.

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.

Authors' response: We reviewed all the comments and instructions and responded point by point.

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 Nov 07, 2019, we will assume you wish to withdraw the manuscript from further consideration.