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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.

Date: Jun 30, 2022
To: "Amir Lueth" [redacted]
From: "The Green Journal" em@greenjournal.org
Subject: Your Submission ONG-22-986

RE: Manuscript Number ONG-22-986

Allostatic Load and Adverse Pregnancy Outcomes

Dear Dr. Lueth:

Thank you for sending us your work for consideration for publication in Obstetrics & Gynecology. Your manuscript has been reviewed by the Editorial Board and by special expert referees. The Editors would like to invite you to submit a revised version for further consideration.

If you wish to revise your manuscript, please read the following comments submitted by the reviewers and Editors. Each point raised requires a response, by either revising your manuscript or making a clear argument as to why no revision is needed in the cover letter.

To facilitate our review, we prefer that the cover letter you submit with your revised manuscript include each reviewer and Editor comment below, followed by your response. That is, a point-by-point response is required to each of the EDITOR COMMENTS (if applicable), REVIEWER COMMENTS, STATISTICAL EDITOR COMMENTS (if applicable), and EDITORIAL OFFICE COMMENTS below. Your manuscript will be returned to you if a point-by-point response to each of these sections is not included.

The revised manuscript should indicate the position of all changes made. Please use the "track changes" feature in your document (do not use strikethrough or underline formatting).

Your submission will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 21, 2022, we will assume you wish to withdraw the manuscript from further consideration.

REVIEWER COMMENTS:

Reviewer #1:

Great article.

The analysis is sound and helpful.

The conclusions is in line with the evidence generated in the study.

However, the authors stratified race into non-hispanic blacks and "others", i feel that combining other race and ethnicities into one group may be misleading as these different ethnicities are very different and outcomes are very different among them

The authors should state in very clear terms how their findings can be converted into important algorithms to improve pregnancy outcomes and women health.

Reviewer #2: The authors report on a secondary analysis of allostatic load and APOs in a large, nulliparous population. They found that high allostatic load is associated with APOs and partially mediated the association between race and APO. Overall, this is an important contribution to the literature as this is a commonly asked question.

- I'm confused by lines 108-110 - why did the participants need to participate in the HHS study?

- Why did you choose to use logistic regression?

- Line 130-133: You provide a reference, but I think it would be helpful to describe why you chose the cutoff of 4 for a high allostatic load.

- Line 177: I might also describe this as effect modification in order to clarify this for your readers (I have only ever heard of this referred to as effect modification, but when I google it, it tells me moderation and effect modification are the same thing).

- Table 1: I feel like in this kind of analysis, I'm used to seeing table 1 stratified by exposure rather than outcome (as this is a cohort study) - why did you choose to have Table 1 looking at outcome?

Reviewer #3: Authors performed a secondary analysis of a prospective observational cohort study of nulliparous, singleton pregnancies to evaluate if high allostatic load in the first trimester was associated with a composite of adverse pregnancy outcomes.

Abstract: Authors define their objectives, cohort, methods, and results.

Introduction:
Line 74-75 Recommend authors include more background on allostatic load, how it is defined/validated, etc. and what prior work has demonstrated with regards to APOs (e.g., mixed results).

Materials and Methods:
Study design is appropriate to study associations between adverse pregnancy outcomes (composite outcome) and high allostatic load (exposure).

Line 115 Recommend lowercase s for "Samples"

Line 118-125 How did the authors modify the NHANES score? Was it validated after modification? Recommend table to describe the quartiles and cut-offs for each biomarker or explanation of how authors handled this (line 288-290). The authors discuss "10-factor allostatic load index" in discussion; recommend introducing this earlier, and comparing to complete allostatic load index and what factors were eliminated and why.

Line 138-139 Was there a lower limit for preterm birth (e.g. 20 weeks)? Did preterm birth outcome include both spontaneous and iatrogenic? How were each category of HDP defined (please be specific)?

What was authors' plan to deal with patients who had more than 1 adverse outcome (e.g. preterm delivery of stillborn in patient with preeclampsia with severe features)?

Line 147-148 Why were American Indian included in "other group" when they are at similar increased risk for high allostatic load and APOs as blacks? Please provide rationale.

Line 148 How did authors choose educational achievement outcomes as they did? I would surmise those with some college are more representative of those who complete college than those who just attain a high school degree.

Line 148 What dose "gravidity any prior miscarriages" mean? Is there a missing comma?
Statistical analysis appears appropriate.

Recommend state whether they following STROBE guidelines and include checklist. Did the authors perform a power analysis?

How did authors deal with missing data?

Results:
Presentation of results is appropriate.

Discussion:
Line 264-265 Are these secondary outcomes? Please clarify.

Line 322-333 Adjudication process should be discussed in methods section.

Line 326-328 Recommend authors call for further investigation to see if interventions to modify high allostatic load will result in decreased APOs.

Figures/Tables:
Line 468 Abbreviation not needed; APO not used in table.

Line 508, 642-644 Please include cAPO, HDP and PTB in abbreviations list.

Line 509, 642-644 Data in this table does not include N(column %). Please remove.

Line 550-552 This footnote does not match this figure.

Line 564-567 Please include abbreviations in footnotes.

Line 601-604 Please define abbreviations used in this table.

References:
Appears consistent with body of work, relevant, and current.

STATISTICAL EDITOR COMMENTS:

General: From the references re: allostatic load cited (esp # 18), it seems that there are many variations on the NHANES implementation of allostatic load calculation. How did the Authors' version compare to the original NHANES version and what documentation validates is the Authors' version?

Table 1: There are several demographic and clinical characteristics that separate maternal adverse outcome groups, notably race, education, smoking, income and public health insurance. To what extent are those characteristics correlated with allostatic load? If a multivariable model included demographic, clinical and allostatic inputs, would the allostatic inputs retain significant association with the occurrence of adverse maternal outcomes? That is, from Table 2, there is almost no change from unadjusted to adjusted ORs, with adjustment for demographic/clinical characteristics. What if the regression was first based on the latter, then the allostatic? Are the demographic/clinical so correlated with the allostatic that the addition of the other to the model makes no statistical change in strength of association with maternal adverse outcomes?

Table 2: The CIs for PTB are (1.0,1.5). Does this meet criteria from lines 185-187? If not, then should omit from conclusions as attaining statistical significance.

Fig 1: How did the cohort with missing serum biomarkers (N ~ 1,000), compare at baseline to those who were included in the analysis? That is, was there any selective exclusion of subgroups thru absence of serum biomarkers? Need to compare as in Table 1 (N = 4266 vs those excluded).

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

2. When you submit your revised manuscript, please make the following edits to ensure your submission contains the required information that was previously omitted for the initial double-blind peer review:
* Funding information (ie, grant numbers or industry support statements) should be disclosed on the title page and at the end of the abstract. For industry-sponsored studies, describe on the title page how the funder was or was not involved in the study.
* Include clinical trial registration numbers, PROSPERO registration numbers, or URLs at the end of the abstract (if applicable).
* Name the IRB or Ethics Committee institution in the Methods section (if applicable).
* Add any information about the specific location of the study (ie, city, state, or country), if necessary for context.

3. Obstetrics & Gynecology's Copyright Transfer Agreement (CTA) must be completed by all authors. When you uploaded your manuscript, each coauthor received an email with the subject, "Please verify your authorship for a submission to Obstetrics & Gynecology." Please ask your coauthor(s) to complete this form, and confirm the disclosures listed in their CTA are included on the manuscript's title page. If they did not receive the email, they should check their spam/junk folder. Requests to resend the CTA may be sent to em@greenjournal.org.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the

manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories.

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

5. ACOG uses person-first language. Please review your submission to make sure to center the person before anything else. Examples include: "People with disabilities" or "women with disabilities" instead of "disabled people" or "disabled women"; "patients with HIV" or "women with HIV" instead of "HIV-positive patients" or "HIV-positive women"; and "people who are blind" or "women who are blind" instead of "blind people" or "blind women."

6. The journal follows ACOG's Statement of Policy on Inclusive Language (https://www.acog.org/clinical-information/policy-and-position-statements/statements-of-policy/2022/inclusive-language). When possible, please avoid using gendered descriptors in your manuscript. Instead of "women" and "females," consider using the following: "individuals;" "patients;" "participants;" "people" (not "persons"); "women and transgender men;" "women and gender-expansive patients;" or "women and all those seeking gynecologic care."

7. Figures:

Figure 1: Please check or explain the n value in the exclusion box (4,508-236 does not equal 4,266). Please upload as a figure file in Editorial Manager.

Figure 2: Is this original to the manuscript? Please upload as a figure file in Editorial Manager.

If Figure 2 has been previously published in another source, both print and electronic (online) rights must be obtained from the holder of the copyright (often the publisher, not the author), and credit to the original source must be included in your manuscript. Many publishers have online systems for submitting permissions requests; please consult the publisher directly for more information.

8. Responsible reporting of research studies, which includes a complete, transparent, accurate and timely account of what was done and what was found during a research study, is an integral part of good research and publication practice and not an optional extra. Obstetrics & Gynecology supports initiatives aimed at improving the reporting of health research, and we ask authors to follow specific guidelines:

STROBE: observational studies

Include the appropriate checklist for your manuscript type upon submission, if applicable, and indicate in your cover letter which guideline you have followed. Please write or insert the page numbers where each item appears in the margin of the checklist. Further information and links to the checklists are available at www.equator-network.org/.

9. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

10. Make sure your manuscript meets the following word limit. The word limit includes the manuscript body text only (for example, the Introduction through the Discussion in Original Research manuscripts), and excludes the title page, précis, abstract, tables, boxes, and figure legends, reference list, and supplemental digital content. Figures are not included in the word count.

Original Research: 3,000 words

11. Specific rules govern the use of acknowledgments in the journal. Please review the following guidelines and edit your title page as needed:

* 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 or indicate whether the meeting was held virtually).
* If your manuscript was uploaded to a preprint server prior to submitting your manuscript to Obstetrics & Gynecology, add the following statement to your title page: "Before submission to Obstetrics & Gynecology, this article was posted to a preprint server at: [URL]."
* Do not use only authors' initials in the acknowledgement or Financial Disclosure; spell out their names the way they appear in the byline.

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

13. Be sure that each statement and any data in the abstract are also stated in the body of your manuscript, tables, or figures. Statements and data that appear in the abstract must also appear in the body text for consistency. Make 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 manuscript.

In addition, the abstract length should follow journal guidelines. Please provide a word count.

Original Research: 300 words

14. 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.

15. The journal does not use the virgule symbol (/) in sentences with words, except with ratios. 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.

16. 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.

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

Express all percentages to one decimal place (for example, 11.1%"). Do not use whole numbers for percentages.

17. Line 314: Your manuscript contains a priority claim, which means you state your study is the first of its kind or the largest study to date. We discourage such claims, since they are often difficult to prove. If this is based on a systematic search of the literature, that search should be described in the text (search engine name, search terms, date range of search, and languages encompassed by the search). If it is not based on a systematic search but only on your level of awareness, please delete or rephrase this statement.

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

19. Please review examples of our current reference style at https://edmgr.ovid.com/ong/accounts/ifa_suppl_refstyle.pdf. Include the digital object identifier (DOI) with any journal article references and an accessed date with website references.

Unpublished data, in-press items, personal communications, letters to the editor, theses, package inserts, submissions, meeting presentations, and abstracts may be included in the text but not in the formal reference list. Please cite them on the line in parentheses.

If you cite ACOG documents in your manuscript, be sure the references you are citing are still current and available. Check the Clinical Guidance page at https://www.acog.org/clinical (click on "Clinical Guidance" at the top). If the reference is still available on the site and isn't listed as "Withdrawn," it's still a current document. In most cases, if an ACOG document has been withdrawn, it should not be referenced in your manuscript.

Please make sure your references are numbered in order of appearance in the text.

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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.

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If you choose to revise your manuscript, please submit your revision through Editorial Manager at http://ong.editorialmanager.com. Your manuscript should be uploaded as a Microsoft Word document. Your revision's cover letter should include a point-by-point response to each of the received comments in this letter. Do not omit your responses to the EDITOR COMMENTS (if applicable), the REVIEWER COMMENTS, the STATISTICAL EDITOR COMMENTS (if applicable), or the EDITORIAL OFFICE COMMENTS.

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

Again, your manuscript will be maintained in active status for 21 days from the date of this letter. If we have not heard from you by Jul 21, 2022, we will assume you wish to withdraw the manuscript from further consideration.

Sincerely,

Ebony B. Carter, MD, MPH
Associate Editor for Equity

2020 IMPACT FACTOR: 7.661
2020 IMPACT FACTOR RANKING: 3rd out of 83 ob/gyn journals

_____

Dear Dr. Wright. Editors and reviewers,

Thank you for allowing me the opportunity to submit a revised version of our manuscript “Allostatic Load and Adverse Pregnancy Outcomes” to the Journal of Obstetrics and Gynecology. I appreciate the time and the effort that you and the reviewers have dedicated to providing constructive and valuable feedback on our manuscript. I also appreciate the insightful comments and questions from the reviewers to improve our paper. I was able to incorporate the suggestions made by the reviewers and they are highlighted within the manuscript. I acknowledge that we have exceed the required word count and although I believe the manuscript flows thoroughly, I would be more than happy to edit the word count down.

Please see below in blue for the point by point response to each reviewers’ comments and questions. All of the page lines refer to the revised version of the manuscript file with tracked changes. I have also uploaded a clean version.

Please let me know if we can make additional edits to further improve the paper.

Thank you

Amir Lueth

REVIEWER COMMENTS:

Reviewer #1:

Great article. The analysis is sound and helpful. The conclusions is in line with the evidence generated in the study.

1. However, the authors stratified race into non-Hispanic blacks and "others", i feel that combining other race and ethnicities into one group may be misleading as these different ethnicities are very different and outcomes are very different among them
   Author's response: Thank you for this comment. We agree with the reviewer but our sample sizes were too small in the different subgroups for meaningful subgroup analyses.

2. The authors should state in very clear terms how their findings can be converted into important algorithms to improve pregnancy outcomes and women health.
   Author's response: Thank you for this comment. We agree that it is aspirational to use allostatic load as risk stratification tool. However, it would be premature to do so based on the current study. We discuss this further and more clearly in the discussion 351-354.

Reviewer #2:

The authors report on a secondary analysis of allostatic load and APOs in a large, nulliparous population. They found that high allostatic load is associated with APOs and partially mediated the association between race and APO. Overall, this is an important contribution to the literature as this is a commonly asked question.

1. I'm confused by lines 108-110 - why did the participants need to participate in the HHS study?
   Author's response: Thank you for this comment. Some of the biomarkers included in the allostatic load were only assessed in parent NuMom2b study participants that also participated in the follow-up Heart Health study. This is now clarified in the methods in line 112.

2. Why did you choose to use logistic regression?
   Author's response: Thank you for this comment. Logistic regression was appropriate in this analysis because our outcome variable is dichotomous (High Allostatic load vs Low Allostatic load); also logistic regression allows for robust adjustment for clinically and biologically important variables.

3. Line 130-133: You provide a reference, but I think it would be helpful to describe why you chose the cutoff of 4 for a high allostatic load.
   Author's response: Thank you for this comment. We chose this cutoff because previous studies have suggested that differences in adverse pregnancy outcomes may arise between groups when allostatic load scores reach 3 or 4. This justification is clarified in lines 144-146.

4. Line 177: I might also describe this as effect modification in order to clarify this for your readers (I have only ever heard of this referred to as effect modification, but when I google it, it tells me moderation and effect modification are the same thing).
   Author's response: Thank you for this comment. We have revised lines 190-191 to reflect the use of both expressions in case readers are familiar with only one or the other.

5. Table 1: I feel like in this kind of analysis, I'm used to seeing table 1 stratified by exposure rather than outcome (as this is a cohort study) - why did you choose to have Table 1 looking at outcome?
   Author's response: Thank you for this comment. We currently have the table you describe as supplemental table 1. We agree that this is confusing, and we have changed the paper so that the requested table is now "table 1." The prior table 1, is now "supplemental table 1." .

Reviewer #3:

Authors performed a secondary analysis of a prospective observational cohort study of nulliparous, singleton pregnancies to evaluate if high allostatic load in the first trimester was associated with a composite of adverse pregnancy outcomes.

Abstract: Authors define their objectives, cohort, methods, and results.

Introduction:

1. Line 74-75 Recommend authors include more background on allostatic load, how it is defined/validated, etc. and what prior work has demonstrated with regards to APOs (e.g., mixed results).
   Author's response: Thank you for this feedback. More background information has been added to the manuscript, lines 78-79.

Materials and Methods:

2. Study design is appropriate to study associations between adverse pregnancy outcomes (composite outcome) and high allostatic load (exposure).
   Author's response: Thank you for this feedback.

3. Line 115 Recommend lowercase s for "Samples"
   Author's response: Thank you for this feedback. We lowered the case for sample in the manuscript, line 119.

4. Line 118-125 How did the authors modify the NHANES score? Was it validated after modification? Recommend table to describe the quartiles and cut-offs for each biomarker or explanation of how authors handled this (line 288-290). The authors discuss "10-factor allostatic load index" in discussion; recommend introducing this earlier, and comparing to complete allostatic load index and what factors were eliminated and why.

Author's response: Thank you for this feedback. We did not include validation of the modified allostatic score in this manuscript. We used a modified version based on the variables (including laboratory studies) that were available. This is clarified in the methods (lines 135-137). There are numerous variations on the variables used to assess allostatic load among studies. Using only one such variation is mentioned as a potential limitation of the study in the discussion (lines 335-336). Also, we provide data on the association between individual components of the allostatic load and our outcomes. However, comparing various combinations of variables is beyond the scope of this analysis. In addition, we now include a table describing the "worst quartile" thresholds in the supplementary tables (lines 721-722).

Biomarker	Cutoff for Worst Quartile
Insulin	20.0
Glucose	95.0
CRP	2.0
Cholesterol	208.0
TRIG	152.0
*HDL	61.0
LDL	106.0
Creatinine	141.4
*Albumin	0.16
BMI	29.8
SBP	118.0
DBP	72.0

*HDL and Albumin were "reverse" coded in calculating their cutoff for worst quartile.

5. Line 138-139 Was there a lower limit for preterm birth (e.g. 20 weeks)? Did preterm birth outcome include both spontaneous and iatrogenic? How were each category of HDP defined (please be specific)?
   Author's response: Thank you for these questions. The lower limit for preterm birth was 20 weeks of gestation. All participants had excellent gestational dating and this threshold is now included in the methods. Our preterm birth variable included both spontaneous and iatrogenic. These issues are also clarified in the methods, line 150. The category for HDP was defined using the nuMoM2b criteria. For any participant with hypertension, proteinuria, or a related condition documented in the chart, a detailed chart review was required by a site investigator or a staff member certified for abstraction of complicated charts. Cases that presented atypically and were difficult to classify according to study criteria were adjudicated by the principal investigators and final classification was reached by consensus. We modified manuscript lines 150 to reflect that the lower limit for preterm birth is 20 weeks of gestation.

6. What was authors' plan to deal with patients who had more than 1 adverse outcome (e.g. preterm delivery of stillborn in patient with preeclampsia with severe features)?
   Author's response: Thank you for this question. Our composite primary endpoint was dichotomous, so multiple triggers of components of the composite would only count once for

each person, and each person is included only once in analysis, even if they have more than one component of the composite outcome. Separately we report each individual component of the composite as a secondary outcome. We do not include a separate endpoint defined as more than one adverse outcome, since these outcomes have shared pathophysiology.

7. Line 147-148 Why were American Indian included in "other group" when they are at similar increased risk for high allostatic load and APOs as blacks? Please provide rationale.
   Author's response: Thank you for this question. We agree with the reviewer. However, due to extremely small sample size in the Native American group (N=8), we are not able to do a subgroup analysis.

8. Line 148 how did authors choose educational achievement outcomes as they did? I would surmise those with some college are more representative of those who complete college than those who just attain a high school degree.
   Author's response: Thank you for this feedback. We agree that the reviewer may be correct. However, this was a particularly educated cohort (noted in limitations), making this a natural break point given the distribution in our population.

9. Line 148 What dose "gravidity any prior miscarriages" mean? Is there a missing comma?
   Author's response: Thank you for this feedback and identification of a typographical error. We added a comma. The edit is reflected in the manuscript, line 162.

Statistical analysis appears appropriate.

10. Recommend state whether they following STROBE guidelines and include checklist. Did the authors perform a power analysis?
    Author's response: Thank you for this feedback. STROBE guidelines were used for both the parent NuMoM2b study and Heart Health studies (see attached). Also, sample size calculations were performed for both cohort studies.
    A sample size calculation was not performed for the current analyses. The care needed in interpreting results in the presence of infrequent events is noted as a limitation in the discussion section (line 328-330)

11. How did authors deal with missing data?
    Author's response: Thank you for this question. Missing data was infrequent in this cohort. In the presence of item non-response, a record was excluded from the analysis. We have modified Figure 1 to better reflect the study population.

Results:

12. Presentation of results is appropriate.
    Author's response: Thank you for this feedback.

Discussion:

13. Line 264-265 Are these secondary outcomes? Please clarify.

Author's response: Thank you for this question. Yes, preeclampsia, low birth weight and PTB were secondary outcomes.

14. Line 322-333 Adjudication process should be discussed in methods section.
    Author's response: Thank you for this feedback. We added a reference to explain the adjudication in detail (line 348).

15. Line 326-328 Recommend authors call for further investigation to see if interventions to modify high allostatic load will result in decreased APOs.
    Author's response: Thank you for this feedback. We have edited our conclusion to reflect this recommendation that further investigation is need to ascertain interventions to modify high allostatic load and potentially decrease APOs.

Figures/Tables:

16. Line 468 Abbreviation not needed; APO not used in table.
    Author's response: Thank you for this feedback. We removed the abbreviation. The edit is reflected in the manuscript's table (line 624).

17. Line 508, 642-644 Please include cAPO, HDP and PTB in abbreviations list.
    Author's response: Thank you for this feedback. We included these abbreviations in the list. The edit is reflected in the manuscript (lines 542, 688-689).

18. Line 509, 642-644 Data in this table does not include N(column %). Please remove.
    Author's response: Thank you for this feedback. We removed this as recommended. The edit is reflected in the manuscript (lines 543, 688-689).

19. Line 550-552 this footnote does not match this figure.
    Author's response: Thank you for this feedback. We edited the footnote for our figure 1. The edit is reflected in the manuscript (line 587).

20. Line 564-567 Please include abbreviations in footnotes.
    Author's response: Thank you for this feedback. We included abbreviations for APO and AL in the footnotes. The edit is reflected in the manuscript (line 601).

21. Line 601-604 Please define abbreviations used in this table.
    Author's response: Thank you for this feedback. We defined abbreviations for this table. The edit is reflected in the manuscript (line 645-646).

References:

22. Appears consistent with body of work, relevant, and current.
    Author's response: Thank you for this feedback.

STATISTICAL EDITOR COMMENTS:

1. General: From the references re: allostatic load cited (esp # 18), it seems that there are many variations on the NHANES implementation of allostatic load calculation. How did the Authors' version compare to the original NHANES version and what documentation validates is the Authors' version?
   Author's response: Thank you for this feedback. The answer is the same for reviewer #3 – point #4. We used a modified version based on the variables (including laboratory studies) that were available. This is clarified in the methods (lines 122-137). There are numerous variations on the variables used to assess allostatic load among studies. Using only one such variation is mentioned as a potential limitation of the study in the discussion (lines 335-336). Also, we provide data on the association between individual components of the allostatic load and our outcomes. However, comparing various combinations of variables is beyond the scope of this analysis.

2. Table 1: There are several demographic and clinical characteristics that separate maternal adverse outcome groups, notably race, education, smoking, income and public health insurance. To what extent are those characteristics correlated with allostatic load? If a multivariable model included demographic, clinical and allostatic inputs, would the allostatic inputs retain significant association with the occurrence of adverse maternal outcomes? That is, from Table 2, there is almost no change from unadjusted to adjusted ORs, with adjustment for demographic/clinical characteristics. What if the regression was first based on the latter, then the allostatic? Are the demographic/clinical so correlated with the allostatic that the addition of the other to the model makes no statistical change in strength of association with maternal adverse outcomes?
   Author's response: Thank you for this feedback. The association of race, education, smoking are significantly associated with allostatic load, however public health insurance was not (supplemental table 1). High allostatic load remained significantly associated with the composite outcomes, hypertensive disorders of pregnancy but not with preterm birth and SGA when we adjusted self-reported race (table 3). The strength of association between allostatic load and each adverse pregnancy outcome persist regardless of model parametrization (tables 2 and 3). Also, we changed the places of table 1 and supplemental table 1 in order to provide clarity.

3. Table 2: The CIs for PTB are (1.0,1.5). Does this meet criteria from lines 185-187? If not, then should omit from conclusions as attaining statistical significance.
   Author's response: Thank you for this feedback. We modified table 2 to reduce ambiguity around the significance in the presence of rounding and we accept the reviewer's suggestion that PTB should be omitted from the conclusion given its p-value of 0.988. The manuscript is modified accordingly.

4. Fig 1: How did the cohort with missing serum biomarkers (N ~ 1,000), compare at baseline to those who were included in the analysis? That is, was there any selective exclusion of

subgroups thru absence of serum biomarkers? Need to compare as in Table 1 (N = 4266 vs those excluded).

Author's response: Thank you for this feedback. We have added language to clarify this issue in Figure 1. Those 1,000 patients did not participate in the Heart health study: they did not attend an in-person visit and were not considered participants in the Heart Health study. They also did not have biomarkers as a consequence. NuMoM2b participants who were included vs not included in the HHS study had similar demographic characteristics to the approximately 4,500 who had in person visits and biomarker assessment. Below we have included this table from the Haas et al. paper on "The association of adverse pregnancy outcomes with hypertension 2 to 7 years postpartum" to display the overall baseline characteristics of women who were included in our analyses. The demographic characteristics of the nuMoM2b-HHS cohort were representative of the overall nuMoM2b cohort and similar to women who did not participate in nuMoM2b-HHS.

Supplemental Table 1
Index Pregnancy Characteristics of Original nuMoM2b Participants, nuMoM2b-HHS Participants Included in Analyses, and nuMoM2b and nuMoM2b-HHS Participants Not Included in Analyses

Baseline Characteristics	nuMoM2b (N=10038)	Heart Health Study Included in Analyses (N=4484)	Excluded from Analyses (N=5554)
Maternal age, mean (SD), years	26.9 (5.7)	27.0 (5.6)	26.9 (5.7)
Category: n (%)			
13-21	2133 (21.3%)	905 (20.2%)	1228 (22.2%)
22-35	7222 (72.0%)	3272 (73.0%)	3950 (71.2%)
>35	673 (6.7%)	307 (6.8%)	366 (6.6%)
Maternal race: n (%)			
White Non-Hispanic	5989 (59.7%)	2786 (62.1%)	3203 (57.8%)
Black Non-Hispanic	1418 (14.1%)	618 (13.8%)	800 (14.4%)
Hispanic	1700 (17.0%)	735 (16.4%)	965 (17.4%)
Asian	407 (4.1%)	135 (3.0%)	272 (4.9%)
Other	514 (5.1%)	210 (4.7%)	304 (5.5%)
Education level: n (%)			
Less than high school graduate	816 (8.1%)	327 (7.3%)	489 (8.8%)
High school graduate or GED completed	1171 (11.7%)	508 (11.3%)	663 (12.0%)
Some college credit, no degree	1948 (19.4%)	889 (19.8%)	1059 (19.1%)
Associate/technical degree	1005 (10.0%)	501 (11.2%)	504 (9.1%)
Bachelor's degree	2772 (27.7%)	1261 (28.1%)	1511 (27.3%)
Degree beyond bachelor's	2308 (23.0%)	996 (22.2%)	1312 (23.7%)
Type of health insurance: n (%)			
Commercial	6778 (68.1%)	3087 (69.2%)	3691 (67.1%)
Government/military	2800 (28.1%)	1219 (27.3%)	1581 (28.7%)
Self-pay/other	381 (3.8%)	152 (3.4%)	229 (4.2%)
Smoked during 3 months prior to pregnancy: n / N (%)	1782/10018 (17.8%)	718/4478 (16.0%)	1064/5540 (19.2%)

EDITORIAL OFFICE COMMENTS:

1. If your article is accepted, the journal will publish a copy of this revision letter and your point-by-point responses as supplemental digital content to the published article online. You may opt out by writing separately to the Editorial Office at em@greenjournal.org, and only the revision letter will be posted.

Author's response: Thank you for this feedback.

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* Name the IRB or Ethics Committee institution in the Methods section (if applicable).

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Author's response: Thank you for this feedback. This edit is reflected in the title page.

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Author's response: Thank you for this feedback.

4. For studies that report on the topic of race or include it as a variable, authors must provide an explanation in the manuscript of who classified individuals' race, ethnicity, or both, the classifications used, and whether the options were defined by the investigator or the participant. In addition, describe the reasons that race and ethnicity were assessed in the Methods section and/or in table footnotes. Race and ethnicity must have been collected in a formal or validated way. If it was not, it should be omitted. Authors must enumerate all missing data regarding race and ethnicity as in some cases missing data may comprise a high enough proportion that it compromises statistical precision and bias of analyses by race.

Use "Black" and "White" (capitalized) when used to refer to racial categories.

Author's response: Thank you for this feedback. This edit is reflected in the manuscript.

List racial and ethnic categories in tables in alphabetic order. Do not use "Other" as a category; use "None of the above" instead.

Please refer to "Reporting Race and Ethnicity in Obstetrics & Gynecology" at https://edmgr.ovid.com/ong/accounts/Race_and_Ethnicity.pdf.

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Author's response: Thank you for this feedback. We modified our manuscript to reflect the use of person-first language. This edit is reflected in the manuscript.

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Author's response: Thank you for this feedback. This edit is reflected in the manuscript.

7. Figures:

Figure 1: Please check or explain the n value in the exclusion box (4,508-236 does not equal 4,266). Please upload as a figure file in Editorial Manager.

Author's response: Thank you for this feedback. This was a typo, it should be 242, and this edit is reflected in the flow diagram.

Figure 2: Is this original to the manuscript? Please upload as a figure file in Editorial Manager.

Author's response: Thank you for this feedback. Figure 2 is original to our manuscript.

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Author's response: Thank you for this feedback. We have addressed this above.

9. 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 data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-obstetrics-data-definitions and the gynecology data definitions at https://www.acog.org/practice-management/health-it-and-clinical-informatics/revitalize-gynecology-data-definitions. If use of the reVITALize definitions is problematic, please discuss this in your point-by-point response to this letter.

Author's response: Thank you for this feedback.

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Author's response: Thank you for this feedback. This edit is reflected.

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Author's response: Thank you for this feedback.

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Author's response: Thank you for this feedback. This edit is reflected.

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Author's response: Thank you for this feedback.

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Author's response: Thank you for this feedback. This edit is reflected in the manuscript.

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