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

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

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

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

Questions about these materials may be directed to the Obstetrics & Gynecology editorial office: obgyn@greenjournal.org.
RE: Manuscript Number ONG-23-261

Structural racism and adverse pregnancy outcomes through the lens of maternal microbiome

Dear Dr. Powell:

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, and STATISTICAL EDITOR COMMENTS (if applicable) below. 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). Upload the tracked-changes version when you submit your revised manuscript.

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 04/25/2023, we will assume you wish to withdraw the manuscript from further consideration.

EDITOR COMMENTS:

Thank you for your submission to the Green Journal! The Journal is willing to consider a revised manuscript that addresses the points raised by the peer reviewers. You will note that all the reviewers found the manuscript and its content important; however, they all made comments on how the manuscript could be better organized or restructured to guide the reader through the conceptual model. Please read through all the comments and then decide how you want to best address the reviewers’ points in the revised manuscript. Your Response to Review should note how each of the points were considered and/or addressed in the revised manuscript.

In your revised manuscript, please include at least 1 figure that represents your conceptual model to provide the reader a visual framework.

Please also note the following:

* Help us reduce the number of queries we add to your manuscript after it is revised by reading the Revision Checklist at https://journals.lww.com/greenjournal/Documents/RevisionChecklist_Authors.pdf and making the applicable edits to your manuscript.

REVIEWER COMMENTS:

Reviewer #1:
Overall the authors present an argument that 1) the lived environment of a person is determined by the racist past/present of the US, 2) the lived environment has an impact on microbiome composition and 2) microbiome is associated with pregnancy outcomes - hence, associations between "race" and microbiome or pregnancy outcomes are likely actually associations between racism and microbiome or pregnancy.

The individual sections are clearly written, well referenced and compelling.

However, the organization of the piece, with the above arguments in discrete blocks, is disjointed enough that the thread is
easy to lose. In order to pull the reader along, especially with topics that (for many green journal readers) are at the edge of their comfort zone, it may help to interweave things a bit more.

First, I think having more up front discussion of microbiome may be helpful to hook the reader - perhaps an intro paragraph about the association between gut and vaginal microbiota and race before the current intro paragraph. I would then suggest interweaving the discussions of microbiome and racist policies that may contribute to differences: e.g. 1) Gut microbiome and pregnancy 2) Structural racism and social determinants shape dietary patterns, 3) Environmental chemicals, 4) Redlining and blockbusting, 5) Vaginal microbiota (which includes the section on stress and perceived racism impacting microbiota), 6) Reproductive health care and racism.

And, while the authors present data that gut microbiome transplant to mice can transfer the clinical phenotype, suggesting some true causality, it is worth stating more explicitly that the associations between microbiome and outcomes may simply be that - associations reflective of the same upstream cause. This is essentially one of the points of the article (I think) and should be stated plainly.

In lines 158-164 the authors state that using race "superficially" in studies of diet and microbiome and pregnancy outcomes may lead to mis-interpretation or perpetuation of racist stereotypes. However, they do not provide an example of how one would use race in a non-superficial way. It would be helpful to hear whether the authors suggest using dietary metrics rather than race, or diet AND race (because race may be a proxy for so many other barriers to a healthy environment) or whether they would suggest use of a perceived racism scale, chronic stress scale, or some other measure in studies seeking a biologic mechanism - something that acknowledges "race" is not the mechanistic feature, but that it is racism at the root of biologic differences.

Minor comments:
- Lines57-61: the last sentence of this paragraph is long and a little convoluted to follow. Please simplify.
- Line 175: In the term 16S, the S is capitalized
- Line 186-188: The term "flora" is no longer preferred. "microbiota" is a more ecologically appropriate term (since bacteria are not plants)
- Line 224: Lactobacillus genus name should be italicized

Reviewer #2:
The authors present a current commentary regarding the use of the maternal microbiome to evaluate racial disparities presented in prior research.

The authors present social and structural forms racism nicely in the opening paragraphs. They do not include a positionally statement.

Abstract: please include a reference in line 9.

The authors discuss dietary patterns and the redlining in a clear fashion. As noted below the authors should work to better connect dietary patterns and structural racism to the impact on the microbiome.

Reproductive health care access: this paragraph does not connect as well to the themes of the article. As the focus is increased rates of Adverse pregnancy outcomes and poor access to adequate food intake.

Line 126- please describe Shannon diversity?
Do the studies note a causative effect? Is this an association? When were samples obtained (before or after diagnosis?)

Line 146- the studies presented note an association with diet and adverse outcomes but minimal data presented regarding the microbiome.

Needs stronger connection to previously presented arguments, this is a nice summation of prior research but unclear how to deconstruct the prior data based on race

Vaginal microbiome
Line 169- clarify that this is the microbiome diversity.
It is not clear how the discussion of BV and race and microbiome differences is related to adverse pregnancy outcomes. Are there areas in which race could be studied differently or it is not evaluated? Can the authors identify strongly the limitations of prior research?

Additional data on the current literature connecting microbiome and diet would strengthen the earlier discussion of food deserts and racism on alterations of microbiome. It seems that the authors are calling for more research in this area and also need to demonstrate some prior data regarding potential connect to diet and microbiome that can now be further explored.

Reviewer #3:
The authors commentary reviewed the literature on and provided commentary on the role of structural racism and food
access, and it's link to gut and vaginal microbiomes, and their subsequent link to birth outcomes. The authors may consider adding a figure (or two) that clearly outlines for the reader their conceptual framework. It does not necessarily need to be a Directed Acyclic Graph (DAG), but just a graphical representation of their theorized casual mechanism to clarify for the reader how structural racism, food accessibility, gut microbiome, and birth outcomes relate to each other, and why considering race as biologic factor is inappropriate and inaccurate. Creating a few figures may guide the authors in restructuring some of their content to mirror their proposed framework so the reader can more easily follow along with their arguments. In addition to these considerations, I listed a number of other specific recommendations below.

1. A minor note - on line 45, did the authors mean "systematic review?"

2. Can the authors clarify this sentence? (Lines 57-61):
This study also showed that food deserts, based on the Food Access Research Atlas, demonstrated a higher percentage of Black women compared to White women, building on prior work by Salow et al showing that residents in neighborhoods with higher levels of racial residential segregation were at higher risk for preterm birth.

3. In the section, "Impact of Redlining on Health," the authors summarize redlining clearly and succinctly. The authors may consider adding additional detail and clarification in the second paragraph about how redlining is connected to reproductive health outcomes. They may consider adding a few sentences that summarize their framework (i.e., redlining leads to exposure to xyz, which impacts reproductive health outcomes).

4. In the section, "Structural Racism and Reproductive Healthcare Access," the authors may consider adding more specificity about what they mean by "poor maternal health outcomes." Further, they may consider adding more detail and clarification about what dismantling racism in healthcare means and how it would impact reproductive health outcomes.

5. In the section, "Gut Microbiome of Pregnancy," there are a number of places the authors may consider rewording and/or cutting sentences for clarity of the scientific concepts for readers with different levels of expertise in gut microbiome. For instance, the below sentence (lines 107-110) is difficult to interpret for a non-expert reader. Could the authors more clearly explain that microbiomes change/shift over the course of pregnancy to resemble metabolic syndrome?
"Over the course of pregnancy, the intestinal microbiome converges on a profile characterized by decreased alpha diversity (or within-sample richness/abundance) that more closely resembles microbiota associated with metabolic syndrome, with features of dysbiosis (altered gut microbiome profile)."

6. Under the same section, the authors may consider clarifying lines 122-124. Did the study find that both PTB was associated with a specific microbiome profile and a higher saturated fat diet? Or are they insinuating that the diet led to the different microbiome profile, which lead to ptb? If it just correlations, backed up with other hypotheses of biologic mechanisms, that's completely fine. Just make that clear to the reader.

7. Under the same section, can the authors clarify what "Shannon diversity" is? (Line 126).

8. Under the same section, can the authors clarify lines 142-144 ("Patients with pre-eclampsia had decreased gut microbiota 143 diversity with a reduced abundance of Firmicutes, Blautia, Eubacterium rectale, and 144 Bifidobacterium (notable SCFA producers).")? How do these specific elements relate to diet?

9. In the section, "Vaginal Microbiome of Pregnancy," the authors may consider how much word count that are using to discussing douching and consider focusing in more so on the stress and structural racism causal mechanism.

10. Under the same section, can the authors more clearly tie structural racism into their discussion about DEA? Where is it found (more clearly), and why might black birthing people be disproportionality impacted?

11. Under the same section, the authors may consider adding a section devoted to recommendations and considerations for researchers in this area. The reader would benefit from potentially less detail about specific studies (they can look up the citations if they are interested), and focus more so on how to formulate better questions that don't perpetuate racism and racial bias in scientific research.

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Sincerely,
Mark A. Clapp, MD, MPH
Editorial Fellow

The Editors of Obstetrics & Gynecology

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 Obstetrics and Gynecology Editorial Team,

We thank you for the opportunity to revise and strengthen our manuscript. Please find our responses to your valuable feedback below. Please note, we have also adjusted authorship order after a discussion of each author's contributions.

REVIEWER COMMENTS:

Reviewer #1:
Overall the authors present an argument that 1) the lived environment of a person is determined by the racist past/present of the US, 2) the lived environment has an impact on microbiome composition and 2) microbiome is associated with pregnancy outcomes - hence, associations between "race" and microbiome or pregnancy outcomes are likely actually associations between racism and microbiome or pregnancy.

Thank you- this is a great summary and we have added an introduction section with this information in lines 34-39. We have also added a concept map to go along (Fig 1).

First, I think having more up front discussion of microbiome may be helpful to hook the reader - perhaps an intro paragraph about the association between gut and vaginal microbiota and race before the current intro paragraph.

I would then suggest interweaving the discussions of microbiome and racist policies that may contribute to differences: e.g. 1) Gut microbiome and pregnancy 2) Structural racism and social determinants shape dietary patterns, 3) Environmental chemicals, 4) Redlining and blockbusting, 5) Vaginal microbiota (which includes the section on stress and perceived racism impacting microbiota), 6) Reproductive health care and racism.

Thank you, paragraphs have been re-organized as suggested.

And, while the authors present data that gut microbiome transplant to mice can transfer the clinical phenotype, suggesting some true causality, it is worth stating more explicitly that the associations between microbiome and outcomes may simply be that - associations reflective of the same upstream cause. This is essentially one of the points of the article (I think) and should be stated plainly.

Thank you for recognizing this key point and prompting us to be clearer in our language. This has been reflected in lines 103-110 and serves as an excellent transition to our exploration of potential upstream causes.

In lines 158-164 the authors state that using race "superficially" in studies of diet and microbiome and pregnancy outcomes may lead to mis-interpretation or perpetuation of racist stereotypes. However, they do not provide an example of how one would use race in a non-superficial way. It would be helpful to hear whether the authors suggest using dietary metrics rather than race, or diet AND race (because race may be a proxy for so many other barriers to a healthy environment) or whether they would suggest use of a perceived racism scale, chronic
stress scale, or some other measure in studies seeking a biologic mechanism - something that acknowledges “race” is not the mechanistic feature, but that it is racism at the root of biologic differences.

Thank you, we have included several suggestions of other scales that we recommend be utilized by researchers. We feel these tools better evaluate the root of observed biological differences (Table 1) and have provided an example at the conclusion of the article as to how to incorporate those into microbiome research.

Minor comments:
- Lines 57-61: the last sentence of this paragraph is long and a little convoluted to follow. Please simplify.
  Thank you- this sentence is now in lines 207-208 and has been clarified.

- Line 175: In the term 16S, the S is capitalized
  Revised.

- Line 186-188: The term “flora” is no longer preferred. “microbiota” is a more ecologically appropriate term (since bacteria are not plants)
  Revised throughout document.

- Line 224: Lactobacillus genus name should be italicized
  Revised.

Reviewer #2:
The authors present a current commentary regarding the use of the maternal microbiome to evaluate racial disparities presented in prior research.

The authors present social and structural forms racism nicely in the opening paragraphs. They do not include a positionally statement.

Thank you, we have now included a position statement that we feel well orients the reader to the rest of the article in lines 34-39.

Abstract: please include a reference in line 9.

We have now added multiple sources to support the statement in line 9.

The authors discuss dietary patterns and the redlining in a clear fashion. As noted below the authors should work to better connect dietary patterns and structural racism to the impact on the microbiome.
Thank you, we have included additional information regarding diet and the microbiome, especially during pregnancy, in lines 55-81. We have also re-organized the article to better outline the relationships between structural racism, diet, the microbiome, and pregnancy outcomes.

Reproductive health care access: this paragraph does not connect as well to the themes of the article. As the focus is increased rates of Adverse pregnancy outcomes and poor access to adequate food intake.

Thank you, we believe we have included the critical information in other ways throughout the article and have removed this specific paragraph as it was not as closely related to the themes identified. Thank you for bringing this to our attention.

Line 126- please describe Shannon diversity?

We have included a simplified of alpha diversity without specifically naming Shannon diversity (to avoid confusion), as previously defined in lines 53-54.

Do the studies note a causative effect? Is this an association? When were samples obtained (before or after diagnosis?)

These studies note associations (language added to clarify), and we have added additional information that describes when the samples were obtained (before diagnosis). This is included in lines 103-105.

Line 146- the studies presented note an association with diet and adverse outcomes but minimal data presented regarding the microbiome.
Needs stronger connection to previously presented arguments, this is a nice summation of prior research but unclear how to deconstruct the prior data based on race

We have included additional data regarding the influence of diet on the microbiome, linking it to pregnancy-related conditions such as gestational diabetes in lines 69-86.

Vaginal microbiome
Line 169- clarify that this is the microbiome diversity.
It is not clear how the discussion of BV and race and microbiome differences is related to adverse pregnancy outcomes.

Vaginal dysbiosis is linked with an increased risk to preterm birth (discussed in lines 207-212.)

Are there areas in which race could be studied differently or it is not evaluated? Can the authors identify strongly the limitations of prior research?

We have added a few examples of ways in which race has been previously studied (both effective and less effective- see lines 109-111 and references *** ) and made
recommendations for future research (see section on Approaching vaginal microbiome research through a lens of structural racism).

Additional data on the current literature connecting microbiome and diet would strengthen the earlier discussion of food deserts and racism on alterations of microbiome. It seems that the authors are calling for more research in this area and also need to demonstrate some prior data regarding potential connect to diet and microbiome that can now be further explored.

We have included additional data highlighting connections between diet and the microbiome to help strengthen our discussion. This is provided in lines 77-94.

Reviewer #3:
The authors commentary reviewed the literature on and provided commentary on the role of structural racism and food access, and its link to gut and vaginal microbiomes, and their subsequent link to birth outcomes. The authors may consider adding a figure (or two) that clearly outlines for the reader their conceptual framework. It does not necessarily need to be a Directed Acyclic Graph (DAG), but just a graphical representation of their theorized casual mechanism to clarify for the reader how structural racism, food accessibility, gut microbiome, and birth outcomes relate to each other, and why considering race as biologic factor is inappropriate and inaccurate. Creating a few figures may guide the authors in restructuring some of their content to mirror their proposed framework so the reader can more easily follow along with their arguments. In addition to these considerations, I listed a number of other specific recommendations below.

Thank you- please see figure 1 at the end of the text.

1. A minor note- on line 45, did the authors mean “systematic review?”

Yes, thank you- this is revised.

2. Can the authors clarify this sentence? (Lines 57-61):
This study also showed that food deserts, based on the Food Access Research Atlas, demonstrated a higher percentage of Black women compared to White women, building on prior work by Salow et al showing that residents in neighborhoods with higher levels of racial residential segregation were at higher risk for preterm birth.

Thank you- please see comments for Reviewer 1- revised lines 207-208.

3. In the section, “Impact of Redlining on Health,” the authors summarize redlining clearly and succinctly. The authors may consider adding additional detail and clarification in the second paragraph about how redlining is connected to reproductive health outcomes. They may consider adding a few sentences that summarize their framework (i.e., redlining leads to exposure to xyz, which impacts reproductive health outcomes).

Thank you, additional sentences were added here for clarification. Lines 190-196 now read: “Redlining may indirectly affect reproductive health outcomes by affecting access. Using Home Mortgage Disclosure Act (HMDA) data, a residential redlining index was constructed to measure institutional racism at the community level in Philadelphia and applied among a cohort of pregnant women. Loan applicants identifying as Black were almost twice as likely to be denied mortgage loans compared to white applicants. Redlining was associated with residential segregation (measured by various indices) and

Commented [sp1]: New sentence added here to address link between redlining and reproductive health outcomes.
may contribute to health disparities by influencing neighborhood structure, composition, development, and wealth attainment."

4. In the section, "Structural Racism and Reproductive Healthcare Access," the authors may consider adding more specifically about what they mean by "poor maternal health outcomes." Further, they may consider adding more detail and clarification about what dismantling racism in healthcare means and how it would impact reproductive health outcomes.

Thank you for this valuable feedback. Ultimately, we felt that the themes of this paragraph were better addressed in other aspects of the article and have decided to remove it. We hope our discussion section better addresses how to dismantle racism through research methodology.

5. In the section, "Gut Microbiome of Pregnancy," there are a number of places the authors may consider rewording and/or cutting sentences for clarity of the scientific concepts for readers with different levels of expertise in gut microbiome. For instance, the below sentence (lines 107–110) is difficult to interpret for a non-expert reader. Could the authors more clearly explain that microbiomes change/shift over the course of pregnancy to resemble metabolic syndrome?

"Over the course of pregnancy, the intestinal microbiome converges on a profile characterized by decreased alpha diversity (or within-sample richness/abundance) that more closely resembles microbiota associated with metabolic syndrome, with features of dysbiosis (altered gut microbiome profile)."

We have added the following sentence to help clarify the significance of the concepts outlined for the reviewer: "These changes suggest that shifts in the gut microbiome are part of physiologic adaptations to pregnancy and thus aberrations may also be implicated in adverse pregnancy outcomes" in lines 53-55.

6. Under the same section, the authors may consider clarifying lines 122-124. Did the study find that both PTB was associated with a specific microbiome profile and a higher saturated fat diet? Or are they insinuating that the diet led to the different microbiome profile, which lead to ptb? If it just correlations, backed up with other hypotheses of biologic mechanisms, that’s completely fine. Just make that clear to the reader.

Thank you, we have added additional information to clarify the hypotheses drawn by the authors regarding the relationships between microbiome profiles, diet, and preterm birth.

7. Under the same section, can the authors clarify what "Shannon diversity" is? (Line 126).

We have included a simplified description of alpha diversity, as previously earlier in the text.

8. Under the same section, can the authors clarify lines 142-144 ("Patients with pre-eclampsia had decreased gut microbiota 143 diversity with a reduced abundance of Firmicutes, Bacteroides, "

Commented [MH2]: Not sure if this adequately addresses reviewer's comment - is this a fair statement? Would you summarize the significance of these changes differently?

Commented [AP3R2]: I think this summarizes it pretty well.
Eubacterium rectale, and 144 Bifidobacterium (notable SCFA producers). How do these specific elements relate to diet?

After closure review of this section, we have decided that there are better examples of pregnancy outcomes (such as gestational diabetes) that can be more closely linked to diet and microbiome alterations. Thus we have replaced this paragraph with one focusing on gestational diabetes that better ties together our themes.

9. In the section, "Vaginal Microbiome of Pregnancy," the authors may consider how much word count that are using to discussing douching and consider focusing in more so on the stress and structural racism causal mechanism.

Thank you, we will actually remove these sentences as they don’t fit as well with the overall theme of the paragraph.

10. Under the same section, can the authors more clearly tie structural racism into their discussion about DEA? Where is it found (more clearly), and why might black birthing people be disproportionality impacted?

Thank you, additional information was added to lines 165-168. Essentially, black/Hispanic birthing people are more likely to have chemical exposures through certain cosmetics which is hypothesized to be in part attributable to Eurocentric beauty standards.

11. Under the same section, the authors may consider adding a section devoted to recommendations and considerations for researchers in this area. The reader would benefit from potentially less detail about specific studies (they can look up the citations if they are interested), and focus more so on how to formulate better questions that don’t perpetuate racism and racial bias in scientific research.

Thank you- we have tried to incorporate these suggestions into Table 1 to summarize clarification of the use of race in research and have incorporated these recommendations into our discussion.