Author's response to reviews

Title: The Impact of an Exercise Intervention on C-Reactive Protein During Pregnancy: a randomized controlled trial

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Author's response to reviews: see over
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Dr. Nawsheen Boodhun
Executive Editor
*BMC Pregnancy and Childbirth*

Dear Dr. Boodhun,

Thank you for your review of our manuscript "The Impact of an Exercise Intervention on C - Reactive Protein During Pregnancy: a Randomized Controlled Trial," MS- 905062771511736. We wish to thank the reviewers for their helpful comments and have revised our manuscript to address their concerns. We believe that these revisions have improved our manuscript and provide a clearer description of our study design and results. Revisions are highlighted in yellow in the manuscript; in addition, we have addressed each comment individually below.

Sincerely,

Marquis Hawkins
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Editorial Comment:

1. Please include a Conclusion heading in the conclusion section.

   We have revised the manuscript to now include a Conclusion heading in the conclusion section.

Reviewer Comments

Reviewer #1:

Major Compulsory Revisions

1) pg 7, line 8: You state that eligibility criteria included physical inactivity. How was physically inactive defined? Was it the reverse of >30 minutes of moderate or vigorous intensity exercise on more than 3 days per week? If so, how was this level of exercise chosen as it is not consistent with US guidelines for pregnant women (>150min of MVPA per week).

   We have revised the eligibility criteria (page 7, lines 11-12) to now provide our definition of physical inactivity (i.e., accumulated <30 minutes of moderate or vigorous intensity exercise on fewer than 3 days per week.) Our goal was to include inactive women. While US guidelines for recommended activity levels have been published (as the reviewer noted above), US guidelines are not currently available to define inactivity. Therefore, this definition was selected to be conservative as were relying upon self-reported activity and to be consistent with prior publications (e.g., references #22, #43).

2) pg 8, line 19-20: Can you state what the actual goals were (i.e., provide the ACOG guidelines here?)

   We have revised the text (page 9, lines 1-2) to clarify the ACOG guidelines for physical activity.

3) pg 9, line 10: What do you mean by “tailoring questionnaires”? I think I understand given the paragraph but not sure this is the best term.

   We apologize for our lack of clarity. The Tailoring Questionnaire assessed current stage of motivational readiness for physical activity adoption, self-efficacy, decisional balance, use of cognitive and behavioral processes of change, and the time spent in physical activity. We have revised this paragraph (page 8, lines 9-10) to include these clarifications. (We used the term “tailoring questionnaire” for consistency with prior publications which used this instrument.)

4) pg 11, line 4-5: In classifying women as decreasing, maintaining, or increasing, was it necessary to decrease or increase by a certain amount to be in that category or even 1min increase would still categorize women as “increasing”?
We have revised the Methods section (page 11, lines 9-12) to clarify that women were classified as decreasing time spent in physical activity if they had >1 MET-hour/week decrease from baseline to post-intervention. Women were classified as maintaining/increasing time spent in physical activity if they maintained their activity (allowing for a ≤1 MET-hour/week decrease) or increased their activity from baseline to post-intervention. Allowing for a 1 MET-hour/week degree of variability was designed to address the error associated with the self-reported measure of activity.

5) Limitations that you could consider adding: adherence to exercise program difficult to assess.

We have revised the manuscript to discuss adherence to the exercise program as a limitation in the Conclusion section (page 19, lines 18-22).

6) Something to consider: Some researchers/scientists take a hard stance regarding any statements which are not supported by statistically-significant findings. Some would say that a non-significant decrease is not a decrease but is rather no-change. I agree, however, that the trend is there in your work and is in line with expectations, just not strong enough. Perhaps you could build a stronger case about how these findings are not conclusive and how more research is necessary in order to draw stronger inferences regarding the relation between exercise and CRP in pregnant women.

The reviewer makes an important point. We have revised the Discussion section (Pages 21, lines 4-10) to emphasize that the findings are not conclusive and stress the need for further studies to help elucidate the relationship between physical activity and CRP in pregnant women.

- Minor Essential Revisions

1) Pg3, line 3: “such as preeclampsia?”

We have revised the manuscript to make this correction.

2) Pg3, line 10: might be worth indicating length of intervention in Abstract (i.e., “Women were randomized to either an 12-week exercise intervention”).

We have revised the abstract to now clarify that the intervention was 12-weeks (page 3, line 10).

Reviewer #2:

1. Introduction - paragraph 1: “a meta-analysis of 18 studies by Rebelo et al. found that CRP was higher in women who developed preeclampsia compared to women that experienced an uncomplicated pregnancy”. As this association seemed to be modified by confounders, such as BMI, this should be mentioned.

We have revised the Introduction (page 5, line 9) to now mention that the meta-analysis by Rebelo et al. found that association between CRP and preeclampsia seemed to be
modified by confounders, such as BMI.

2. Introduction “paragraph 1: CRP has been associated with oxidative stress and endothelial dysfunction”? please cite reference.

   We have added a citation to support this association:


3. Introduction, paragraph 2: A review of 16 trials by Soares et al. reported reductions in CRP ranging from 30% to 53% with aerobic training or lifestyle (diet and exercise) interventions in non-pregnant women - Not all trials reported reduction in inflammatory markers. Three studies showed no change and one study showed an increase in inflammatory markers. I would suggest re-wording to reflect accurate interpretation of systematic review.

   We have revised the introduction section (page 5, line 23 and page 6, line 1) to more accurately reflect the interpretation of the systematic review. When limited to the 10 studies that measured CRP, 2 found no relationship, and 8 found reductions in CRP.

4. Conclusions, paragraph 1: women in the exercise intervention experienced an approximately 3% decrease in CRP while the comparison health and wellness arm experienced an approximately 24% increase in CRP? -figures expressed in percentages can be misleading since any change in CRP is quite small, it might be best to express in absolute values rather than percentages.

   We have revised the Conclusion section (page 16, lines 11-12) to now report the actual values.

5. Conclusions, paragraph 2: would suggest using same denominator for comparison of the various studies cited- ideally absolute values.

   We have now revised the conclusion section throughout to use the same unit of measure (mg/dL) and absolute values for cited studies.

6. Conclusions, paragraph 2: Following point should be taken into consideration during interpretation- intensity of exercise may not have been enough to achieve the observed degree of change in CRP as reported in previous studies (ref 31) which may have been limited due to pregnancy or exercise regime. Data should be provided in an appendix to look at intensity of exercise undertaken by participants in this study to be able to draw meaningful comparisons. This is also suggested by the fact that participants who maintained/ increased the exercise showed greater changes in CRP.

   We have revised the Conclusion section (page 19, lines 18-23 and page 20, 1st paragraph) to now state that the intensity of exercise may not have been sufficient to
achieve the observed degree of change in CRP as reported in previous studies. We now describe and cite our recent publication which provides the data on the intensity of exercise undertaken by participants in this study, as requested by the reviewer.


7. Conclusions, last paragraph: while we had 80% power to detect a clinically significant mean difference in change in CRP of 1.95 mg/dL contradicts “We had 80% power to detect a mean difference in CRP between arms of 0.76 mg/dL based on a standard deviation of 1.50 mg/dL using a two group t-test with a 0.05 two-sided significance level” in last paragraph of ”Methods”. Please clarify.

We apologize for this typographical error and have corrected the manuscript to be consistent.

8. Figures show CRP measurements in mg/L instead of mg/dL.

We have revised figure 2 to show measurements in mg/dL instead of mg/L.