## PEER REVIEW HISTORY

BMJ Open publishes all reviews undertaken for accepted manuscripts. Reviewers are asked to complete a checklist review form (**http://bmjopen.bmj.com/site/about/resources/checklist.pdf**) and are provided with free text boxes to elaborate on their assessment. These free text comments are reproduced below.

## ARTICLE DETAILS

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| **TITLE (PROVISIONAL)** | Identifying women who may benefit from higher-dose omega-3 supplementation during pregnancy to reduce their risk of prematurity: exploratory analyses from the ORIP trial |
| **AUTHORS** | Yelland, Lisa; Sullivan, Thomas; Gibson, Robert; Simmonds, Lucy; Thakkar, Sagar; Huang, Fang; Devaraj, Surabhi; Best, Karen; Zolezzi, Irma; Makrides, Maria |

## VERSION 1 – REVIEW

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| **REVIEWER** | Corrine Hanson<br>University of Nebraska Medical Center |
| **REVIEW RETURNED** | 10-Jan-2023 |

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| **GENERAL COMMENTS** | The objective of this analysis was to identify maternal characteristics that predict subgroups of pregnant women who could benefit from omega-3 fatty acid supplementation. The authors conducted a secondary analysis of data from the ORIP trial, a large, multi-center RCT thta proveided 900 mg/day of omega-3 fatty acids to pregnant women. The hypothesis that there are subgroups of women who would benefit from nutritional supplementation is sound, as supplementing replete individuals would not be expected to impact outcomes. This also allows for personalized nutrition approaches to be implemented in populations at higher risk, as noted by the authors. The methods section provides a concise description of the parent study, inclusion/exclusion criteria with rationale for the proposed analysis, and an excellent table in the supplementary materials that provides a clear definition of all variables. Rationale for lack of adjustment is clearly stated and the authors are clear in the cautious interpretation of results. The results are clearly presented, the tables enhance the overall presentation and are clear and easy to understand. Results are interpreted in a cautious and appropriate fashion. This paper is very well written and makes a significant contribution to the overall body of literature in omega-3 fatty acids and preterm birth, providing an area for future research as well as clinical implications for personalized nutrition. Statistical analysis appears appropriate to me but the editors may wish to have a statistical review conducted. I have no concerns with this paper and believe it important to publish. |

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| **REVIEWER** | Timothy Ciesielski<br>Case Western Reserve University School of Medicine, Population And Quantitative Health Sciences |
| **REVIEW RETURNED** | 19-Jan-2023 |

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| **GENERAL COMMENTS** | This manuscript reanalyzes valuable RCT data to probe the relationships between baseline maternal omega-3 sufficiency |



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| | status, prenatal omega-3 supplementation, and preterm birth (PTB). I applaud the authors for collecting this rich set of covariates and for using the data to perform secondary analyses. The conduct of thoughtful reanalyses is an important step in developing hypotheses and honing interventions, but this step is often ignored. In this exploratory analysis, prenatal omega-3 supplementation was associated with lower the risk of early PTB (<34 weeks gestation) among those with low baseline omega-3 PUFA levels (<4.2% of the total fatty acids in whole blood). Unfortunately, the use of these same pills was associated with higher risk of early PTB among those with high baseline omega-3 PUFA levels (>4.9% of the total fatty acids in whole blood). When the authors folded near term PTB into the analyses, prenatal omega-3 supplementation was associated with lower risk of PTB (<37 weeks gestation) in the study group overall, but there were 2 subgroups of interest. The association was stronger among women who had previously experienced a pregnancy, and the association was not evident among those who drank alcohol in the three months prior to their pregnancy.<br><br>Overall, this is an important set of exploratory analyses that can advance our thinking about the role of omega3 PUFA in preterm birth. Additionally, the manuscript is concise and well written. I have a few comments for the authors to consider as they hone this very good work.<br><br>1) Details on the control and intervention pills:<br>The pills deserve some more attention in the methods and discussion. As the authors know, this research area is rife with physiologic and epidemiologic complexities, and even the best trials have small caveats to consider. In this light, the reader could benefit from having brief text on the ALA (omega3) and LA (omega6) content of both pills. In short, ALA can be converted into EPA/DHA in vivo and this conversion tends to be most efficient in reproductive age females https://pubmed.ncbi.nlm.nih.gov/12323090/ https://pubmed.ncbi.nlm.nih.gov/27842299/ , thus it is possible that the control pills also served as a source of EPA/DHA precursors. This is complicated by the fact that omega-6 PUFA can counteract a number of omega-3 functions related to preterm birth https://pubmed.ncbi.nlm.nih.gov/15850143/ https://pubmed.ncbi.nlm.nih.gov/30287519/ https://pubmed.ncbi.nlm.nih.gov/29031403/ The potential implications this ALA and LA content could get a sentence or two as well.<br><br>2) Discussion: How might EPA/DHA supplements increase the risk of PTB in those who are baseline replete?<br>There is some evidence that omega-3 supplements may increase the risk of post-term birth https://pubmed.ncbi.nlm.nih.gov/30480773/ , so could the authors speculate briefly about the increased risk of PTB among those who are already omega3 replete. Perhaps this pattern needs corroboration prior before it rises to the level of speculation, but since much of the value of a paper like this lies in its ability to generate hypotheses . . . adding this text could help. This speculation may help supplement producers to identify the existence of potentially harmful components in the pills that could be removed (e.g., heavy metals, xenobiotic contaminants, or oxidized |



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| | lipids). Alternatively, it may help researchers to think more about the physiology, dose response shapes, interactions and biases that could generate this pattern.<br><br>3) Discussion: Planetary scale of the problem and how this might help:<br>Low total omega-3 intakes appear to be a common feature of diets as estimated on the country level, and the countries with lower net intakes (accounting for ALA conversion) do have higher rates of PTB https://pubmed.ncbi.nlm.nih.gov/31005937/ . This ecologic finding is not highly useful for causal inference on the individual level but it indicates that the scope of the problem may be very widespread. Where are we going to get the uncontaminated omega3s that we need in a sustainable fashion? https://pubmed.ncbi.nlm.nih.gov/18676983/ Perhaps marine plant sources will prove sustainable, but either way, omega3 distribution efficiency should help us. Precision medicine and precision public efforts that flow from this area of research may reduce the amount of Omega3 that needs to be dispersed and increase its utility where it is used. This likely deserves mention.<br><br>4) Discussion: Preconception approaches to sufficiency vs intrapregnancy approaches to sufficiency:<br>The exploratory findings in this study point to the potential importance of pre-pregnancy sufficiency. For example: The rate of PTB in the control group decreases dramatically with increasing baseline omega-3 levels. Additionally, Omega3 supplements appear to be putatively more protective among women who have been depleted through prior pregnancies. Furthermore, this study identified putative risks of intrapregnancy supplementation for some subgroups. Is it possible that efforts to achieve sufficiency should begin preconception? Should this involve pills or food system intervention? These issues have been raised before https://pubmed.ncbi.nlm.nih.gov/32338238/ , and you could mention that your paper addresses some of the calls made here.<br><br>_____<br><br>Minor points<br><br>Adjustment for recent omega3 supplement use:<br>I understand why the authors are adjusting for the use of omega-3 supplements in the last three months, however this variable is almost certainly correlated with the primary predictor interest (baseline total omega3 levels). Thus, even though the use of omega-3 supplements in the last three months was a stratification feature of the original trial design, some readers will want to see a sensitivity analysis without adjusting for this variable. In other words, if baseline omega-3 is the predictor you wish to assess then adjusting for a strong correlate of this predictor may alter associations with this predictor. These analyses could potentially be presented in the supplement. Of note my suggestion here is not based on causal reasoning. I appreciate and respect the authors' explanation about not considering the causal effect of the predictors on prematurity, as they are being used here simply to define subgroups of interest. |



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| | Lipid threshold identification:<br>A brief explanation could be provided in this manuscript, so that readers do not have to look for Simmonds et al 2020 to learn how the lipid thresholds were identified. |

**VERSION 1 – AUTHOR RESPONSE**

**VERSION 2 – REVIEW**

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| **REVIEWER** | Timothy Ciesielski<br>Case Western Reserve University School of Medicine, Population And Quantitative Health Sciences |
| **REVIEW RETURNED** | 22-Mar-2023 |

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| **GENERAL COMMENTS** | Thank you to the authors for their thoughtful comments and edits. I think this is an important manuscript. I am aware that U-Shaped dose-responses have been observed, but I remain curious as to the mechanism(s) that generates this shape. I figured that I would gauge your thoughts, but I agree that it is fine to not speculate on that here. Thank you again. |



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