Reviewer’s report

Title: The effect of a lifestyle intervention in obese pregnant women on change in gestational metabolic profiles: findings from the UK Pregnanacies Better Eating and Activity Trial (UPBEAT) RCT.

Version: 0 Date: 23 Apr 2018

Reviewer: Sjurdur Olsen

Reviewer's report:

General comments: This is a well-designed and well-written study based on the combination of a well-executed randomized controlled trial of a lifestyle intervention in pregnancy in obese women and an earlier published observational longitudinal study. The study documents that the increases observed in obese pregnancies of specific metabolomics markers - which presumably reflect harmful processes - can be reduced by the intervention, and that these changes are pregnancy specific.

My main concern is the multiple assessments: is the report a fair representation of the evidence generated from these massive amounts of data? My understanding is that the results shown in the tables are only those, where tests met the conventional p<0.05 after they had been (somehow) adjusted for multiple comparisons (by controlling the false discovery rate); which is fine. However - and I may be wrong here as am not a statistician - I think the authors could be more circumspect about how they present the results particularly in the abstract. For instance, expressing differential changes as multiples of standard deviation units may be misleading. To the uncritical reader they may give an exaggerated picture of what this study really shows, as the standard deviation units were (presumably) not adjusted for multiple comparisons (or were they?).

Overall, I think this is an important study as it suggests that the intervention applied resulted in improved health profiles in obese pregnancy, as expressed by the assessed biomarkers. However, only further follow in mothers and children can document whether or not this will have implications in terms of improvements in hard health outcomes.

Specific comments:

Abstract

Page 5, line 12: Please insert pregnant in "… (BMI) PREGNANT population …".

Line 48: "… particles increasED .."
Lines 44-48: Please reword this sentence, e.g., by using parentheses "All (extremely large, … , and very small) VLDL particles … , WHEREAS SPECIFIC (large, medium, and small) LDL particles …"

Line 55: "larger than in unselected women from an independent, previously published study" - I think an abstract needs to contain the number of observations used, most readers will want to know that as basic information. Please somehow get this into the description.

Line 4-7. Please work more on the conclusion. Do the two statements, "Systemic metabolism …" and "with some evidence …", provide any real information? These statements seem a little too unspecific or general as a conclusion for this study - do you think they do enough justice to the large amounts of data that it generated?

Also, the abstract should also somehow contain information indicating that the multiple comparison issue was addressed in this study. (Please also see my comment in "General comments" above.)

Introduction

Page 6, line 1: I think that I would take "improved fatty acid profiles" out ("improved" in which sense? This can be debated.)

Page 8, line 1: You could help the reader if you added a few more words to explain "recent addition".

Methods

Page 11, 38-46: This sentence is too long, and as written the latter part ("… profiled between becoming pregnant after not being and vice versa …") is not understandable. Please amend.

Results

Page 13, lines 7-14. The characterization, "Indirect comparisons", seems a bit strange and maybe also imprecise? Does it mean "non-randomized (i.e., in reality, potentially biased comparisons, as opposed to the comparisons within the randomized setting)? Furthermore, and more importantly, it is not clear where the reader can see the actual data underpinning the specific statements in this paragraph. Please refer to a specific table or figure.

Line 23: I wondered if the word "stratified" is the correct term to describe this?
Discussion

Page 14, line 34-46. I am not sure that the fact that "there was similar loss to follow-up and proportions with metabolic profiles at each assessment in the two arms of the trial" necessarily can be taken to support "that any missing data on the metabolic profiles is missing at random". Couldn't they still be non-random in both arms? (Maybe equally 'non-random' across the two arms, we cannot know this.) Please consider this.

Page 14, line 58: In my mind the multiple comparison issue is a more important issue for replication, than whether or not the model depicts the changes correctly or whether there may be some deviation from linearity. (We rarely have truly linear relationships in biology.)

Table 2

In columns 2 and 3, what is given in brackets, it seems to be some ranges - is it 95% CIs, IQRs? And are these ranges somehow adjusted for multiple comparisons? This may be stated in the Methods section, but it needs also to be completely clear from the table text. I cannot see it in the legend text or in the footnotes.

I apologize for the delay. I had limited time due to disease in a close family member.

Yours sincerely

Sjurdur F Olsen

https://www.cfp-research.com/Publications.aspx

https://www.hsph.harvard.edu/sjurdur-olsen/

Are the methods appropriate and well described?
If not, please specify what is required in your comments to the authors.

Yes

Does the work include the necessary controls?
If not, please specify which controls are required in your comments to the authors.

Yes
Are the conclusions drawn adequately supported by the data shown?
If not, please explain in your comments to the authors.

Yes

Are you able to assess any statistics in the manuscript or would you recommend an additional statistical review?
If an additional statistical review is recommended, please specify what aspects require further assessment in your comments to the editors.

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