BMJ - Decision on
Manuscript ID
BMJ.2018.043863

Body: 27-May-2018

Dear Dr. Bisgaard

Manuscript ID BMJ.2018.043863 entitled "Fish-Oil Supplementation in Pregnancy Causes a Proportional Increase in Bone-, Lean- and Fat Mass at 6 Years: A Randomized Clinical Trial"

Thank you for sending us your paper. We sent it for external peer review and discussed it at our manuscript committee meeting. We recognise its potential importance and relevance to general medical readers, but I am afraid that we have not yet been able to reach a final decision on it because several important aspects of the work still need clarifying.

We hope very much that you will be willing and able to revise your paper as explained below in the report from the manuscript meeting, so that we will be in a better position to understand your study and decide whether the BMJ is the right journal for it. We are looking forward to reading the revised version and, we hope, reaching a decision.

Please remember that the author list and order were finalised upon initial submission, and reviewers and editors judged the paper in light of this information, particularly regarding any competing interests. If authors are later added to a paper this process is subverted. In that case, we reserve the right to rescind any previous decision or return the paper to the review process. Please also remember that we reserve the right to require formation of an authorship group when there are a large number of authors.

Thanks!

Georg Roeggla
groggla@bmj.com

Report from The BMJ's manuscript committee meeting

These comments are an attempt to summarise the discussions at the manuscript meeting. They are not an exact transcript.

Manuscript meeting 18.04.2018

Wim Weber (chair), Tim Cole (stats), Elizabeth Loder, Jose Merino, John Fletcher, Sophie Cook, Georg Roggla, Tiago Villanueva, Daoxin Yin.

Decision: ask for revision

The committee was interested in the topic of your research. The following concerns were mentioned:

• Why do you report just one secondary outcome of a Fish oil asthma study published in the NEJM in 2016?
• The RCT appears to be competently done, and the results are both interesting and credible.

• It’s odd that the title and abstract outcomes do not mention BMI, yet the abstract results and conclusions focus mainly on BMI. This to my mind is wrong as it distorts both the trials findings and interpretation.
• The focus on BMI implies that the intervention affects fat mass, yet it doesn’t. What changes is weight and lean mass, as the title makes clear. There should be more emphasis on the non-fat changes in the abstract conclusion, which rather negatively says the intervention does not increase obesity.
• Note too that BMI was added to the statistical plan only as an afterthought.
• The abstract does not say how obesity was defined (they used IOTF cut-offs).
• Marsal’s growth curves for birthweight centile sound odd and need better explanation.
• Table 1 does not need significance tests (see text page 11).
• Sub-analyses mentioned in the Results should first appear in the Methods and should be pre-specified.
• The numerical presentation is very uneven. DXA results are given in grams to 5 or 6 significant digits whereas fat % has 3 significant digits (see Table 3). DXA should be in kg to match weight.
• Not sure how useful the longitudinal BMI measures are if they are not modelled – see Figures 1 and 2. The dip at 1-6 months in Figure 2 may reflect a difference in growth timing, which could be detected with SITAR modelling.
• Reviewers concerned about missing data, particularly BMI.
• Why do you call it a “study” and not a “trial”. It is misleading.
• Reporting could be improved. The methods include some results (but some are only listed as “see supplementary…”
• Sample size calculated post hoc based on how many children they had. As we understand it, you tell us what difference you could find. But is this clinically meaningful? Why? The difference you found was less than what you had identified…
• It is an interesting finding, contradicting earlier research. The clinical significance of a 0.14 difference in BMI Z-score is not clear.
• Clinically 0.4kg doesn't seem like much.....
• We don’t think that BMI is not a great measure to use in children.
• If you look at the actual effects of the fish oil it seems to have led to an increase in lean mass and possibly bone density but not an increase in body fat. Aren't those "good" outcomes?
• It was concerning to see no patient and public involvement (PPI) declaration with this RCT of pregnant women and no dissemination plan of the findings for pregnant women given the country of Denmark's focus on the importance of PPI in healthcare and research. The PPI declaration is mandatory for The BMJ; perhaps somehow this was missed (https://www.bmj.com/campaign/patient-partnership).

I regret the delay between the meeting of the manuscript committee and our decision mail. This was caused by the need of additional review after the committee.

First, please revise your paper to respond to all of the comments by the reviewers. Their reports are available at the end of this letter, below. Please also respond to the additional comments by the committee.

In your response please provide, point by point, your replies to the comments made by the reviewers and the editors, explaining how you have dealt with them in the paper.

Comments from Reviewers

Reviewer: 1

Recommendation:

Comments:
This is an interesting manuscript.
It is based on a well-conducted and comprehensive randomised controlled trial with fish oil vs olive oil supplementation during pregnancy. The study follows up children to the age of 6y with anthropometric measurements. The study is not the first of its kind, but it is relatively large, it has repeated measurements during follow up and has an extensive battery of measurements.
Generally, the manuscript is well written and overall it complies with the Consort Statement.
There are however a few general and some more specific comments.
General comments:
Attrition is generally low but there is some attrition in the study up to the age of 6y (particularly for the DEXA scans). Have the authors considered whether exchangeability between the two interventions groups is still present after 6 years? Did you consider adjusting for potential risk factors for the outcome?
A number of sub-analyses are described in the result section, which have not been described in the method section (consort checklist 12b). This includes both stratified analyses, interaction analyses and also the sub-analysis concerning FADS. I suggest that these analyses also should be included in the method section.
Specific comments:
pp6 line 9: Is "growth" the right word to use?
pp8 line 33-38: It is unclear at this point what this information should be used for. I suggest that either it is introduced as a secondary aim or that it is shortly explained here in the method section.
pp9 line 28-29: Self-reported birth weight and length were validated against information from the Danish National Birth Register. How valid was the self-reported information? What did you do in case of discrepancy? What was the correlation? Generally it is unclear what this validation showed and what you used the information for.
pp10 line 14: Twins were excluded. They usually come in pairs. How come three twins are excluded from the LCPUFA group?
pp10 line 17 and 22. The use of "cross sectional" in this context is a bit confusing.
pp10 statistical analysis: A number of sub-analyses have been performed. They should be described in this section.
pp11 line 19-21: The sentence is a bit unclear. Consider revising.
pp11 line 34: "Only" 76% of participants had DEXA scans performed. Was the attrition similar in the two groups? Could the attrition have affected the results? The problem might be even higher at 3.5 y. A short discussion about this could be included in the discussion
pp15 line 10: Z-scores were not used in ref 36.
pp15 line 17. Could this be due to the effect decreasing over time?
Table E3: Something goes wrong with the splitting of the text. In addition, why are only the significant p-values highlighted?

Additional Questions:
Please enter your name: Dorte Rytter

Job Title: Associate Professor

Institution: Department of Public Health, Aarhus University

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here:

Reviewer: 2

Recommendation:

Comments:
This paper is well written and the study appears to have been well-conducted. My main concern is the potential impact of missing data on the findings – I would like some reassurance from the authors that this has been considered, and that it has not led to bias. Some indication of the extent of the missing data (i.e. numbers of children with missing data points at each time point of measurement) and whether this is equally balanced between the treatment groups would also be helpful. I also think the authors need to make a stronger case for the study, in particular highlighting how their study differs from other previous trials – since the argument could otherwise be made that this topic is done and dusted. My specific comments/questions are below:

1. The introduction needs to make the point that the increase in birthweight in infants exposed to an increased supply of omega-3 during pregnancy is largely a consequence of the increase in gestation length
2. The introduction should also make clear that the data from animal studies are not conclusive, since there is at least one study that shows that omega-3 LCPUFA supplementation during pregnancy/lactation actually increases body fat mass in the offspring, and many others do not isolate the omega-3 supplementation to the perinatal period.
3. Think the introduction would benefit from some additional detail/context regarding the need for this study, especially given that much larger studies have shown null effect on body composition – perhaps highlighting the need to understand whether different fatty acids (i.e. EPA vs DHA) may have different effects?
4. Can the authors provide a rationale as to why they selected the rs1535 SNP for analysis in this cohort? Were other SNPs also analysed?
5. It would be interesting to know the number of children who had 1,2,3,4,5 or complete sets of anthropometric measures, and whether this was equivalent between treatment groups. If the missing data weren't equally balanced between treatments, then would this lead to bias in the results? How did the authors ensure that this wasn't the case? Would it be possible to do a sensitivity analysis which included only children with complete sets of measures?

6. I am particularly interested by the finding that BMI z-scores weren't different between treatments between 1 week and 6 months, but were at all other time points – do the authors have an explanation for this?
7. In the results section, the authors need to make it clear whether they are referring to BMI or BMI z-scores – I assume that it is always BMI z-scores, but these terms seem to be used interchangeably in the text, which is confusing.
8. The finding of a higher BMI in the n-3 LCPUFA group at 6 years is certainly interesting. What happened if the analyses were adjusted for birth weight (as opposed to size for gestational age)? This is particularly important given that the children in the n-3 LCPUFA group were heavier at birth (as stated in the discussion)?
9. It would also be helpful for the authors to add some additional context about this cohort – particularly whether the children were, on average, representative of the broader population, and what the rates of overweight/obesity were in this group.

Additional Questions:
Please enter your name: Beverly Muhlhausler

Job Title: Research Fellow

Institution: The University of Adelaide

Reimbursement for attending a symposium?: No

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: Yes

Funds for a member of staff?: No

Fees for consulting?: Yes

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: I am a member of the advisory board of the Nestle Nutrition Institute in Australia, for which I receive an honorarium of $2000 per year. I have prepared review articles on the role of n-3 LCPUFA In pregnancy for BASF AS. I have given talks on maternal and infant nutrition for Aspen and Danone Nutricia. All income from these sources is paid to me instituion and used to support professional development and travel for students and ECRs in my group or independent research projects.

Reviewer: 3

Recommendation:

Comments:

The study describes a double blind RCT of maternal pregnancy LCPUFA supplementation from week 24 to 1 week postnatally. The trial appears to be well done, and the results are both interesting and credible. The primary trial outcome was asthma, while this secondary analysis involved body composition outcomes at 6 years.

1. It looks odd that the title and Abstract outcomes do not mention BMI, yet the Abstract results and conclusions focus mainly on BMI z-score. This is odd because BMI is a crude measure of obesity that does not distinguish between lean mass and fat mass, yet the hypothesis relates to body composition, so that BMI is a particularly poor outcome to use. Framing the results and conclusions around BMI distorts both the trial findings and interpretation (incidentally the Abstract does not say how obesity was defined).

2. Weight, another secondary outcome but not mentioned in the Abstract, would be better than BMI z-score as it is more transparently related to changes in lean mass and fat mass, and it is not directly associated with obesity. Weight should be adjusted for height to increase power, as it is in Table 3 for body mass and the DEXA outcomes, although the two groups did not differ in mean height. Maybe this was why BMI was added belatedly to the statistical analysis plan, to provide a form of weight adjusted for height.

3. But the focus on BMI gives quite the wrong impression – it implies that the research question involves obesity and that the intervention disproportionately affects fat mass, yet it doesn't. What changes is weight and lean mass and fat mass, as the title makes clear. And BMI as a z-score is in different units from every other outcome in Tables 2 and 3, again an anomaly. There should be more emphasis on the non-fat changes in the Abstract conclusion, which rather negatively says the intervention did not increase obesity.

4. It is also disappointing that five of the six figures focus on BMI, by far and away the least interesting of the outcomes. The longitudinal analysis of BMI also adds little; the difference between arms is essentially constant from 1 year (Figure 2), and what matters is the difference at 6 years, so the longitudinal analysis can be omitted as it is a distraction.

5. The Methods state that "A subgroup from the cohort also participated in a nested; factorial designed, double-blind, RCT of 2,400IU/day of vitamin D3 supplementation (N=576)." But nothing more is said about it, and there is no adjustment for the intervention in the analysis. It needs to be properly documented and adjusted for. Also the sample size of 756 is unhelpful at this point as the sample size of the main study has not yet been given.

6. Maternal FADS genotype first appears in the Methods, with no mention in the Abstract or Introduction. How did it feature in the research question? – it needs properly framing. Why was FADS, given its association with BMI, included in the original protocol which focussed on asthma?

7. The term is Anthropometry not Anthropometrics (Methods).

8. Why was birthweight adjusted against Marsal's intrauterine growth curves rather than using a birthweight reference to generate z-scores, as is usually done?

9. Statistical analysis: including children with at least one measurement at age 0-6 years only applies to the longitudinal anthropometry. The DEXA outcomes were at 3.5 and 6 years, so a measurement at 6 years should define the analysis group.

10. And why exclude twins? – they could easily be adjusted for in the analysis.

11. What is the value of a post hoc power analysis, particularly using an outcome which was added only retrospectively to the analysis plan? The study size was defined by the primary outcome, and a post hoc analysis does not alter the study size.

12. There are anthropometry results for 605 children in Table 2, but for DEXA in Table 3 there are only 523. Out of 736 women recruited these correspond to 82% and 71% respectively, yet nothing is said about how representative they are.

13. Table 1 should not be tested for significance (see text page 11).

14. Table E2 needs to test for a sex interaction, otherwise it is uninformative.

15. Sub-analyses mentioned in the Results should first appear in the Methods with a statement as to whether or not they were pre-specified. If they were not pre-specified they should be omitted.

16. In the body composition section the adjustment for height (and apparently height squared, according to the footnote) of body mass and the other outcomes in Table 3 was not stated in the Statistical Analysis section.

17. The FADS analysis results on page 13 are unclear. There was said to be a FADS effect in the control group but not the supplemented group, yet there was no significant FADS interaction. Is this correct? Table E3 should include the significance of the interaction terms. Also please remove the bold emphasis from the significant p-values in Table E3.

18. The numerical presentation is very uneven. The DEXA results are given in grams to 5 or 6 significant digits whereas fat % has 3 significant digits (see Table 3). The results should be rounded to a maximum of 3 significant digits – see http://adc.bmj.com/cgi/content/full/archdischild-2014-307149.

19. In summary I feel that the main outcomes should be those at 6 years, excluding (or at least toning down) BMI, and including height adjustments. I'm not convinced that the FADS analysis adds anything useful to the trial results, so that it and the longitudinal results can be omitted. What remains is useful evidence that LCPUFAs in the third trimester of pregnancy stimulate healthy somatic growth to age 6.

Tim Cole

Additional Questions:
Please enter your name: Tim Cole

Job Title: professor of medical statistics

Institution: UCL Great Ormond Street Institute of Child Health

Reimbursement for attending a symposium?: Yes

A fee for speaking?: No

A fee for organising education?: No

Funds for research?: No

Funds for a member of staff?: No

Fees for consulting?: No

Have you in the past five years been employed by an organisation that may in any way gain or lose financially from the publication of this paper?: No

Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this paper?: No

If you have any competing interests <A HREF='http://www.bmj.com/about-bmj/resources-authors/forms-policies-and-checklists/declaration-competing-interests'target='_new'> (please see BMJ policy) please declare them here: