Reviewer’s report

Title: The influence of prenatal exposure to trans-fatty acids for development of childhood haematopoietic neoplasms (EnTrance): a natural societal experiment and a case-control study

Version: 0 Date: 24 Jul 2017

Reviewer: Yeyi Zhu

Reviewer’s report:

In this paper, the authors reported the study protocol including background, objective, design, and methods of the EnTrance study. The study objectives are two-fold: 1) to investigate whether the Danish iTFA legislation ban influenced the risk of childhood haematopoietic neoplasms in children born either before or after the change in legislation in a natural societal experiment; and 2) to examine the associations between trans-fatty acid concentrations measured from stored dried blood spots and childhood haematopoietic neoplasms in a nested case-control study. The research question is of importance to the field and is of interest to the readership of the journal. However, the manuscript may be improved by addressing several concerns.

1. Indeed, trans-fat is a type of unsaturated fat common in industrially produced foods (iTFA). However, industrially produced foods are not the exclusive source of trans-fat. It is important to acknowledge that two dietary sources exist for the TFAs present in the food supply: industrial production and natural sources, in which TFAs are found in smaller amounts in ruminant-derived food products. Emerging evidence suggests that TFAs from industrially produced and from natural sources have different effects on cardiometabolic outcomes. Given that the reported methodology of fatty acid measurement using gas chromatography "allows a complete separation, identification and quantification of sixty fatty acids including 15 individual isomers of industrial trans fatty acids and natural trans fatty acids (CLA, vaccenic acid)." The authors may need to clarify whether Aim 2 focuses on the former (industrial source) or the latter (natural source). If the former, it would be important to assess both the independent and mutually adjusted associations with childhood haematopoietic neoplasms.

2. The authors reported that identification and quantification of sixty fatty acids will be conducted by the International Agency of Research of Cancer; however, more information is needed regarding the methodology for fatty acids measurement. First, how will the fatty acid concentrations be reported and analyzed, in absolute concentrations or relative % weight of the total fatty acids? Second, for certain trans-fatty acids, particularly for measurements using up to 20-year-old dried blood spots, it is likely that a considerable amount of measurements may have concentrations below the LODs. If levels are below the LODs, what are the corresponding data preprocessing procedures? Third, report the laboratory CVs for fatty acids, particularly trans-fatty acids measurement.
3. For Aim 2, it is not entirely clear how the control will be selected. Specifically, which control will be selected if more than one participant meets the matching criteria? On the other hand, what if there are no qualified controls meeting the matching and selection criteria - would the matching criteria be modified and how?

4. Also for Aim 2, it is important to consider whether trans-fatty acids of interest are truly bioactive, or are related to food products rich in trans-fat, such as baked foods, fried foods, and dairy products. Is diet data available in the study via dietary assessment such as food frequency questionnaire and dietary recalls or records? The residual confounding due to total energy, afore-mentioned foods, and overall dietary pattern would be a major concern.

5. Further, the authors would like to examine whether levels of trans-fats in dried blood spots from newborns are associated with the risk of haematopoietic neoplasms by age of 7 years. A potential issue of residual confounding may arise due to the lack of data (or description if such data are available?) on trans-fat levels in childhood and other important factors such as breastfeeding.

Level of interest
Please indicate how interesting you found the manuscript:

An article whose findings are important to those with closely related research interests

Quality of written English
Please indicate the quality of language in the manuscript:

Acceptable

Declaration of competing interests
Please complete a declaration of competing interests, considering the following questions:

1. Have you in the past five years received reimbursements, fees, funding, or salary from an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

2. Do you hold any stocks or shares in an organisation that may in any way gain or lose financially from the publication of this manuscript, either now or in the future?

3. Do you hold or are you currently applying for any patents relating to the content of the manuscript?

4. Have you received reimbursements, fees, funding, or salary from an organization that holds or has applied for patents relating to the content of the manuscript?

5. Do you have any other financial competing interests?
6. Do you have any non-financial competing interests in relation to this paper?

If you can answer no to all of the above, write 'I declare that I have no competing interests' below. If your reply is yes to any, please give details below.

I declare that I have no competing interests

I agree to the open peer review policy of the journal. I understand that my name will be included on my report to the authors and, if the manuscript is accepted for publication, my named report including any attachments I upload will be posted on the website along with the authors' responses. I agree for my report to be made available under an Open Access Creative Commons CC-BY license (http://creativecommons.org/licenses/by/4.0/). I understand that any comments which I do not wish to be included in my named report can be included as confidential comments to the editors, which will not be published.

I agree to the open peer review policy of the journal