Author’s response to reviews

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

Authors:

Ina Specht (ina.olmer.specht@regionh.dk)
Inge Huybrechts (HuybrechtsI@iarc.fr)
Peder Frederiksen (Peder.frederiksen@regionh.dk)
Eva Stelianova-Foucher (stelianova@iarc.fr)
Veronique Chajes (Chajesv@iarc.fr)
Berit Heitmann (berit.Lilienthal.Heitmann@regionh.dk)

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Reviewer #2: The protocol is on an interesting topic but the authors need to address certain concerns:

1. The protocol is based on the assumption that fetal exposure of TFA can lead to childhood cancers specifically hematopoietic cancers. And wants to correlate TFA levels in neonates born before and after a legislation was brought into effect in 2003-2004 banning use of TFA to hematopoietic cancers. Is there any previous studies showing that there was a marked decrease in hematopoietic cancers after the ban of iTFA in Denmark to back up the research protocol proposed by the authors. If not, the authors should do a survey on the incidences on hematopoietic cancers before and after the iTFA ban.

Reply: No studies have confirmed a decrease in hematopoietic neoplasms in Denmark after the TFA legislation, but we propose to make the comparison suggested by the reviewer in this study. As written in line 231, we will investigate the incidence from 1988-2008.

2. Since the study looks into prenatal exposure, the study may not have much relevance unless the results are back up with studies showing that there is a reduction in iTFA levels in mother’s blood in the same period.

Reply: We are not aware of studies showing differences in iTFA levels in women/mothers following the introduction of the law. Measuring iTFA levels in the blood of neonates is a more direct exposure measure for the outcome in question than measuring the iTFA levels in the blood of mother. In our study we investigate serum levels of TFA both before and after the legislation
in the case-control study, which will answer the question on change of iTFA level in neonates, possibly due to the legislation.

3. The selection of controls is not clear. As the samples will be taken at two different times (before and after legislation), how are the authors going to match "exact date of birth" (line 195 and 204).

Reply: The reviewer is referring to the case-control study (objective 2). Cases and controls will be selected in the entire time period, 1988-2008. Date of birth and other information on all children born in this period in Denmark are recorded in the Danish Birth Registry and we are allowed to access this information for the purpose of this study. We can therefore pick the controls based on their date of birth and place of residence at the time of birth, for the entire study period, including before and after the legislation. In objective 1 we divide cases and controls in time (before and after the low) as a proxy for TFA exposure in fetal life, in Objective 2 we measure the exact TFA levels in neonatal blood regardless of the TFA law.

4. For the same reason as in comment 3, how will "potential degradation of TFA affect equally cases and controls" (line 204 and 205)

Reply: There is no reason to believe that TFA degradation in time will affect cases and controls in a different way.

5. The methodology is not structured. Inclusion of a flow chart will help in making the protocol more clear.

Reply: We have now included a figure to illustrate workflow in objective 1 and a flow chart to clarify the constitution of case and control groups in objective 2.

We are grateful to the reviewers for their useful comments, which helped to improve our manuscript.