Reviewer’s report

Title: Association between plasma phospholipid saturated fatty acids and metabolic markers of lipid, hepatic, inflammation and glycaemic pathways in eight European countries: a cross-sectional analysis in the EPIC-InterAct Study

Version: 0 Date: 26 Jul 2017

Reviewer: Anthony Hanley

Reviewer’s report:

This is an important and timely paper given the ongoing controversy regarding the role of saturated fatty acids and cardiometabolic health. This paper will make a particularly strong contribution to the literature as the findings are based on the analysis of a large, well-characterized sub-cohort from the multi-national EPIC-InterAct study, (n=15919), which includes measures of a large number of phospholipid fatty acids and a comprehensive set of lipid, liver function, glycemic and inflammatory measures. I have some comments and suggestions for the authors to consider:

1. In discussing previous research in in general (Introduction) and in comparison to the present findings (Discussion), it will be worthwhile to expand on the comments regarding previous studies utilizing different lipid fractions. In other words, is this a limitation or a possible explanation for differing results across previous studies? In this context, a brief sentence (Introduction or Methods) will be helpful to indicate the rationale for conducting the measurements of fatty acids in the phospholipid lipid fraction in the present study.

2. Please indicate the length of time that the samples were stored in the freezer and whether there are any implications for the results. Were these fasting samples?

3. It appears that some of the participants had CRP concentrations ≥10 mg/l, which would indicate an acute inflammatory response at the time of the clinic visit. Are the study results different once these individuals are excluded as a sensitivity analysis?

4. Are the results similar when using waist circumference or another measure of central adiposity, instead of BMI, as a covariate or in interaction testing? There is some evidence that odd-chained fatty acids are inversely associated with central obesity in particular.

5. It may be of value to report correlations of the fatty acids that are thought to be exogenous (15:0, possibly 17:0 and 18:0) with food sources. As mentioned by the authors, 15:0 and 17:0 are thought to be markers of dairy and/or fibre intake but may also mark fish consumption in some populations. Also, what is the correlation between 15:0 and 17:0?

6. A correlation matrix or heat map of the fatty acids themselves may also be of interest to the journal readership, as this information would help the reader interpret the statement in the
Discussion (page 15, lines 5-17) regarding independent effects of different classes of fatty acids on lipids;

7. The results regarding effect modification by alcohol intake are very interesting. Did the transaminase concentrations correlate with alcohol intake? Would an additional sensitivity analysis in which heavy drinkers are excluded be of interest?

8. The authors have provided a thoughtful limitations section. One other issue that would be worth mentioning is that only one marker of inflammation was available, and that future studies on this topic would benefit from an expanded panel of inflammatory cytokines, acute phase reactants and adipokines.

**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.

I am able to assess the statistics

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