Reviewer’s report

**Title:** Methodologic Considerations in the Design and Analysis of Nested Case-Control Studies: Association between Cytokines and Postoperative Delirium

**Version:** 1  **Date:** 21 Mar 2017

**Reviewer:** Christina Dahm

**Reviewer’s report:**

I thank the authors for their thoughtful replies and revisions to their manuscript. Many aspects of the work have been improved. I am also appreciative of their constraints in terms of previously published work on this topic. However, I am not convinced that the changes made to the manuscript address the substance of some of my concerns.

1. A nested case-control study sampled on delirium cases is no longer a case-control study once events and factors (eg IL6 levels) taking place after delirium are to be studied. It is then a cohort study of exposed (to delirium) and unexposed (to delirium). This use of terminology is important, because the interpretations of the measures of association differ between the two designs. In fact, the authors already interpret their measures of association using language from these two designs. Therefore I do not agree that the study design the authors describe specified 4 time points. These 4 time points cover two different study designs.

1a. I agree that normality is not a formal requirement for independent variables in logistic regression. Nevertheless, given that IL-6 is not normally distributed, an OR calculated per unit change in IL-6 on the original scale may be unduly influenced by observations in the tail, thus distorting model fitting for the bulk of the observations. Of course a transformation alters the interpretation of the variables scale, and I appreciate that the original scale is simpler to interpret. A sensitivity analysis excluding outliers could cast light upon whether the tail is unduly influencing the OR on the original scale.

1b and 2. The authors have, as they note, a small data set. I would be more concerned with clinically relevant differences between matched and unmatched controls, as well as matched and unmatched cases, than whether differences are statistically significant. I am pleased to see that differences have been investigated; perhaps the authors could comment on the clinical significance of observed (statistically not significant) differences?

Over all, the manuscript would benefit from a round of careful editing and sorting. For example information on data management and the statistical package used, while useful, is placed at the end of the Results section, but ought to be in the Methods section.

**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

Quality of written English
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