**Reviewer’s report**

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

**Version:** 0 **Date:** 23 Nov 2016

**Reviewer:** Yian Gu

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The Issue 1 study is interesting and well done, but it is only tailored to this particular study. A big concern is that the number of controls in the current study was relatively small, making the selection of a matching control difficult and sometimes impossible. Would the results (comparing greedy algorithm and optimal algorithm) be different if there was a large number of control available? Will the results be the same if there is a 1:2 match, or other ratio match? How about other calipers, for example, 6 units of difference? What are the range and mean(SD) for age and GCP in this population? Does '5 units' a big or relatively small range compared to the whole range? Overall, the idea of comparing the two methods for matching is great, but the study cannot sufficiently answer this question, or the results may not be extrapolated into other studies.

On page 10, line 47-49, the authors mentioned "... the odds ratio from conditional logistic models help to assess how IL-6 influences delirium risk across different time points." Most cohort study design, or even nested case-control study usually examine the long-term prospective relationship between an exposure and the outcome, by using the baseline, usually years before the outcome occurs, specimen for biomarker measures. Here in this study, it seems that for each time point, the IL-6 and delirium status at that time point were used for analysis. This would make the study similar to a cross-sectional analysis rather than a prospective study.

Also for Issue 2, the authors need to explain further what does the result mean. Why IL-6 and delirium was associated only on POD2? While the study's goal was more for the analytic examination and exploration, the findings still need to be supported by biological explanation.

For Issue 3, the authors mentioned that one of the reasons for using nested case-control study is that the exposure measurement is too expensive or impossible. However, to test ISSUE 3, it will be really helpful to obtain the IL-6 level in all cohort participants. On page 6, it is mentioned that blood sample is available for each patient, it would make sense to measure IL-6 for each patient. This would be more powerful and more reasonable for the purpose of Issue 3 than using the simulation data.

Overall, the study aimed to examine a few important and very interesting design issues in nested case-control studies. The study would have been more powerful should the study population/sample be larger, more general, and IL-6 measured in everyone. In addition, the manuscript is in general well written but it can be shortened for a more concise presentation.

**Are the methods appropriate and well described?**
If not, please specify what is required in your comments to the authors.

No

**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.

No

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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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