Reviewer’s report

Title: Application of the matched nested case-control design to the secondary analysis of trial data

Version: 0 Date: 11 Mar 2020

Reviewer: Rebecca Cannings-John

Reviewer’s report:

Thank you for letting me review this paper which I enjoyed reading.

1. Introduction: on page 4 line 3 you say that you will "...answer a challenging research question". please state what it is.

2. Cohort time axis: Page 5, line 26 it states that "it was possible for an outcome event to occur prior to randomisation". If you are saying that NEC could occur before randomisation then it suggests that randomisation was carried out in early post-partum period. It would be helpful if in the description of the ADEPT trial to highlight who was recruited (mother or baby), and at what time point (late gestation, after birth etc) so that this is clear.

3. There are some terminology that to me, overlap: Risk set identifies the cohort specific to a case in which the sample of controls can be sampled from; Non-cases are those without NEC but are these the same as those in the risk-set? How do these differ?

4. Just so I am clear, if controls could go on to become a case and therefore be included in the risk sets for other cases, is this because they have a different exposure status at control status and then when they are a case? Also you don’t say how many controls then go on to be cases, and what duration is between the two events? This would be helpful.

5. The Methods under Selection of Controls section says that you chose sampling without replacement which indicates that for a case, a control could only be selected once but the same control could also be chosen to be a control for a different case. is that correct? I think maybe the paragraph could be clarified but maybe once the terms non-cases and risk set are clarified in point 3 above, it might be clearer to me.

6. You state that you would run both an unadjusted and adjusted analysis for trial arm. The results only shows the adjusted analysis. Please either state the results in text or add the unadjusted results in to table 4.

7. Table 1. how important are the imbalance of the factors hypertension and ventilated at study entry.

Minor comment

1. Abstract. Please expand the abbreviation of NEC in the Results
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?
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