Author’s response to reviews

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

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Editor Comments
No ethical approval was required for this study, since it used only previously collected, fully anonymised research data. This has been clarified in the declarations section of the article.

Claudia Pedroza, PhD (Reviewer 1)
We thank the reviewer for their positive comments about the manuscript. We also thank the reviewer for their thoughtful and constructive comments, which we have addressed in turn below.

1) There is no general consensus on the rationale for adjusting for matching variables, since the aim of a matched design is to generate comparable groups for which further adjustment is not necessary. Indeed, using conditional logistic regression, it is not possible to adjust for binary matching factors (e.g. sex), because within each matched cluster the variable takes only one value.

We do however, accept the reviewer’s point that the matching for GA and BW was not perfect (point 8) and have added a sentence to the description of the baseline characteristics on page 9 to highlight this. In addition, we have conducted a sensitivity analysis, adjusting for GA and BW and referenced this on page 9. The sensitivity analysis did not materially alter the conclusions of the study.

2 & 3) We agree with the reviewer that in general feeding policy may be influenced by site, but in the ADEPT trial, a detailed feeding guideline was provided to all sites participating in the trial, which participants were encouraged to follow. Also, based on other trial data, we know that centre not strongly associated with the outcome NEC, so it is likely that matching for site would lead to overmatching. We have already stated in the paper on page 7:
“Overmatching is caused by inappropriate selection of matching factors (i.e. factors which are not associated with the outcome of interest), which may harm the statistical efficiency of the analysis.”

Also, as there were a large number of sites relative to the number of events, matching infants within sites would have negatively impacted the tightness of matching for BW and GA, which are far more important prognostic factors and associated strongly with both feeding and NEC.

4) Thank you for raising this point. We agree that the definition of the exposures is not sufficiently clear. We have removed the term ‘NEC event’ from the definition in the hope that this prevents any confusion with regards to how these exposures are defined for controls.

5) We agree that the reviewers suggested rewording is clearer and have updated the manuscript accordingly.

6) Apologies for any confusion. Within our design infants in fact could be selected as controls if they had been selected as a control for another case. However, sampling of controls for a particular case was done without replacement, as per the guidance of Lubin (1986).

7) The number of matched controls with a subsequent diagnosis of severe NEC (8) is presented in Table 1, however, as per the reviewer’s suggestion we have added a sentence to clarify this on page 8.

8) We thank the reviewer for raising this important point. While we matched for GA and BW, it was not possible to obtain perfect matching with the respect to both factors.

As noted in point 1, we have added a sentence to page 9 highlighting the imbalance between infants <750g. In addition, we have conducted a sensitivity analysis, adjusting for GA and BW and referenced this on page 9. The sensitivity analysis did not materially alter the conclusions of the study.

9) Thank you for pointing out this omission from the description of Figure 4. For clarity the caption now includes a description of the matching factors and covariate adjustment.

Rebecca Cannings-John (Reviewer 2)
We thank the reviewer for their positive comment about the manuscript and are glad they enjoyed reading it. We also thank the reviewer for their thoughtful and constructive comments, which we have addressed in turn below.

1) We have rephrased the closing paragraph of the introduction to be more specific about the research question of the case study under investigation in this paper.

2) That is correct. In ADEPT, consent and randomisation occurred in the first 2 days after birth. We have added a sentence to the description of the ADEPT trial to clarify this.
3) Thank you for the opportunity to clarify the terminology we have used throughout the article. Non-cases refer to infants that do not develop the outcome of interest (e.g. Severe NEC) at any point during the study.

The risk set is the cohort from which matched controls can be sampled for a particular case. This includes non-cases, but can also include infants who have yet to develop the outcome at the failure time of the case.

We acknowledge that on page 7 (selection of controls) we have used the term ‘non-cases’ in a different context and so have reworded this section to avoid confusion.

4) The decision to include future cases as controls in earlier risk sets, is motivated by the fact that their exclusion can lead to biased estimates (Lubin, 1984).

The number of matched controls with a subsequent diagnosis of severe NEC (eight) is presented in Table 1, however, as per the reviewer’s suggestion we have added a sentence to clarify this on page 8.

5) Yes, that is correct. As mentioned in our response to point 3, we have removed reference to non-cases in this section to avoid any confusion. We hope that this has added clarity to this section.

6) The full results will be reported in an upcoming paper, however unadjusted results for severe NEC are now included in as part of the supplementary material. We have added a line to the manuscript sign-posting readers to the supplementary material.

7) We acknowledge that there is a noticeable imbalance for two of clinical characteristics presented in Table 1, and thank the reviewer for giving us an opportunity to address it.

It was felt that maternal hypertension was unlikely to be directly related to feed exposure and it is not something which has been previously identified as a risk factor NEC. Similarly, whether the infant was ventilated at trial entry is not known to be associated with the risk of NEC.

We have slightly reworded the paragraph on baseline characteristics within the results on page 9 and have added a sentence to clarify this.

Minor comment 1) Thank you for identifying this undefined acronym, which has now been replaced with the expanded text.