Reviewer’s report

Title: Rehabilitation of the nested case-control design in diagnostic research

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Reviewer: Yana Vinogradova

Reviewer’s report:

This study by Biesheuvel et al is interesting – and reassuring about the use of nested case-control studies in diagnostic research. The introduction gives a good overview of the appropriate modern designs in this field, considering their strengths and limitations. The methods are well described. The example sample and study selected for analysis is a good one for demonstrating the advantages of the nested case-control approach.

Major issues

1. As 100 samples were drawn for each ratio, it is not clear what Table 1 represents with respect to the samples. Have the authors calculated average statistics for the 100 samples for each ratio or does each column represent the statistics for just one sample?

2. The statistics in Table 1 for the samples do not seem appropriate because controls were randomly selected for each case-control ratio and are, therefore, not comparable with the original sample. It would be useful to have the cases and controls figures presented separately for each of the different case-control ratio groups and the full study population.

3. Figure 2 shows good agreement between the measures of diagnostic accuracy obtained from the original sample and the measures obtained from the drawn samples. The only concern relates to Specificity. In the original sample, the 95% CI for Specificity is between 0.37 and 0.40, but the corresponding graph shows quite a wide spread of Specificity derived from the 100 samples – even the smallest 95% CI for 1:4 ratio samples is between 0.36 and 0.42. This implies that we could easily miss the true value for Specificity when using nested case-control design and withdrawing just one random sample. It would be useful to see the authors’ comments on Specificity results as part of the discussion.

Minor issues:

In References, the journal name for N19 is missing.

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: Yes, and I have assessed the statistics in my report.