Author's response to reviews

Title: A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia

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Author's response to reviews: see over
Dear Editor,

Re: Manuscript with id MS: 4124356924016268

Thank you for your response to our manuscript (Id MS: 4124356924016268). We are now enclosing a revised manuscript which addresses the referees’ comments in full. A point-by-point response to the comments is given below. We hope the revised manuscript is now acceptable for publication in BMC Psychiatry.

Reviewer’s report

Title: A systematic review and meta-analysis of neurological soft signs in relatives of people with schizophrenia

Version: 3 Date: 14 June 2011

Reviewer: Marie-Odile Krebs

Reviewer’s report:
The manuscript correctly addresses almost all the remarks. A few points could further be improved in the manuscript:

1). Conclusion of the abstract:
“If neurological soft signs are an endophenotype or biological marker of schizophrenia, they may have value when used in conjunction with prodrome assessment tools in improving the detection of the prodrome of schizophrenia.”

I still believe that this sentence is not an appropriate conclusion and should be removed from the abstract since the question of NSS in prodromes is not addressed in the work and remains speculative. The value of NSS as markers of prodromal markers needs to be directly explored before any conclusion.
Response:

As suggested by the reviewer we have removed the sentence.

2.) P 7 “although adequate blinding is difficult to establish” should be rephrased for “… is difficult to attain”

Response:

We have amended the text from:

“although adequate blinding is difficult to establish”

to

“although adequate blinding is difficult to attain”

3.) P 7 “Since there is considerable overlap between these scales, data were included if any of these three measures were used [13].”

The remarks about the heterogeneity of scales should be better addressed by adding : “However, despite some similar labels, it should be kept in mind while interpreting the meta analysis that the rating and the tasks that correspond to the individual NSS items vary between the different scales.”

Response:

We have added further remarks about the difference between the scales in the discussion section. The following text has been added:

“Despite some similar labels, it should be kept in mind while interpreting the meta-analysis that the rating and the tasks that correspond to the individual NSS items vary between the different scales”

4.) In the conclusion :
“A key limitation of this review was the finding of significant heterogeneity across all comparisons.”

The authors should further quote the main sources of heterogeneity (sample size, age, kind of first degree relative, scales and ratings, medication, clinical features etc).

Response:

We have quoted the main sources of heterogeneity among the studies. The text reads as:
“A key limitation of this review was the finding of significant heterogeneity across all comparisons. The variance among studies could be due to factors such as variation among sample size of studies, source of normal controls, kind of first degree relatives, scales used and clinical factors such as being on medication. Insufficient studies were available to permit investigation of this heterogeneity using meta-regression. Likewise, higher scores for some signs in patients may be due to use of anti-psychotic medication and we could not conduct moderator analysis exploring the extent of its effects. Despite some similar labels, it should be kept in mind while interpreting the meta-analysis that the rating and the tasks that correspond to the individual NSS items vary between the different scales.”

5.) the discussion about NSS being biomarkers rather than only endophenotype does not rely on the present study and remains confusing. It is not clear why the author discuss that. It could be removed.

Response:

We have removed the discussion relating to biomarkers. The following text (red colored) has been removed from the third and fourth paragraphs of the discussion section.

“However, there are alternative explanations. For example, the findings are also consistent with the possibility that soft signs are not an endophenotype, but a biomarker. The term “biomarker” encompass a wider category of diagnostically valuable physical parameters that includes not only endophenotypes but also parameters that are wholly or partially environmentally determined [7]. For example, soft signs would be a biomarker for schizophrenia, if they reflected an underlying defect in neural integration that had arisen from the interaction of a genetic predisposition and an environmental insult in utero [31].”

“Paradoxically, if soft signs were a biomarker, they might be of greater clinical utility than a true endophenotype.”

6.) the author should be more nuanced in their conclusions by quoting the limitation of their study: only 7 studies meeting the criteria and heterogeneity that could not be further explored. The conclusion is thus that more studies using a consensual rating tool and homogeneous samples are needed.

Response:

We have considered the reviewer’s comments and amended the conclusion. We have now added the following text in the conclusion:

“The findings are based on a small number of studies. There is a need for more studies using a consensual rating tool and homogeneous sample in order to establish that neurological soft signs are an endophenotype of schizophrenia.”
We hope the responses on the referees’ comments are acceptable. Thank you for considering the revised manuscript for publication in BMC Psychiatry.

Yours sincerely,

Dr Kishen Neelam
Consultant Psychiatrist