Reviewer's report

Title: Familial association of neurological soft signs in schizophrenia: a systematic review and meta-analysis

Version: 1 Date: 21 January 2011

Reviewer: Michael Compton

Reviewer's report:

The authors have conducted an interesting meta-analysis using all extant data on neurological soft signs rated across three groups, patients with schizophrenia-spectrum disorders, first-degree biological relatives, and non-psychiatric controls. The manuscript is generally well written, though it would benefit from attention to the following critiques.

1. I think that the term “familial association” in the title is a little unclear. It is not until the Abstract that the reader really understands the question being addressed by the meta-analysis. I think the title would be clearer by replacing this term with something about “neurological soft signs in first-degree relatives of patients with schizophrenia.”

2. In the last sentence of the Conclusions portion of the Abstract, the authors suggest that neurological soft signs may have value as a simple clinical test for helping to identify people in the prodrome of schizophrenia. However, to do so, there would need to be evidence that such signs are specific to schizophrenia, as opposed to attentional disorders, mood disorders, anxiety disorders, etc. Since the article does not comment on the specificity of soft signs, I think that this suggestion may be over-stated. The same is true for the last paragraph of the Discussion section, which also comments on the issue of “increasing pre-test probability that an individual was developing prodromal symptoms…”

3. In the second paragraph of the Background section, it would be helpful to provide parenthetical explanations of what is mean by “co-segregation” and “heritability.”

4. In the sentence that follows that sentence, I think that “gene expression than psychopathology” would be clearer as “gene expression than is psychopathology” (add “is”).

5. At the end of the third paragraph of the Background section, the authors note that neurological soft signs meet the criterion of being state-independent. But does “because they do not vary with duration of illness, or receipt of neuroleptic medication” really provide any evidence state independence? Those don’t seem to be tests of state independence. State independence would indicate that soft signs are traits, present whether or not the illness is active.

6. In the last paragraph of the Background section, the authors present their hypothesis around familial association. What about research looking at correlations between patients’ scores and their respective relatives’ scores?
Wouldn’t that also get at the issue of familial association?

7. In the section on Study Selection, I think that “between were resolved” should be “between them were resolved” (add “them”).

8. In the second paragraph of the Data Extraction section, it may be clearer to change “data were accepted from all three” to “data were included if any of these three measures were used.”

9. Although the authors consider the issue of whether the studies’ raters were blinded to group allocation, I think they need to acknowledge that when patients with schizophrenia are involved, blinding can be very difficult due to the behavioral manifestations of the illness. It is really difficult to ever ensure blinding to patient status when doing a neurological examination. Thus, there may be a bias that is very difficult to remove.

10. On page 9, the terminology “the control group of first-degree relatives” would be clearer as “the group of first-degree relatives” so that the term “control” is reserved for describing the non-psychiatric controls.

11. In the Results section, each time the authors present data from the sensitivity analyses, I think it would be helpful to explicitly state the number of studies involved and the number of participants involved. That way, it is clearer to the reader to what extent the loss of significance may be related to a much smaller sample size in the subsequent analyses.

12. On page 12, the authors state, “Thus, in summary, soft signs appear to be…consistent with the inheritance of a polygenic trait.” However, it is not clear how the preceding sentences led the authors to conclude anything about a polygenic trait. I think some of the reasoning here is missing such that the reader may not see how the authors arrived at this conclusion based on these results.

13. There is inconsistency in the formatting of the references; for example, the title of reference #6 is capitalized whereas the others are not.

14. In reference #24, the names of the three authors appear to be duplicated.

15. Throughout the references, the authors should go back to the original articles as they were published and confirm the initials of all authors. There are many instances in which only the author’s first initial is given, even though the published article used both first and middle initial. This is important for indexing purposes. Additionally, authors may be offended if the reference list does not accurately represent the authors’ names as published in the original articles (i.e., both first and middle initials).

Level of interest: An article of importance in its field

Quality of written English: Acceptable

Statistical review: No, the manuscript does not need to be seen by a statistician.

Declaration of competing interests:
I declare that I have no competing interests.