Reviewer’s report

Title: Neurodevelopmental profile of Fetal Alcohol Spectrum Disorder: A systematic review

Version: 2 Date: 04 Jun 2017

Reviewer: Heather Carmichael Olson

Reviewer's report:

This paper is much improved, and it was already a very high-quality submission. We applaud the caution and care with which the authors have approached this difficult but important topic. The various research programs working toward screening for FASD have been carefully analyzed and critiqued, with directions forward offered to the field.

We appreciate that the authors were responsive to all earlier suggestions by the current reviewer. The addition of an estimate of uncertainty is quite helpful, as it better portrays sensitivity and specificity of the screening methods. Noting that some of the specificity estimates were unfavorably low is more precise. We especially appreciate the clear statement in the Discussion section that the lack of convergent validity among different diagnostic guidelines is a major barrier to progress in both screening and diagnosing FASD—and also inclusion of the ideas that the phenotype of FASD may be complex and/or pleiotropic. These modifications to the manuscript mean that it better summarizes the very complicated situation when trying to screen for, and diagnose, FASD.

We have a few further recommendations, which we ask the authors to consider if they feel they are relevant.

1. It seems important to specify for the NST studies whether the comparison groups (e.g., children with ADHD, ODD/CD and typical development) were screened to ensure they were not prenatally alcohol-exposed, at least according to parent report at the time of the study. We highly recommend this be specified in the paper. (Description of the Mattson et al research program does include that comparison groups were unexposed.)

2. Line 34, p4. Replace the word "the" with "one," as the term "neurobehavioral disorder associated with prenatal alcohol exposure" is actually just given in DSM-5 as one specifier (even though it is the only example provided). While this might seem like a minor detail, it is quite possible that in the future there will be other specifiers offered as possibilities within the broader term of "Other Specified Neurodevelopmental Disorder." (In other words, ND-PAE is simply one possible other specified neurodevelopmental disorder.)

3. On page 5, it is interesting that the authors have made edits that now move them away from suggesting that ADHD, ODD and CD are co-occurring or comorbid diagnoses with FASD… and toward FASD as the potentially "more correct" or appropriate classification. To this
reviewer, it seems that there are two viewpoints diagnosticians can hold at this time (that FASD can be one of a set of co-occurring diagnoses, vs FASD should be diagnosed instead of other conditions). Screening for FASD is important to those holding both viewpoints. It is suggested that the authors consider addressing this (perhaps controversial) point, and clarifying which viewpoint they hold. This reviewer is certainly in agreement with the statement that has also now been added that "As a result, individuals with FASD often receive multiple diagnoses before actually being assessed for and diagnosed with FASD." Often diagnosticians halt the diagnostic process before even considering FASD.

4. A few minor details:
   a. Page 5, line 43. Replace "things" with "conditions".
   b. Page 5, line 46. Consider using "similar to" rather than "mimicked by"
   c. Page 22, line 34. Add the word(s) "non-teratogenic" (or non-prenatally alcohol-exposed) before the acronym "ADHD"

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?
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Yes

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