Reviewer’s report

Title: Bias in a protocol for a meta-analysis of 5-HTTLPR, stress, and depression

Version: 2  Date: 30 April 2014

Reviewer: Matthew C Keller

Reviewer’s report:

In this critique of a published plan to meta-analyze the much debated 5-HTTLPR*stress interaction on depression, Moffit and Caspi make two points: 1) that the second analysis plan will include retrospective in addition to prospective studies, and 2) that the meta-analysis will exclude studies with n<300. The authors make cogent points and I cannot see a reason why their views should not be published (although with some modification; see below). This is not to say I agree with their points, and I fear that they are preemptively forming a defense in case the meta-analysis’s results disagree with their original findings.

My main problem with their argument, and something I believe they should be asked to respond to in a revision (“major compulsory revision”), is that they need to demonstrate that any downward bias in effect size introduced by lower-precision measures of stress or depression is not countervailed by increased power afforded by larger sample size. My intuition is that, given realistic differences in precision between prospective and retrospective reports, the largest studies will have greater power to detect GxE effects despite having potentially downward biases in effect size estimates.

In any event, I would argue that retrospective studies should be included in the meta-analysis, and that the role of measurement type (retrospective/prospective) should be estimated alongside that of sample size to see which of the two have the largest unique effect (if any) on the GxE effect size estimates. Unfortunately, should it turn out to be difficult to disambiguate measurement from sample size effects, and that small sample/prospective reports are the ones that show the largest GxE effects (as I suspect will be the case), there are two alternative and non-mutually exclusive explanations for this: a) publication bias and b) downward bias in effect sizes in large retrospective studies. This puts the scientific community in an awkward position, because even after this great effort, we still may not know much more than we know now about the status of the purported GxE effect.

Thus, my main problem with the proposed original meta-analysis (not that this is necessarily relevant to this review) is that meta-analyses must rely on potentially biased samples of studies to make conclusions. A much more definitive study would be a large, direct replication of the original report with agreed upon (perhaps pre-published) methodologies, which would also ensure that any finding is published regardless of the direction of effect.
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.

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