Reviewer’s report

Title: The association of telomere length with substance use disorders: systematic review and meta-analysis protocol

Version: 1 Date: 09 Jul 2019

Reviewer: Maya Mathur

Reviewer's report:

OVERALL COMMENTS

This protocol manuscript is nicely improved, and the authors have resolved most of my previous concerns. I do still have two remaining major comments, which should be easy to address in a revision. I wish the authors best of luck with conducting this meta-analysis.

MAJOR COMMENTS

Re: R.2.2) The plan regarding confounding is improved, but still needs a bit more specificity. Again, confounding may well be the most important methodological limitation of the meta-analyzed studies, so I think it's worth another round of revisions here. Regarding this sensitivity analysis:

"Third, when studies report all the potential confounding factors, or the majority of them, a multiple regression model will be applied in order to determine predicted effect sizes once adjusted for confounding factors."

Which confounders will you consider to be a sufficient set? Are you referring to age, sex, education, % Caucasian, and life stressors? Also, I don't fully understand the model that will be fit. Do you plan to meta-regress on an indicator for whether the study adjusts for this set of covariates? I would prefer a simple subset analysis to only the "appropriately adjusted" studies instead. Also, for the covariates that can change over time potentially in response to SUD (education, life stressors, other behavioral variables), I would stipulate that "appropriately adjusted" studies are those adjusting for these variables measured *before* the measurement of SUD, not contemporaneously or afterward. See my previous comment about mediation for why the distinction is important.

Re: R.2.10.) The revised manuscript states:

"As a large number of moderator variables will be extracted from the studies, the potential nonindependence of these studies due to similarity of methods or sample characteristics will be controlled for in subsequent subgroup analyses."

What do you mean by "will be controlled for"? Do you plan to fit a model that allows for nonindependence, like a multilevel model or a model with robust variance estimation?
Signed,
Maya B. Mathur
Department of Epidemiology
Harvard University

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