Reviewer’s report

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

Version: 0 Date: 31 May 2019

Reviewer: Maya Mathur

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OVERALL COMMENTS

This is a promising protocol for an interesting meta-analysis on substance use disorders and telomere length. My most important concerns are statistical; in order of importance, these concerns pertain to confounding (#2), methods for assessing publication bias (#5), and reporting on heterogeneity and moderators (#3-4). However, I am optimistic that each of these could be fully addressed in a revision, and I have given specific (and hopefully easily implemented) recommendations on how the authors might do so.

MAJOR COMMENTS

1.) Although I am not an expert in search term design, the search terms appear to be appropriately sensitive to my eye. The search strategy was designed in collaboration with an author who seems to be an academic reference librarian (ARV), in which case I would recommend explicitly stating this in the manuscript since search term design is a critical component of a high-quality systematic review. I was also pleased that there is a strong plan in place for searching grey literature.

2.) My most important concern is that confounding of the relationship between substance use and telomere length will likely represent a considerable methodological threat to the validity of this meta-analysis' findings. Yet confounding is currently not discussed at all. Not exhaustively, variables such as socioeconomic status, education, and life stressors likely affect both substance use and telomere length. If the meta-analyzed studies do not adjust for nearly all important confounders of this relationship, or if they are cross-sectional so that confounders and mediators cannot be distinguished (e.g., [8]), then the meta-analytic estimate may be quite biased.

I therefore think it is critical that the authors: (1) plan to conduct subset analyses (or similar) on studies whose designs most effectively minimize confounding (i.e., longitudinal studies controlling for, at minimum baseline telomere length); and (2) plan to conduct some form of sensitivity analysis to assess robustness to residual confounding. The latter will be important if, as I suspect, there are few longitudinal studies. See reference [1] for an approach for doing so that is implemented in R (the package EValue).

3.) The authors refer to meta-regressively examining moderators of the relationship between substance use and telomere length, but the moderators are not specified. Lines 117-118 briefly
mention different types of substances and refer without specificity to other "factors implicated in this heterogeneity". What moderators will be examined? Or will this decision be made post hoc?

4.) Also regarding heterogeneity, the statistics I^2 and Q (while useful to report) characterize heterogeneity relative to the total variation in point estimates and are a function, for example, of the meta-analyzed studies' sample sizes. For the authors' intended purposes, I think these measures should be supplemented with an absolute measure of heterogeneity (tau or tau^2), and that decisions about the amount of heterogeneity should consider tau and its confidence interval as well [2].

Additionally, since heterogeneity seems to be a central focus of this protocol, the authors should consider reporting statistical metrics that, unlike the pooled point estimate alone, directly describe the heterogeneous distribution of effect sizes. Two options that complement each other well are a prediction interval for the effect size in a new study [2-3] and the estimated proportion of true effect sizes that are of scientifically meaningful size [4].

5.) I appreciate the attention to publication bias. However, funnel plots and their corresponding statistical methods (trim & fill and Egger's test) have some important limitations. For example, they assume that publication bias operates on effect sizes rather than p-values and that publication bias is the only source of correlation between effect sizes and standard errors) [5]. For this reason, I would recommend: (1) using the funnel plot-based methods only with strong caveats about their limitations; and (2) supplementing or replacing these measures with one of various likelihood-based "selection model" approaches [5-6]. For example, reference [7] has a nice approach that also has an R package, weightr.

6.) Otherwise, the statistical methods look good. The choice of REML with Knapp-Hartung SE adjustments is a good one.

7.) I commend the section stating that the authors will explicitly disclose deviations from the preregistered protocol.

8.) Will data and code be made publicly available upon publication?

MINOR COMMENTS

9.) Why restrict the search to studies published before 12/18 (per Abstract)? Has the search already been conducted? If so, was the protocol written prior to conducting any analyses? (I believe this is also journal policy.)

10.) Lines 173-177: If an article reports on multiple, separate samples, will the largest still be used? Or will all point estimates be included with some modification to the meta-analysis model to account for possible non-independence due, e.g., to similarity of methods or sample characteristics within a paper?

Signed,
REFERENCES


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