Author’s response to reviews

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

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Author’s response to reviews:

Response to the reviewers’ comments
14th August 2019

Dear Dr. Yen-Fu Chen,

Thank you for the comments on our manuscript entitled "The association of telomere length with substance use disorders: systematic review and meta-analysis protocol" (SYSR-D-19-00084).

Please find attached our point-by-point responses to reviewers’ comments as well as a marked-up copy of the changes made to the previously submitted version of the article.

We hope this revised version will be acceptable for publication.
Editors Comments to Author:

Please indicate whether you intend to conduct regression to assess the potential impact of confounding by various factors; or conduct a subset analysis as suggested by the reviewer; or adopt both approaches with justification for the chosen approach(es).

Response:

We intend to assess the potential impact of moderating variables using a combination of subgroup and meta-regressions analyses as described below in our responses to the Reviewers.

Reviewer reports:

REVIEWER #1

R.1.1) My previous comments have been adequately addressed.

If you are going to carry out multiple regression/meta-regression, will adjusted effect sizes be used in the analysis? If unadjusted effect sizes are used, then it would not be possible to assess the influence of statistical adjustment, and instead you will need to calculate and use the differences between the SUD and control groups in the potential confounders as indicators of imbalance in these factors and then estimate their impact on unadjusted effect sizes? Please clarify.

Response:

Thank you for your comment. We have revised the manuscript to state that unadjusted effect sizes will be used (lines: 210-211, marked copy) as we expected adjustments based on different variables that will not require the combination of the adjusted effect sizes presented to obtain a global effect size index. We have clarified the description of the meta-regression and the subgroup analyses (lines: 259-269, marked copy).

The revised text reads as follows:

“In addition, to apply subgroup analyses to the risk of bias item on comparability of the NOS, simple meta-regressions will also be conducted using the SMDs as a dependent variable and the mean difference in age between cases and controls, the difference in age SDs, the difference in the proportion of males and of Caucasians, and the difference in education levels. Third, another
set of subgroup analyses will be conducted with other covariates related to telomere length, such as smoking status, exposure to childhood adversities or other stressful events, and the presence of mental or physical comorbidities.”

REVIEWER #2:

R.2.2) 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.

Response:

We thank the Reviewer’s comment highlighting the importance of this particular paragraph that might generate some confusion. We expect a high heterogeneity in the number of potential confounding factors the studies adjust for. At the same time, we do not expect to find studies with identical adjustments to allow for specific analyses. To date, we believe there has been insufficient research in this area to limit the inclusion to studies that have adjusted for priori-defined confounding factors. This will be acknowledged as a limitation of the present study when publishing our results. This limitation has already previously recognized in the field of telomere length analyses [1].

Nonetheless, the Reviewer highlights the importance of those variables that can change over time as a consequence of SUD, or in relation to other circumstances (e.g.: smoking status, other mental disorders or physical illnesses). Though we do not expect to find such a refined panel of studies in the telomere length literature, we agree with the reviewer that this distinction should be an objective in our study. We have therefore included a new categorical variable (yes/no or not
specified) evaluating whether any covariate has been specifically assessed before the onset of SUD (lines 175-176, marked copy) in order to be able to address the effect of this circumstance in posterior subgroup analyses. This would allow us to evaluate the differences between non-adjusted, adjusted and “appropriately adjusted” studies.

As mentioned in our previous response, we do not expect to find longitudinal studies, but rather case-control and cross-sectional designs. In the latter designs it would be very difficult to determine the causal relation between SUD and the potentially related covariates that can change over time. In the revised manuscript, we propose to delete the paragraph and to add another set of covariates influencing telomere length we had already mentioned in the list of data extracted from each study but not mentioned in the analysis. As these types of variables have been designed with a dichotomous answer (Yes/No), the proposed analysis is similar to that proposed in the analysis of the risk of bias items (lines 262-268, marked copy).

“Third, another set of subgroup analyses will be conducted with other covariates related to telomere length, such as smoking status, exposure to childhood adversities or other stressful events and the presence of mental or physical comorbidities.”

R.2.3) 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?

Response:

We thank the Reviewer for highlighting a section that deserves some clarification. We do not expect to find a meaningful number of studies to evaluate their non-independence. Our proposal is to delete the mentioned paragraph to clearly state that we only plan to analyze independent samples as it was stated in the initial version of the document (lines 182-189, marked copy: “The unit of analysis will be studies (rather than reports) to ensure data are not counted twice. As a result, in cases of multiple articles stemming from a single study, only the results of the publication with the highest number of participants will be included. If an article reports on two or more studies with independent samples, then each independent study will be included as an analysis unit in the meta-analysis”).