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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Version: 3 Date: 14 Oct 2019

Author’s response to reviews:

Response to the reviewers’ comments

14th October 2019

Dear Mr. Ferrán Catalá-López,

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.
Yours sincerely,

Fernando Navarro-Mateu, MD, PhD

Reviewer reports:

REVIEWER #3

Abstract.

R.1) p.2. Methods. Lines 47 and 48. Authors' state: "Potential studies will be identified through electronic databases (PubMed/MEDLINE, EMBASE, Psyclit/PsychINFO and Web of Science) up until December 2018". Please, update the database coverage, or consider the inclusion of "from inception onwards". For example: "Potential studies will be identified through searches in the following electronic databases: PubMed/MEDLINE, EMBASE, PsycINFO, and Web of Science (from inception onwards".

Response: Thank you for your suggestion. It has been changed in the abstract and in the method section (lines: 48 and 135-136, marked copy).

R.2) p. 2 Methods. Line 47. "PsychINFO" should be "PsycINFO".

Response: Thank you for your correction. It has been corrected throughout the document.

R.3) p.2 Methods. Please, delete subsections: "Study selection:" (line 48), "Data extraction:" (line 52), "Risk of bias assessment:" (line 55), "Statistical analysis:" (line 57).

Response: All of the mentioned subsections have been deleted.

R.4) p.2 Methods. 48-52. Authors' state: "Study selection: The focus will be on published or unpublished observational studies reporting telomere length in persons with substance use disorder compared with a control group. Non-human studies or other study designs such as reviews, case-only, family-based and/or population-based studies with only health participants will be excluded, as well as those focused solely on nicotine addiction". Please, be more explicit about study designs ("observational studies: case-control, cohort?), patient population (e.g. adult patients with substance use disorder), etc…
Similarly, please list all outcome(s) for which data will be sought, including prioritization of main and additional outcomes. For example: "The primary outcome will be [please, include]. Secondary outcomes will be [please, include].

Response:

Thank you for your comments. The text has been updated as (lines: 54-55, marked copy):

“The main outcome will be telomere length in adults with substance use disorder (primary) and, specifically, in those with alcohol use disorder (secondary).”

R.5) p. 2 Discussion. Where: "To our knowledge, this meta-analysis will be the first systematic review and meta-analysis to assess (…), should be "This systematic review will assess the association (…). Please, revise.

Response:

The text has been revised (lines: 66-67, marked copy):

“This systematic review will assess the association of telomere length …”

Methods

R.6) p.6 line 126. Where: "The study protocol was designed according to (…)", should be: "The study protocol was reported according to (…)". To clarify, PRISMA-P is a reporting guideline (no a methodological/conducting guideline). Please, revise through the text.

Response:

Thank you for your comment. The text has been changed (lines: 129, marked copy) and revised through the text:

“The study protocol was reported according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses Protocol (PRISMA-P) 2015 …”

R.7) p.6 line 131-133. Where: "Studies will be identified through PubMed/MEDLINE, EMBASE, Psychlit/PsychINFO and Web of Science databases (Web of Knowledge up until December 2018 using the following search terms for SUDs: "drug, substance, addiction, alcohol*, heroin, cocaine, opium, opioid, methamphetamine, morphine" and for telomeres: Telomeres, telomerase, and telo*" (see Additional file 2)." should be: "We will search
PubMed/MEDLINE, EMBASE, PsycINFO, and Web of Science (from inception onwards) using the following search terms for SUDs: (...) (see a draft search in Additional file 2).

Response:

The text has been modified following your suggestion (lines: 134-139, marked copy):

“We will search PubMed/MEDLINE, EMBASE, PsycINFO and Web of Science (from inception onwards) using the following search terms for SUDs: “drug, substance, addiction, alcohol*, heroin, cocaine, opium, opioid, methamphetamine, morphine” and for telomeres: telomeres, telomerase, and telo*” (see a draft search in Additional file 2).”

R.8) p.7 lines 143-156. Please, delete and revise this subsection as follows (and as appropriate):

Eligibility criteria: Studies will be selected according to the following criteria: study design, participants, comparator and outcome(s) of interest.

Study design: We will include observational studies (e.g. cohort, case-control, cross-sectional studies) reporting reporting telomere length in persons with SUDs compared with a control group (e.g. without SUDs). We will exclude studies in animals, experimental studies, reviews, case reports, case series, studies conducted in healthy populations and/or families.

Participants: We will include adult people with SUD (regardless of age or sex) assessed by clinical interviews or established standard diagnostic instruments including, but not limited to, the Structured Clinical Interview for DSM-IV (SCID), Computerized National Institute of Mental Health Diagnostic Interview Schedule (CDISIV), Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, or Composite International Diagnostic Interview (CIDI). We will exclude participants with nicotine addiction.

Comparator (or control group): [please, define/clarify. For example , if appropriate: "The comparator group will be based on subjects with no history of SUDs (e.g., the general population, the community, unexposed outpatient, or hospital-based controls”).

Outcome(s): [Please, list and define study outcomes e.g. "telomere length”?]
“ELEGIBILITY CRITERIA:

Studies will be selected according to the following criteria: i) study design, ii) participants, iii) comparator and iv) outcome(s) of interest. i) Study design: We will include observational studies (e.g. cohort, case-control and cross-sectional studies) reporting telomere length in persons with SUDs compared with a control group (e.g. without SUDs). We will exclude studies in animals, experimental studies, reviews, case reports, case series, studies conducted in healthy populations and/or families. ii) Participants: We will include adults with SUD (regardless of age or sex) assessed by clinical interviews or established standard diagnostic instruments including, but not limited to, the Structured Clinical Interview for DSM-IV (SCID), Computerized National Institute of Mental Health Diagnostic Interview Schedule (CDISIV), Diagnostic and Statistical Manual of Mental Disorders (DSM-IV) criteria, or Composite International Diagnostic Interview (CIDI). We will exclude participants who exclusively meet criteria for nicotine addiction. iii) Comparator (or control group): The comparator group will be based on subjects with no history of SUDs (e.g., the general population, the community, unexposed outpatient, or hospital-based controls). iv) Outcome(s): The outcome of interest will be telomere length.”

R.9) p.7 line 157. "DATA EXTRACTION (SELECTION AND CODING)", should be renamed: "Selection and data collection".

Response: The section has been renamed (lines: 176-177, marked copy):

“SELECTION AND DATA COLLECTION”

Discussion

R.10) p.13 line 283. Please, delete subheading: "Ethics and disseminations".

Response: The subheading has been deleted. (lines: 314, marked copy)

R.11) p.13 line 286. Please, delete subheading: "Amendments".

Response: The subheading has been deleted. (lines: 317, marked copy)

R.12) p.13. Please, discuss potential limitations at study (outcome) level, and at review level you anticipate.
Response: Potential limitations at both levels (study and review levels) are discussed in the revised manuscript (lines: 298-309, marked copy)

“The results of this systematic review should be interpreted with caution as there are some potential limitations at study and review level. At study level: i) The study design of the original studies might limit causal inferences as cross-sectional and case control designs are expected to be found, rather than longitudinal studies; and ii) a high level of heterogeneity in the quality of the designs is expected. At review level: i) the analyses will be based on unadjusted estimates as different adjustments by different potential confounders are expected in original studies. The potential impact of those moderating variables (age, gender, tobacco smoking, among others) will be assessed by a combination of subgroup and meta-regression analyses; ii) differences in the tissue types and methods used to measure telomere length is expected; and iii) the scarcity of studies may limit some subgroup or stratified analyses by individual substances.”

Additional comments from Associate Editor:

AE.1) The authors may have forgotten to update the abstract entered in the Editorial Manager system; the abstract shown in the Editorial Manager seems to be one of the older versions rather than the latest ‘R2’ version.

Response: Thank you for your comment. We have updated the latest version of the abstract.

AE.2) Line 174: presumably ‘presence of other mental disorders or medical illness’ should be recorded for both cases and controls, not just for cases?.

Response: Yes, we have updated the text to avoid this misinterpretation (lines: 191-196, marked copy):

“…; iv) sample characteristics for both cases and controls separately (gender ratio, mean age and standard deviation (SD), ethnic background, education level, type of substance use in cases, duration of substance use disorder in cases, presence of other mental disorders or medical illness, smoking status, exposure to childhood adversities and other stressful life events and if the latest or any other variable has been measured before the onset of SUD in cases); …”