Author's response to reviews

Title: Protocol for a Systematic Review on the association between chronic stress during the life course and telomere length

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Version: 3
Date: 19 March 2014

Author's response to reviews: see over
March 18, 2014

RE: Revisions to submission
MS: 9296322881182938
Protocol for a Systematic Review on the association between chronic stress during the life course and telomere length
Jacklyn Quinlan, Mai Thanh Tu, Etienne V Langlois, Mohit Kapoor, Daniela Ziegler, Hassan Fahmi and Maria-Victoria Zunzunegui

Dear editors of Systematic Reviews,

We are thankful for the comments we received on our original submission to Systematic Reviews entitled “Protocol for a Systematic Review on the association between chronic stress during the life course and telomere length” and we believe that they have improved the content of our protocol. Below are the responses to the reviewers comments.

We appreciate your consideration. Sincerely,

Jacklyn Quinlan
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Maria-Victoria Zunzunegui
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Response to reviewer's report
We thank the reviewer for their comments. The following are our responses to the comments as well as the tracked modifications we made to the protocol.

Title: Protocol for a Systematic Review on the association between chronic stress during the life course and telomere length

Version: 2

Date: 17 February 2014

Reviewer: Alexander Tsertsvadze

Response to reviewer's report:

Abstract – Methods/Design

• We revised the following sentence: “Study selection criteria will include individual demographic…” The sentence now states our study eligibility criteria in terms of PICO domains as follows: “Studies of any design investigating the association between chronic social stress and telomere length in healthy and diseased adults and children will be eligible for inclusion in the review.”

• The sentence above is followed by “For each study we will extract individual demographic and socioeconomic characteristics, research setting, method of measuring telomere length, reported outcome and, determinants of interest.” Studies will also be stratified by 1) age into 3 groups: childhood (0-18 years), adulthood (19-64 years) and late life (65+); 2) cell type; 3) study design; and 4) telomere length assessment method.

• We deleted “All designs will be considered”

Protocol text - Methods

• Page 9: We changed the heading to ‘Study Inclusion Criteria’ (not criterions)

• Page 9: We specify that individuals of any age and both sexes are eligible.

• Page 9: We moved this paragraph to “Data Synthesis” section: “Because the sources of chronic social stress may be different in lower and middle income countries as compared to high income countries, we will also stratify (if possible) participants based studies originating from each of these settings. We will use The World Bank Group’s classification to identify those countries (see appendix in Additional file 3) [33].”

• Page 10: We specify that chronic stress (e.g., violence, poverty, being a caregiver) will be considered at all ages.

• Page 10: We deleted the ‘Results’ section.
• Page 9: We deleted ‘Screening’ and ‘Eligibility’ subheadings leaving only ‘study selection procedure’ subheading which describes both title/abstract and full text screening.

• Page 10: In Data collection process: we removed type of social stress from participants’ characteristics and put it under ‘study exposure’;

• Page 10: We now say that we will extract timing of social stress.

• Page 11: Scientific quality assessment: we deleted the following: “…to identify studies with the best internal validity – i.e. with the smallest probability of type I statistical errors or spurious associations - confounded or biased.”

• Page 11: Scientific quality assessment: we deleted the following: “Inter-rater reliability will be computed using the intraclass correlation coefficient (ICC), or Cohen’s Kappa. A value above 0.80 will be considered as excellent [38,43]’’

• Page 12: Data synthesis: We explain in more details the following:

a) How will the authors decide when to pool the studies? In what characteristics should these studies be similar to be able to combine them (e.g., design, population age, type of stress, method of telomere measurement, or type of outcome)?

In the data synthesis section, we state that we will pool studies by age group, cell type, study design, telomere measurement method, and type of stress.

The cohort-specific standardised regression coefficients and standard errors will be grouped and analyzed, if possible, by 1) age group (childhood (0-18 years), adulthood (19-64) and aged (65+)), 2) cell type, 3) study design, 4) telomere length measurement method, and 5) type of stress.

b) How will the authors assess heterogeneity during pooling (regardless of the fixed or random effects model they use); will it be I2 only? Above what value of I2 the authors would declare the presence of heterogeneity which would prevent them from pooling? Will the authors examine heterogeneity in the effect estimates via visually inspecting forest plots?

We will first qualitatively examine heterogeneity in the study designs, settings, populations and exposure/outcome definitions and measurements. We will then quantitatively assess heterogeneity via Cochran’s Q Test with a liberal significance level (Lau et al 1997), and quantify such heterogeneity via the $I^2$ statistic using Higgins et al’s (2003) classification. Due consideration will be provided to possible outlier results in the effect estimates by visually inspecting forest plots.

c) The authors mentioned binary outcomes such as RR, OR, IRR, HR, and prevalence ratio. Please, explain how this is possible when the primary outcome which is telomere length, is measured on a continuous scale? Can this outcome be dichotomized at some threshold length? Perhaps it is more possible that
some or most studies would report linear regression coefficients (effect of stress on telomere length) for telomere length measured at continuous scale?

In fact, TL is measured as a continous variable and regression coefficients will be compared. We now include this in the data synthesis section:

p.11
This involves using linear regression models to analyse the association between stress and telomere length. To take account of protocol variability in blood storage, DNA extraction, and measurement method of telomere length, we will convert the absolute measures to study-specific z-scores (regression coefficients and corresponding standard errors will be divided by the standard deviation of telomere length).

p.12
Where feasible, we will carry out separate random effects meta-analyses [48] of adjusted vs. non-adjusted (or insufficiently adjusted) standardised linear regression association measures between stress and TL.

d) Will the authors provide measures of variation such as 95% CIs, p values for each effect point estimate?

We will provide measures of variation such as 95% CIs and p values for each point estimate. This is now stated in the data synthesis section.

e) Will the authors make any efforts to assess the presence/extent of publication bias? If yes, how?

Yes, we will make efforts to assess the presence and extent of publication bias by generating graphical diagnostics, such as funnel plots, and statistical methods to test for this bias. The following sentence has now been added to the Data synthesis section:

To assess the possible influence of publication bias on the results, funnel plots and statistical tests to measure the extent of this bias will be performed [48].

Protocol text - Discussion

• Page 13: It would be very useful if the authors highlight or elaborate around the importance of their hypothesis, because uninitiated reader may doubt the plausibility of this hypothesis and downgrade any implications this research may have in future. Will the authors discuss around the following issues listed below?

a) Why it is important to know if the effect of social stress on morbidity is mediated by telomere length?

It is important to know if the effects of stress on disease are mediated via telomere erosion. If an association is found, then TL is a promising new target for research into the long-term effects of stress throughout the lifespan. Elucidating the molecular mechanisms that regulate telomere dynamics, identifying intervening biological substrates that could serve as potential treatment targets, and discovering coping resources or protective health behaviours that may
b) How will this knowledge be translated into practice? Do we have any mechanisms to control or manipulate the telomere length?

It is hoped that this knowledge will translate into prioritising “societal stress reduction” plans. It has been shown that healthy behaviours and a healthy environment can help to buffer the deleterious effects of stress on telomere erosion (Puterman and Epel, 2012). Given that individuals who are exposed to stress during their early years show a faster erosion rate of TL, early intervention and prevention strategies can potentially ameliorate the acceleration of physiological aging processes. It is also hoped that the knowledge from this review will push future research in identifying novel targets (that act to maintain or elongate telomeres, for example) for intervention to help individuals recover from exposure to stress.

c) If there is a true causal association between stress and telomere length/activity, how would this inform future research? Which point along the causal link will be the target of research, telomere itself or whatever lies between social stress and telomere?

Telomeres are key elements in the causal chain of premature senescence. By identifying if the association between telomere dynamics and stress are causally associated, future research could then focus on stress reduction plans as preventative plans, improving our understanding of the mechanisms that stress have on telomere length (inflammation, oxidation, etc), which could be targeted in future interventions. These interventions could be individual (for example physical activity, or meditation) or societal (for example, improving social benefits such as the Canadian supplement of security of income, assuring financing for community centers leisure and cultural programs or assuring parks and green spaces in urban environments). We have added some sentences in the last paragraphs of the protocol.

- Will the authors provide a statement on potential limitations and strengths of their review (e.g., differences in methods of telomere length measurement, cross-sectional studies will not allow to determine temporal relationship between stress and telomere length limiting inferences on causality)?

The following sentence has been added:

The results from this review are limited by study design. Longitudinal findings on TL indicate that results should be interpreted with caution since the temporal process of telomere erosion is complex. In addition, use of different telomere length measurement methods and/or tissue types may limit valid comparisons between studies.