Reviewer's report

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

Reviewer's report:

Abstract – Methods/Design

• Please, revise the following sentence: “Study selection criteria will include individual demographic...” The sentence should state your study eligibility criteria in terms of PICO domains (i.e., design, population, intervention, comparator, and outcome). In your case, intervention/comparator is chronic social stress. So you could state something in this line: "Studies of any design investigating the association between chronic social stress and telomere length in... [please, specify your population of interest: e.g., healthy adults and children] will be eligible for inclusion in the review.”

• The sentence above should be 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 be stratified by age into 3 groups: childhood (0-18 years), adulthood (19-64 years) and late life (65+).

• Delete “All designs will be considered”

Protocol text - Methods

• Page 9: should be ‘Study Inclusion Criteria’ (not criterions)
• Page 9: please specify are individuals of any age and both sexes eligible?
• Page 9: Please move 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: Chronic stress (e.g., violence, poverty, being caregiver) will be considered at all ages or up to a certain age?
• Page 10: Delete ‘Results’ section altogether
• Page 10: Delete ‘Screening’ and ‘Eligibility’ subheadings leaving only ‘study selection procedure’ subheading which will describe both title/abstract and full text screening
• Page 11: In Data collection process: please remove type of social stress from participants’ characteristics and put it under ‘study exposure’;

• Page 11: Will the authors extract timing of social stress?

• Page 11: Scientific quality assessment: please delete 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 12: Scientific quality assessment: please delete 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 13: Data synthesis: will the authors explain in more detail 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)?
  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?
  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?
  d) Will the authors provide measures of variation such as 95% CIs, p values for each effect point estimate?
  e) Will the authors make any efforts to assess the presence/extent of publication bias? If yes, how?

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?
  b) How will this knowledge be translated into practice? Do we have any mechanisms to control or manipulate the telomere length?
  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?

• 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)?