ENVIRONMENTAL-RISK (E-RISK) LONGITUDINAL TWIN STUDY
CONCEPT PAPER FORM

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Sponsoring Investigator (if the proposing author is a student, a post-doc or a colleague): N/A

Proposed co-authors: Louise Arseneault, Aaron Reuben, Ben Williams, Karen Sugden, Renate Houts, Helen Fisher, Andrea Danese, Idan Shalev and anyone else interested

Provisional Paper Title: Victimisation and Telomere Erosion

Date: 24 January, 2017

Objective of the study and its significance:

It is widely hypothesized that stress arising from adverse experiences in childhood and adolescence (maltreatment, sexual abuse, neglect, domestic violence, bullying, and other forms of violence exposure) alters the length of telomeres, which are caps on the ends of chromosomes. In fact, we reported from a small subsamples of E-Risk twins initial evidence that maltreatment between ages 5 and 10 years was associated with shortened telomeres (Shalev et al. 2013, Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study**.** Molecular Psychiatry).

Because it is unethical to randomly assign children and adolescents to victimization in an experimental design, the evidence base remains observational. Moreover, much of the literature relies on retrospective recall of childhood victimisation by adults in clinical samples. Thus, there is room in the literature for a paper that goes as far as possible in rigorously testing whether victimization predicts change in telomere length from Time 1 to Time 2, and whether that prediction is environmentally mediated. The E-risk design lends itself to such tests, because we can study within-individual change from before to after victimization, and we can compare twins who are discordant for their victimization experiences. The E-Risk cohort at age 18 is at the ideal age for this research, soon after victimization.

This project will follow a template for a series of analyses that we have already established, and that can be applied to test effects of victimisation on a variety of outcomes measured in E-Risk, cognitive, psychiatric, and biological (it has been used for outcomes of methylation, neuropsychological test scores, and psychopathology).

Whether findings are positive or negative, the paper will make a publishable contribution.

Statistical analysis approach:

We will begin with an ACE twin model of telomere length, to report the genetic and environmental influences on telomere length at age 18.

Next we will conduct a basic test of the hypothesis that age-18 telomeres are shorter at increasing levels of adolescent polyvictimisation. We will show telomere length among 18 year olds who experienced physical abuse, sexual abuse, neglect, domestic violence, bullying, criminal assault, and other forms of violence exposure as an adolescent (age 12-18). The comparison group is age peers who have not been victimised.

We will also show age-18 telomere length among twins who experienced polyvictimization before age 12 (count of physical abuse, sexual abuse, neglect, domestic violence, or bullying, as a child). To rule out the possibility that adolescent victimization and telomere length are artifactually associated because both are merely products of earlier victimsation during childhood, we will control statistically for a measure of childhood polyvictimisation, and we will also estimate the additive effects of childhood and adolescent victimization.

We will also assess the association between cumulative victimization across childhood and adolescence and age-18 telomere length. Cumulative victimization is measured via a latent class analysis, using combined victimization information across the two developmental periods, to capture participants who have been exposed to a high cumulative stress load.

To rule out the possibility that adolescent victimization and telomere length are artifactually associated because both are products of low SES, we will control statistically for a measure of childhood SES level.

To rule out the possibility that adolescent victimization and telomere length are artifactually associated because both are products of a maternal history of victimisation, we will control statistically for mums CTQ.

To rule out the possibility that adolescent victimization and telomere length are artifactually associated because both are products of unmeasured background factors, we will carry out a comparison of DZ twin siblings, who grew up with the same background. We will test whether discordance between the twins for victimization risk predicts discordance between twins for age-18 telomere outcome.

To rule out the possibility that adolescent victimization and telomere length are artifactually associated because both are products of a genetic liability for abnormal health and behaviour, we will repeat the test of whether twin discordance for victimization risk predicts twin discordance for telomere outcome, but using only genetically identical MZ twins.

To rule out any possibility of self-report bias, we will replace each twin’s report of their

own victimization with measures of their victmisation history collected from informants who know them well (their mothers and co-twins).

To rule out the possibility that adolescent victimization and telomere length are artifactually associated because young people who already had short telomeres are for some unforeseen reason more likely to be selected by perpetrators as easy victims, we will control statistically for each cohort member's telomere length assessed in buccal DNA at age 5 and 10. (NB, this requires ascertaining the correlation between telomeres assayed from buccal and blood DNA at age 18 years.)

To rule out the possibility that victimization and telomeres are artifactually associated because individuals who abuse substances are likely to be victimized while intoxicated and substance abuse might erode telomeres, we could control statistically for substance dependence assessed at age 18.

Some prior research (including ours from the Dunedin Study; Shalev et al 2014) has suggested that stress-related mental disorders are associated with telomere erosion. We can test if polyvictimisation predicts telomere length as a function of PTSD and MDD.

Variables Needed at Which Ages (names and labels):

Study: E-Risk

Zygosity, sex, SES, twinID, order

Age 5 buccal telomere length

Age 7

Age 10 buccal telomere length

Age 12 polyvictimisation-phase-5-12, Mum's CTQ

Age 18 JVQ polyvictimisation and each victimisation type, buccal telomere length, blood telomere length, informant-report victimization, substance dependence18 (alcohol, cannabis, tobacco), PTSD18, MDD18.

Cumulative victimization: results of LCA analysis.

References cited:

Shalev et al. 2013, Exposure to violence during childhood is associated with telomere erosion from 5 to 10 years of age: a longitudinal study**.** Molecular Psychiatry, 18*,* 576–581

Shalev, I, Moffitt TE, Braithwaite AW, Danese A, Fleming, NI, Goldman-Mellor S, Harrington HL, Houts, RM, Israel, S Poulton R, Robertson S, Sugden K, Williams B, Caspi A. (2014). Internalizing disorders and leukocyte telomere erosion: A prospective study of depression, generalized anxiety disorder and post-traumatic stress disorder. Molecular Psychiatry, 19, 1163-1170.

Data Security Agreement

Provisional Paper Title	Victimisation and Telomere Erosion
Proposing Author	Temi and Avshalom
Today's Date	January 21, 2017

Please keep one copy for your records
(Please initial your agreement)

___x_ I am current on Human Subjects Training (CITI (www.citiprogram.org) or training in human subject protection through my post or courses.

__x__ My project is covered by Duke or King's IRB OR I have /will obtain IRB approval from my home institution.

__x__ I will treat all data as "restricted" and store in a secure fashion.

__x__ I will not share the data with anyone, including students or other collaborators not specifically listed on this concept paper.

___x_ I will not post data online or submit the data file to a journal for them to post.
Some journals are now requesting the data file as part of the manuscript submission process. The E-Risk Study cannot be shared because the Study Members have not given informed consent for unrestricted open access. Speak to Terrie or Avshalom for strategies for dealing with data sharing requests from Journals.

__x__ Before submitting my paper to a journal, I will submit my draft manuscript and scripts for data checking, and my draft manuscript for co-author mock review, allowing three weeks.

__x__ I will submit analysis scripts and new variable documentation to project data manager after manuscript gets accepted for publication.

__x__ I will return all data files to the Data Manager after the project is complete. Collaborators and graduates of DPPP may not take a data file away from the DPPP office. The data remains the property of the Study and cannot be used for further analyses without express, written permission.

__x__ I will ensure geographical location information, including postcodes or geographical coordinates for the E-Risk study member's homes or schools, is <u>never</u> combined or stored with any other E-Risk data (family or twin-level data)

Signature: ....

CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author

Proposing Author: Temi and Avshalom

xx☐ I have read the E-Risk data-sharing policy guidelines and agree to follow them

Provisional Paper Title: Victimisation and Telomeres

Potential co-authors: Louise Arseneault, Aaron Reuben, Ben Williams, Karen Sugden, Helen Fisher, Andrea Danese, Renate Houts, Idan Shalev, and anyone else interested

Potential Journals:

Intended Submission Date (month/year): early 2018

Please keep one copy for your records and return one to Louise (louise.arseneault@kcl.ac.uk)

B. To be completed by potential co-authors:

☐ Approved ☐ Not Approved ☐ Let's discuss, I have concerns

Comments:

Please check your contribution(s) for authorship:

☐ Conceptualizing and designing the longitudinal study

☐ Conceptualizing and collecting one or more variables

☐ Data collection

☐ Conceptualizing and designing this specific paper project

☐ Statistical analyses

☐ Writing

☐ Reviewing manuscript drafts

☐ Final approval before submission for publication

☐ Acknowledgment only, I will not be a co-author

Signature: .....