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

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Provisional Paper Title:
Does childhood adversity predict a new measure of chronic inflammation?

Date:
October 11, 2018

Objective of the study and its significance:

To measure plasma levels of the inflammatory biomarker soluble urokinase plasminogen activator receptor (suPAR) in E-Risk phase 18 and:

- Assess genetic and environmental influences on suPAR levels
- Assess the effect of childhood adversities or victimization in childhood and adolescence on suPAR level at age 18 years
- Assess if victimization in childhood is differentially associated with inflammation at age 18 years than victimization in adolescence
- Assess the effect of cumulative victimization across childhood and adolescence on inflammation at age 18 years.
- Compare suPAR and C-reactive protein (CRP), the current gold standard inflammation marker, and test if victimization is differentially related to these measures of inflammation
- Test correlations with poor health behaviors to investigate whether exposure to childhood adversities increases the likelihood of poor health behaviors that in turn causes increased inflammation

Exposure to adversities and victimization during childhood and adolescence is associated with an elevated risk of physical and mental health problems in adulthood.

Inflammation is a strong predictor of poor health, chronic disease, and mortality, and it has been suggested that inflammation could constitute the underlying mechanism responsible for the biological embedding of childhood trauma, thereby linking exposure to early life adversity to adverse health outcomes in later life.[1,2]

In the Dunedin study, we have previously shown that exposure to more childhood risk factors, including adverse childhood experiences, was associated with higher levels of the inflammation marker suPAR in

midlife, independent of smoking and BMI.[3] Similarly, different types of childhood victimization have been shown to be associated with increased inflammation as measured with the gold standard marker of inflammation, CRP,[4] including polyvictimization,[5] childhood maltreatment,[6] and bullying.[7,8]

While CRP is an acute-phase reactant and a marker of acute inflammation and infections,[9] suPAR seems to be a marker of chronic inflammation and organ damage.[10,11] Elevated plasma levels of suPAR are predictive of development and progression of disease, adverse clinical outcomes, and mortality,[12,13] and suPAR levels are elevated across a wide range of diseases, acute and chronic.[14–18]

Statistical analyses:

suPAR levels at age 18 years of age in is measured in blood samples from the E-Risk Longitudinal Twin Study (n=2,232; 56% monozygotic and 44% dizygotic twin pairs; 49% male).

We will test if variation in suPAR levels at age 18 is genetically influenced in the E-Risk sample, using a univariate twin model to decompose the variation in suPAR into additive genetic, shared environmental, and unique environmental components.

Multiple linear regression models will be employed, investigating associations between inflammation (assessed by CRP or suPAR) and risk factors or adversities in childhood and adolescence (ACEs, polyvictimization, CTQ).

We will explore the possibility of correlating twin differences in exposures with twin differences in suPAR, if we have sufficient variation in twin differences in exposure variables. A twin difference analysis would allow us to rule out unmeasured variables (both environmental in the case of DZ twins) and genetic as well (in the case of MZ twins).

All analyses will be adjusted for sex, and regression analyses will be further adjusted for BMI and smoking, except when BMI and smoking are used as potential mediators of health-behavior.

Variables needed at which ages:

Study:
E-Risk

Age 5:
- FAMILYID (Unique family identifier)
- ATWINID (Twin A ID)
- BTWINID (Twin B ID)
- RORDERP5 (Random twin order)
- RISKS (Sample groups)
- COHORT (Cohort)
- SAMPSEX (Sex of twins)
- ZYGOSITY_2018 (Zygosity)
- SESWQ35 (Social class composite)

Age 10:
- LOWSC510E/LOWSC510Y (Low self-control elder/younger twin)

Age 12:
- POLYVE512/POLYVY512 (Polyvictimization elder/younger twin)
- FSIQ12E/FSIQ12Y (Full scale IQ elder/younger twin)

Age 18:
- FSIQ18E/FSIQ18Y (Full scale IQ elder/younger twin)
- Health measures:

- BMIE18/BMIY18 (BMI elder/younger twin)
- SMKCURE18/SMKCURY18 (Smoking daily elder/younger twin)
- PHYACTE18/PHYACTY18 (Physical activity elder/younger twin)
- PSQIE18/PSQIY18 (PSQI, Global sleep difficulties elder/younger twin)
- BTEMPE18/BTEMPY18 (Body temperature, celcius)
- CURHEA012E18/CURHEA012Y18 (Current illness/injury elder/younger twin)
- DXALCDEPE18/DXALCDEPY18 (Alcohol dependency elder/younger twin)
- DXMARJE18/DXMARJY18 (Marijuana dependency elder/younger twin)

- Victimization:
  - POLYVCTZCE18/POLYVCTZCY18 (Polyvictimization elder/younger twin)
  - ACES_conventE18/ACES_conventY18 (Conventional ACEs elder/younger twin)
  - ACES_expandE18/ACES_expandY18 (Expanded ACEs elder/younger twin)
  - ACES_totalE18/ACES_totalY18 (Combined ACEs elder/younger twin)
  - CTQCTOTE18/CTQTOTY18 (CTQ combined elder/younger twin)
  - CTQABUCE18/CTQABUCY18 (CTQ abuse elder/younger twin)
  - CHADVICTGRPE18/CHADVICTGRPY18 (Latent class variable for victimization types elder/younger twin)
- Inflammatory markers:
  - CRPmgLE18/ CRPmgLY18 (Plasma CRP elder/younger twin)
  - IL6pgmlE18/IL6pgmlY18 (IL-6 elder/younger twin)
- suPARngml_E/suPARngml_Y (suPAR elder/younger twin)

References cited:

1. Danese, A. & Baldwin, J. Hidden Wounds? Inflammatory Links Between Childhood Trauma and Psychopathology. *Annu. Rev. Psychol.* 517–44 (2017). doi:10.1146/annurev-psych-010416-044208
2. Danese, A. & McEwen, B. S. Adverse childhood experiences, allostasis, allostatic load, and age-related disease. *Physiol. Behav.* **106,** 29–39 (2012).
3. Rasmussen, L. J. H. *et al.* Cumulative childhood risk is associated with a new measure of chronic inflammation in adulthood. *J. Child Psychol. Psychiatry* IN PRESS (2018).
4. Baumeister, D., Akhtar, R., Ciufolini, S., Pariante, C. & Mondelli, V. Childhood trauma and adulthood inflammation: a meta-analysis of peripheral C-reactive protein, interleukin-6 and tumour necrosis factor-α. *Mol. Psychiatry* **21,** 642–649 (2015).
5. Baldwin, J. R. *et al.* Childhood victimization and inflammation in young adulthood: A genetically sensitive cohort study. *Brain. Behav. Immun.* **67,** 211–217 (2018).
6. Danese, A., Pariante, C. M., Caspi, A., Taylor, A. & Poulton, R. Childhood maltreatment predicts adult inflammation in a life-course study. *Proc. Natl. Acad. Sci.* **104,** 1319–1324 (2007).
7. Copeland, W. E. *et al.* Childhood bullying involvement predicts low-grade systemic inflammation into adulthood. *Proc. Natl. Acad. Sci.* **111,** 7570–7575 (2014).
8. Takizawa, R., Danese, A., Maughan, B. & Arseneault, L. Bullying victimization in childhood predicts inflammation and obesity at mid-life: A five-decade birth cohort study. *Psychol. Med.* **45,** 2705–2715 (2015).
9. Rhodes, B., Fürnrohr, B. G. & Vyse, T. J. C-reactive protein in rheumatology: Biology and genetics. *Nat. Rev. Rheumatol.* **7,** 282–289 (2011).
10. Desmedt, S., Desmedt, V., Delanghe, J. R., Speeckaert, R. & Speeckaert, M. M. The intriguing role of soluble urokinase receptor in inflammatory diseases. *Crit. Rev. Clin. Lab. Sci.* **54,** 117–133 (2017).
11. Lyngbæk, S. *et al.* CRP and suPAR are differently related to anthropometry and subclinical organ damage. *Int. J. Cardiol.* **167,** 781–5 (2013).
12. Eugen-Olsen, J. *et al.* Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. *J. Intern. Med.* **268,** 296–308 (2010).
13. Rasmussen, L. J. H. *et al.* Soluble urokinase plasminogen activator receptor (suPAR) in acute care: a strong marker of disease presence and severity, readmission and mortality. A retrospective cohort study. *Emerg. Med. J.* **33,** 769–775 (2016).

14. Hayek, S. S. *et al.* Soluble Urokinase Receptor and Chronic Kidney Disease. *N. Engl. J. Med.* **373,** 1916–25 (2015).
15. Koch, A. *et al.* Circulating soluble urokinase plasminogen activator receptor is stably elevated during the first week of treatment in the intensive care unit and predicts mortality in critically ill patients. *Crit. Care* **15,** R63 (2011).
16. Persson, M. *et al.* Soluble Urokinase Plasminogen Activator Receptor: A Risk Factor for Carotid Plaque, Stroke, and Coronary Artery Disease. *Stroke* **45,** 18–23 (2014).
17. Rasmussen, L. J. H. *et al.* Inflammatory biomarkers and cancer: CRP and suPAR as markers of incident cancer in patients with serious nonspecific symptoms and signs of cancer. *Int. J. Cancer* 1–9 (2017). doi:10.1002/ijc.30732
18. Wittenhagen, P. *et al.* The plasma level of soluble urokinase receptor is elevated in patients with Streptococcus pneumoniae bacteraemia and predicts mortality. *Clin. Microbiol. Infect.* **10,** 409–15 (2004).

Data Security Agreement

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Today's Date	October 11, 2018

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

LJHR I am familiar with the King's College London research ethics guidelines (https://www.kcl.ac.uk/innovation/research/support/ethics/about/index.aspx) and the MRC good research practice guidelines (https://www.mrc.ac.uk/research/policies-and-guidance-for-researchers/good-research-practice/).

LJHR My project has ethical approval from my institution.

LJHR I am familiar with the EU General Data Protection Regulation (https://mrc.ukri.org/documents/pdf/gdpr-guidance-note-3-consent-in-research-and-confidentiality/), and will use the data in a manner compliant with its requirements.

LJHR My computer is (a) encrypted at the hard drive level, (b) password-protected, (c) configured to lock after 15 minutes of inactivity, AND (d) has an antivirus client which is updated regularly.

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

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

LJHR I will not merge data from different files or sources, except where approval has been given by the PI.

LJHR 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 the study PI for strategies for dealing with data sharing requests from Journals.

LJHR 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.

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

LJHR I will delete the data after the project is complete.

N/A **For projects using location data:** I will ensure geographical location information, including postcodes or geographical coordinates for the E-Risk study member's homes or schools, is never combined or stored with any other E-Risk data (family or twin-level data)

N/A **For projects using genomic data:** I will only use the SNP and/or 450K data in conjunction with the phenotypes that have been approved for use in this project at the concept paper stage.

Signature: .....Line Hartmann Rasmussen.....

CONCEPT PAPER RESPONSE FORM

A. To be completed by the proposing author

Proposing Author: Line Jee Hartmann Rasmussen

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

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Potential co-authors: Andrea Danese, Louise Arseneault, Helen Fisher, Tim Matthews, Ben Williams, Karen Sugden, HonaLee Harrington, Renate Houts, Temi Moffitt, Avshalom Caspi

Potential Journals:

Intended Submission Date (month/year):

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: .....