## CONCEPT PAPER TEMPLATE

**Provisional Paper Title:** suPAR, a new marker of chronic inflammation useful for studies of early-life risk and adult health

**Proposing Author:** Line Jee Hartmann Rasmussen

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**P.I. Sponsor:** Terrie Moffitt, Avshalom Caspi

**Today's Date:** July 26, 2017

**Objective of the study:**

To measure plasma levels of the chronic inflammation marker soluble urokinase plasminogen activator receptor (suPAR) and assess:

- Associations between childhood risk factors and suPAR at age 38 years
- Associations between suPAR and adult health outcomes, including measures of aging
- Associations between suPAR and DNA methylation patterns
- Compare suPAR and CRP, the current gold standard inflammation marker

**Data analysis methods:**

Correlation analyses investigating correlations between CRP or suPAR with clinical characteristics and biomarkers, including inflammatory markers and white blood cell counts.

Multiple linear regression models will be employed, investigating associations between childhood risk factors (childhood health, SES, IQ, self-control, prospectively collected adverse childhood experiences) and inflammation (assessed by CRP or suPAR) at age 38 years or associations between inflammation and adulthood health outcomes (including self-reported health, physical function, IQ, measures of aging, and telomere length).

All analyses will be adjusted for sex, and regression analyses will be further adjusted for BMI and smoking.

**Variables needed at which ages:**

**Family history of disease:**

- Any heart disease
- High blood pressure
- Stroke

- High cholesterol
- Diabetes

**Childhood predictors:**

- Self-control
- Social isolation
- SES, average high SES age 1-15
- ACEs
- Childhood IQ, full scale ages 7-11
- Childhood health

**Variables at age 38:**

- Self-rated health
- Body temperature
- Telomere length, from blood
- Smoking; current and life-time
- Physical activity; sport/leisure activity, “mets” per week
- Diet
- Anti-inflammatory medication
- Menstruation, week of cycle
- IQ, full scale
- Processing speed
- Physical limitations
- Balance
- Grandparent longevity
- Anthropometry:
    - BMI
    - Waist-hip ratio
- Markers of aging:
    - Biological age, Klemera-Doubal method
    - Pace of aging, scaled to years
    - Facial aging
- Inflammatory markers:
    - CRP
    - Fibrinogen
    - IL-6
    - Inflammatory Factor Score
    - suPAR
- White blood cells (WBC, neutrophils, monocytes, lymphocytes, basophils, eosinophils)

**<u>Significance of the Study (for theory, research methods or clinical practice)</u>:**

A major public health challenge is to extend health span in the context of an ever-expanding aging population.[1,2]

The basic foundations for lifelong health are thought to be constructed in the early years of life.[3] Life-course research has drawn attention to several childhood risk factors that may compromise lifelong health[4]: poor health, socioeconomic disadvantage, low IQ,[5] low self-control,[6] and adverse childhood experiences (ACEs).[7]

Inflammation burden in the body is a strong predictor of clinical outcomes and mortality. Markers of inflammation have been used to link early life risk with adulthood health.[8,9]

While the acute-phase reactant C-reactive protein (CRP) is commonly used as the gold standard inflammation marker both in the clinic and in life-course research,[10] soluble urokinase plasminogen activator receptor (suPAR) is a newer biomarker of inflammation,[11] which appears to be correlated with chronic rather than acute inflammation. And although the two are positively correlated, they appear to capture different aspects of inflammation.[12]

suPAR concentration in blood is elevated upon activation of the immune system, and suPAR is associated with the development, presence, and progression of disease.[11,13,14] Thus, suPAR levels are elevated across a wide range of diseases,[15] including cardiovascular disease,[16] type 2 diabetes,[17] cancer,[18,19] renal disease,[20] and infections.[21] In addition, suPAR is a strong predictor of mortality, both in the general population and in patient populations.[13,15]

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**Data Security Agreement**

**A**

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| LJHR | I am current on Human Subjects Training (CITI (www.citiprogram.org) or equivalent) |
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| 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 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 Dunedin 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.* |
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| LJHR | 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. |

**Signature: Line Jee Hartmann-Rasmussen**

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**CONCEPT PAPER RESPONSE FORM**

**A**

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| Provisional Paper Title | suPAR, a new marker of chronic inflammation useful for studies of early-life risk and adult health |
| Proposing Author | Line Jee Hartmann Rasmussen |
| Other Contributors | Terrie Moffitt, Avshalom Caspi, Ben Williams, Jesper Eugen-olsen, Dan Belsky, HonaLee Harrington, Renate Houts, Karen Sugden, Richie Poulton |
| Potential Journals | JAMA Pediatrics, Biological Psychiatry, Molecular Psychiatry |
| Today's Date | July 26, 2017 |
| Intended Submission Date | |

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**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:**

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