

Concept Paper Form

Provisional Paper Title: Investigating PTSD and the inflammatory biomarker suPAR in three cohorts
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Objective of the study:

Trauma and adversity are associated with poor health across the lifespan¹⁻⁵. This includes risk for cardiovascular disease (CVD) among people with posttraumatic stress disorder (PTSD) after the experience of trauma, encompassing risk of developing coronary heart disease and premature death⁶⁻⁸. One physiological mechanism that has been theorized to link PTSD to poorer health and CVD is increased levels of systemic inflammation⁹⁻¹⁰. Higher levels of inflammation are linked to increased risk of cardiovascular diseases and cardiovascular events¹¹⁻¹². If PTSD were consistently linked to higher levels of systemic inflammation¹³, this would provide further evidence that this mechanism could contribute to poorer downstream cardiovascular health.

Although the association between PTSD and inflammation has been previously studied in established inflammatory biomarkers like C-reactive protein (CRP) and interleukin-6 (IL-6)¹³, it is unclear whether these associations extend to newer biomarkers, such as soluble urokinase plasminogen activator receptor (suPAR). suPAR is released to the blood during inflammation, immune activation, and disease, and it is thought to be a biomarker of systemic chronic inflammation¹⁴. Prior studies of stress and adversity have found that suPAR shows associations with adversity spanning childhood to midlife^{10,15}, with some evidence suPAR is a more reliable marker of psychosocial stress than CRP and IL-6^{11,16}. In the current study, we seek to extend prior studies of adversity and suPAR¹⁰ to investigate associations between PTSD and suPAR in two longitudinal cohorts, the Dunedin Study and the E-Risk cohort. Both cohorts include multiple measurements of inflammatory biomarkers and mental health, which would allow us to examine and replicate the association between PTSD and suPAR.

Data analysis methods:

We aim to extend our prior work examining stressful life events and inflammation¹⁰ to test the association between PTSD and suPAR in the E-Risk and Dunedin studies and the Danish patient cohort suPAR-29K. The suPAR-29K cohort consists of n~29,000 acutely admitted medical patients with suPAR measured at admission to the Emergency Department, Hvidovre Hospital, between 2013-2017 and with data on ICD-diagnoses from the Danish National Patient Registry.

Primary Analyses: We will test the association between PTSD and suPAR at the study visits in which these measures were assessed in E-Risk (age 18) and Dunedin (age 38 and 45). This will include associations for a recent PTSD diagnosis, as well as recent PTSD diagnosis and trauma exposure at each occasion. In Dunedin, we will also assess whether experiencing PTSD between ages 38 and 45 is associated with changes in suPAR

from age 38 to 45. Our models will control for sex, body mass index, and smoking status.

In addition, we will test the association between both PTSD (in the past 1, 2, 5 years or lifetime PTSD) and F.43 disorders (i.e., Reaction to severe stress, and adjustment disorders) and suPAR in the suPAR-29K cohort, controlling for age, sex, and Charlson score (body mass index and smoking not available in this cohort). Comparisons will be made to A) patients without any F43 diagnoses and B) patients without any F43 diagnoses and without other chronic illness (including other F-diagnoses).

We hypothesize that PTSD will be associated with higher levels of suPAR in all three cohorts.

Sensitivity analyses: We will conduct two sensitivity analyses to supplement the primary analyses.

1. We will test our models in each cohort while including childhood adversity (ACEs, childhood SES), to provide context as to the extent to which measures of adversity are predictive of suPAR.
2. We will compare associations observed between PTSD and suPAR with those for CRP and IL-6.
3. We will compare associations between suPAR and PTSD for diagnoses using DSM-5 versus DSM-IV criteria in E-Risk
4. We will examine associations between PTSD and suPAR when controlling for number of co-morbid psychiatric diagnoses (summed).

General analysis methods: Participants will be included if they have at least one measure of PTSD and suPAR. Models will use multiple regression to assess the association between PTSD and suPAR at each of the Dunedin and E-Risk study visits, as well as the analyses in the suPAR-29K cohort described above. We will first run bivariate models for the three predictors individually, then in a combined model. All models will be run in MPLUS¹⁷ using full information maximum likelihood estimation¹⁸ and sex, body mass index, and smoking status will be used as covariates in Dunedin and E-risk, whereas age, sex, and Charlson score will be used in suPAR-29K.

Variables needed at which ages:

- Dunedin
 - o suPAR at all ages assessed (age 38 and 45)
 - o CRP and IL-6 (ages 38 and 45)
 - o PTSD at all ages assessed (age 26, 32, 38, 45)
 - Lifetime, past 5 years, and current
 - Interference
 - o Trauma exposure at age 38 and 45
 - o Prospective ACEs
 - o Childhood SES
 - o Total count of all psychiatric disorders (ages 38 and 45)
- E-Risk
 - o suPAR at all ages assessed (age 18)
 - **suPARe18_4SD** - suPAR conc. ng/mL, p18 with outliers (4SDs above mean) removed, Elder
 - o CRP and IL-6 (age 18)
 - **InIL6e18_4SD** - log transformed IL6 pg/mL at 18 with outliers (4SDs above mean) removed, Elder
 - **InCRPe18_4SD** - log transformed CRP mg/L at 18 with outliers (4SDs above mean) removed, Elder
 - o PTSD at all ages assessed (age 18)

- Lifetime and current
 - **DXPTSD5CUE18** - PTSD Current dx, dsm5 - P18 – Elder
 - **DXPTSD5LFE18** - PTSD Lifetime dx, dsm5 - P18 – Elder
 - **DXPTSDCUE18** - PTSD Current dx, DSM-IV - P18 - Elder
 - **DXPTSDLFE18** - PTSD Lifetime dx, DSM-IV - P18 - Elder
 - Interference
 - **PTSD5_G_E18** - PTSD (DSM5) - interference - P18 - Elder
 - Trauma exposure (age 18)
 - **PTSD5_A_E18** - PTSD (DSM5) - trauma exposure - P18 - Elder
 - Psychiatric comorbidities (will use to create sum score)
 - **DXMDEE18** - Major depressive episode, dsm4 - P18 – Elder
 - **DXGADE18** - Gen Anxiety Disorder, dsm4_based - P18 – Elder
 - **DXADHD5X_18E** - DSM-5 ADHD Dx (based on >=5 Symp) [incl 4 NEET & meds] - P18 – ET
 - **DXALCDEPE18** - Alcohol dependent, dsm4_based - P18 – Elder
 - **DXMARJE18** - Marijuana dependency, dsm4 - P18 – Elder
 - **CDMODE18** - Moderate Conduct Disorder (>=5 count) - P18 – Elder
 - **SMKDXFTNDE18** - Fagerstrom Dx for Nicotine Dependence - P18 - Elder
 - Childhood adversity
 - CTQ at age 18
 - **CTQE18** - Childhood Trauma (CTQ) - P18 – Elder
 - Childhood ACEs
 - **ACESE512** - Adverse Childhood Experiences (ACEs) - [total] - thru P12 - ET
 - **ACES04E512** - Adverse Childhood Experiences (ACEs) - [trunc at 4] - thru P12 – ET
 - Childhood SES
 - **SESWQ35** - Social Class Composite at age 5
- suPAR-29K
 - suPAR at admission
 - CRP at admission
 - PTSD (ICD-10 F43.1 and F43)
 - During the past 1 year before admission
 - During the past 2 years before admission
 - During the past 5 years before admission
 - Lifetime (diagnoses going back to the inception of the Danish National Patient Registry in 1977)
 - Total count of all psychiatric disorders at admission
- Covariates
 - Sex
 - **SAMPSEX** - Sex of Twins: In sample [E-Risk]
 - Age (in suPAR-29K)
 - Body mass index (age 38 and 45 in Dunedin, 18 in E-Risk, not available in suPAR-29K)
 - **BMIE18** - BMI - P18 – Elder [E-Risk]
 - Smoking status (age 38 and 45 in Dunedin, 18 in E-Risk, not available in suPAR-29K)
 - **SMKCURE18** - Smoking daily - current - P18 – Elder [E-Risk]
 - **SMKDLYE18** - Ever a daily smoker - P18 – Elder [E-Risk]
 - Charlson score (in suPAR-29K)
 - Anti-inflammatory medication usage at age 18
 - **AntinflSteroid18_E** - 1+ Anti-inflammatory, steroid in last 2 weeks

Significance of the Study (for theory, research methods or clinical practice):

This study will help provide new knowledge about PTSD and systemic inflammation, specifically as assessed by suPAR. Although there is some prior evidence linking CRP and IL-6 to PTSD, it is important to test whether this association is reflected in suPAR, particularly given recent evidence that suPAR may better index chronic proinflammatory phenotypes associated with stress and adversity^{10,14}. This knowledge will provide important new context as to how PTSD might influence health, as well as a biomarker of systemic inflammation that might be particularly relevant as a physiological mechanism linking PTSD to CVD. In addition, this work could help support future intervention research hoping to assess whether PTSD treatment can result in concomitant changes in wellbeing and physical health.

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