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HUMAN DEVELOPMENT, BIRTH TO DEATH

Moffitt & Caspi
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Concept Paper template form

Provisional Paper Title: suPAR and mental health [PLEASE NOTE THAT THIS IS AN UPDATE OF A PREVIOUS CP SUBMITTED IN 2021]
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Today's Date: 9/2/2025

Please describe your proposal in 2-3 pages with sufficient detail for helpful review.

Objective of the project:

A growing body of evidence has shown that inflammation is elevated among individuals with a wide range of mental disorders[1]. While the depression-inflammation link is well-established[2,3], elevated inflammation has also been observed in patients with bipolar disorder, anxiety disorders, post-traumatic stress disorder (PTSD), autism spectrum disorder, suicidal behavior, and schizophrenia[4–6]. Upthegrove et al. (2025) highlight that systemic inflammation—particularly markers such as IL-6, CRP, and complement—may precede onset, relate to symptom severity, and contribute causally in subgroups across diagnoses[1]. However, findings remain inconsistent, often due to underpowered studies, lack of longitudinal data, inadequate control for confounding (e.g., smoking), and reliance on acute-phase markers[1,5,7].

Inflammation in psychiatric research is typically measured via circulating biomarkers such as acute-phase proteins, cytokines, chemokines, and leukocyte counts[1,7]. Acute markers like CRP are widely used, but may miss chronic, low-grade inflammation relevant to psychopathology, as infections or other acute physical illness could mask the presence of psychopathology-related chronic inflammation. The *soluble urokinase plasminogen activator receptor* (suPAR) reflects sustained immune activation and is associated with disease development, presence, and progression[8–10]; physical and cognitive decline[11,12]; accelerated aging[11]; and mortality[10,13,14]. Thus, suPAR levels are elevated across a wide range of diseases[13], including cardiovascular disease[15], diabetes[16,17,18] cancer[19,20], renal disease[21–23], infections[24,25], and in stress-related contexts[26–28]. Notably, in longitudinal cohorts (Dunedin, E-Risk), suPAR—unlike CRP or IL-6—captures inflammation linked to early-life adversity[27,29], stressful life events[26], and social isolation[30], including in individuals with otherwise low CRP and IL-6[27].

Although research is limited, several studies report elevated suPAR in psychiatric populations. Compared with healthy controls, higher levels of suPAR have been observed in patients with major depressive disorder (MDD)[31–33], psychotic episodes/disorder[33,34], schizophrenia[35,36], or a suicide attempt[31]. In a large cohort of

blood donors, both incident antidepressant use and hospital diagnosis of depression were associated with higher baseline suPAR[37]. Individuals with schizophrenia showed higher suPAR, even after adjusting for BMI, whereas CRP did not significantly differ between cases and controls[36]. suPAR also demonstrated superior discriminatory ability (AUC 0.92) compared with CRP (AUC 0.72, *p*=0.0053) when differentiating patients with attempted suicide from controls[31]. Our own work using data from the Dunedin Study, E-Risk, and a 29,000-patient Danish cohort found robust associations between PTSD and suPAR, while CRP and IL-6 showed inconsistent or no associations (Bourassa et al., in review). A recent meta-analysis (k=7 studies) reported no overall difference in suPAR between psychiatric cases and controls, likely due to small sample sizes, diagnostic heterogeneity, and methodological variation; notably, studies analyzing suPAR in plasma showed significant case–control differences whereas serum-based analyses did not[38]. However, some studies report null associations with schizophrenia[39], reduced suPAR in bipolar disorder[40], or insufficient adjustment for major confounders such as smoking[31,37]. Overall, existing findings—though mixed—suggest that suPAR may capture chronic inflammation relevant to multiple psychiatric disorders and could offer advantages over acute-phase markers in certain contexts.

This study will **test whether elevated suPAR is broadly associated with psychopathology and mental disorders** across six independent cohorts: (1) Dunedin (life-course mental health, suPAR at two timepoints); (2) E-Risk (life-course mental health and suPAR at age 18); (3–5) Danish population-based cohorts (Inter99, Health2006, CAMB; suPAR baseline and some with 5-year follow-up suPAR, registry-based diagnoses); and (6) the 29K suPAR acute medical cohort (suPAR at admission, registry-based diagnoses). In addition to our primary analysis of suPAR and mental disorders, a secondary analysis will assess CRP and IL-6 in parallel, enabling direct comparison of acute versus chronic inflammatory markers for psychiatric risk profiling. Thus, this study gives us the opportunity to test broad associations of suPAR with a variety of mental disorders in patients and community samples, to see if this could be a potential new marker for psychopathology-related inflammation compared to conventional markers of inflammation.

Hypotheses:

- Primary hypothesis: Elevated suPAR is associated with higher scores of the general psychopathology ("*p*") factor and with presence of mental disorders in both general population samples and unselected medical patients.
- Secondary hypothesis 1: Elevated suPAR shows non-specific associations with mental disorders, both when disorders are grouped into externalizing, internalizing, and thought disorder categories, and when examined individually.
- Secondary hypothesis 2: Improvements in mental health are associated with attenuated age-related increases in suPAR relative to individuals who maintain at-risk status.

Data analysis methods:

Cohorts:

- **Dunedin** (*The Dunedin Multidisciplinary Health and Development Study*; New Zealand): population-representative, life-course mental health, n=875 with suPAR at age 45, n=895 with suPAR at age 38.
- **E-Risk** (*The Environmental Risk Longitudinal Twin Study*; UK): life-course mental health, n=1447 with suPAR measured at age 18.
- **CAMB** (*Copenhagen Aging and Midlife Biobank*; Denmark): population-based, n=5484 with suPAR measured at baseline in 2009-2011; follow-up in national registries through 2022.

- **Inter99** (Denmark): population-based; n=5573 and n=2885 with suPAR at baseline and again at 5-year follow-up, respectively; baseline in 1999-2001, follow-up in national registries through 2022.
- **Health2006** (Denmark): population-based; n=3315 and n=2206 with suPAR measured at baseline and again at 5-year follow-up, respectively; baseline in 2006-2008, follow-up in national registries through 2022.
- **The 29K suPAR cohort** (Denmark): unselected acute medical patients, n=29,285; suPAR at admission; registry-based mental health data.

A P value < 0.05 is a priori designated as statistically significant. Bonferonni-corrected P levels will be reported.

Primary analyses: Is suPAR associated with mental health burden?

Aim 1a: Is elevated suPAR associated with higher *p* factor?
We will investigate cross-sectional associations between *p* factor and suPAR at age 45 in Dunedin and age 18 in E-Risk. Models will control for sex, BMI, and smoking, and models in E-Risk will account for clustering within family for twin pairs.

Aim 1b: Is elevated suPAR associated with any diagnoses of mental disorders in general populations?
We will test whether baseline suPAR is cross-sectionally associated with mental disorders in the past 10 years (using ICD-10 F-diagnoses recorded in the Danish National Patient Registry) in the three Danish population-based cohorts CAMB, Health2006, and Inter99. Models will control for age, sex, BMI, and smoking.

Aim 1c: Do acute medical patients with mental disorders have higher suPAR levels than patients without mental disorders?
We will test whether unselected acute medical patients with any diagnoses of mental disorders in the past 10 years (using ICD-10 F-diagnoses recorded in the Danish National Patient Registry) have higher suPAR levels than patients without mental disorders (patients without F-diagnoses). Models will control for age, sex, Charlson score, and infection at admission.

Sensitivity analyses (can be published in Supplement):
For the Danish cohorts (Aim 1b and Aim 1c), while mental diagnoses will be primarily ascertained using ICD-10 F diagnoses, we will also conduct sensitivity analyses using prescribed medication (ATC codes within chapters N05A, N05B, N06A, N06B, N06C) to ascertain mental disorders (at least 3 filled prescriptions within a chapter within the past 2 years), or a combination of ICD-10 codes and prescription data.

Additionally, for Aim 1c, a sensitivity analysis will compare patients with any F-diagnoses to a control group of patients with a Charlson score of 0 (i.e., no chronic illnesses).

Secondary analyses (can be published in Supplement):

Aim 2: Is elevated suPAR non-specifically associated with different mental disorders?
We will investigate cross-sectional associations between higher order factors (internalizing, externalizing, thought disorders) and suPAR at age 45 in Dunedin and age 18 in E-Risk with controls for sex, BMI, and smoking.

We will investigate cross-sectional associations between individual blocks of ICD-10 F-diagnoses or disease groups (e.g., mood disorders, substance use disorder, schizophrenia) and suPAR in the Danish population-based and patient cohorts, with controls for sex, age, Charlson score, BMI, and smoking. We will also

investigate cross-sectional associations between subgroups of psychiatric medication use and suPAR in the Danish population-based and patient cohorts, with controls for age, sex, Charlson score, BMI, and smoking where available.

In each case, we will run models in which the total number of cases is large enough to provide stable effect estimates (i.e., at least n=100 cases).

Aim 3: Is elevated suPAR associated with age of onset, persistence/recurrence, and comorbidities?
If elevated suPAR is found to be associated with *p* factor in the Dunedin Study, we will further test associations between suPAR at age 45 with age of onset, recurrence of mental disorders, and number of comorbidities, hypothesizing that elevated suPAR would be associated with earlier age of onset (longer duration of illness), more waves with presence of mental disorders, and with more comorbidities.

Similarly, in the Danish cohorts, we will test associations between suPAR and number of comorbidities.

Aim 4: Temporality: Does mental illness precede inflammation and/or does elevated inflammation precede mental illness?
In cohorts with two measurements of suPAR (the Dunedin Study, Health2006, and Inter99), we will test (A) whether mental illness at baseline (first measurement) is associated with elevated suPAR at follow-up assessment, and (B) vice versa, whether baseline suPAR is a prognostic factor for later mental disorder (increase in count of mental disorders/unique diagnoses from baseline to follow-up). This will be over a 7-year period in the Dunedin Study and a 5-year period in the Health2006 and Inter99 cohorts.

Aim 5: Are improvements in mental health associated with a decrease in suPAR (or a smaller age-related increase in suPAR) compared to individuals who maintained a high-risk status?
In cohorts with two measurements of suPAR and mental health diagnosis count (the Dunedin Study, Health2006, and Inter99), we will calculate change scores (Δ) for mental disorders and for suPAR (follow-up level – baseline level). The change in suPAR (ΔsuPAR) will be regressed on the change in mental disorders (ΔMH; e.g., based on number of different disorders at age 38 vs 45), controlling for the baseline level of each risk factor at baseline and sex. In this way, we will test the effect of how change in the number of psychiatric diagnoses might be associated with change in suPAR.

Aim 6: Co-twin analysis of p factor
In the E-Risk study, we will investigate whether the twin (within twin pairs) with higher p-factor also has higher suPAR, as well as whether this difference is similar between monozygotic (MZ) and dizygotic (DZ) twin pairs.

Aim 7: Is elevated CRP/IL-6 associated with mental disorders in general populations and acute medical patients?
To test the associations of mental disorders with conventional inflammation markers, we will perform parallel analyses of Aims 1a-1c, investigating associations of CRP and IL-6 with *p* factor, internalizing, externalizing, and thought disorders in Dunedin and E-Risk, and with mental disorders in the Danish population-based and patient cohorts.

Variables needed at which ages:

Dunedin	Mental health variables at <u>both</u> age 38 and 45: - *p* factor - Any mental health dx - Number of different mental health dx - Internalizing

	- Externalizing - Thought disorders - Age of onset of first mental disorder - Number of waves with mental disorders - Number of comorbidities - ADHD - Conduct disorder - Alcohol dependence - Tobacco dependence - Cannabis dependence - Drug dependence - Anxiety (GAD) - Depression (MDE) - Fears - Eating disorder - PTSD - OCD - Mania - Mood disorders - Schizophrenia Systemic inflammation: - suPAR, CRP, IL-6 Covariates: - Sex - BMI - Current smoking status
E-Risk	Mental health variables at age 18: - *p* factor - Internalizing - Externalizing - Thought disorders - ADHD - Conduct disorder - Alcohol dependence - Tobacco dependence - Cannabis dependence - Drug dependence - Anxiety (GAD) - Depression (MDE) - Fears - Eating disorder - PTSD - OCD - Mania - Mood disorders - Schizophrenia Systemic inflammation:

	- suPAR, CRP, IL-6 at age 18 Covariates: - Sex, BMI, current smoking status at age 18, clustering by family - Twin zygosity
29K suPAR CAMB Health2006 Inter99	Mental health variables at baseline/index admission and from the past 10 years: - Any F-diagnoses - F-diagnoses grouped by ICD-10 chapters: o F00-F09 Organic, including symptomatic, mental disorders o F10-F19 Mental and behavioural disorders due to psychoactive substance use o F20-F29 Schizophrenia, schizotypal and delusional disorders o F30-F39 Mood [affective] disorders o F40-F48 Neurotic, stress-related and somatoform disorders o F50-F59 Behavioural syndromes associated with physiological disturbances and physical factors o F60-F69 Disorders of adult personality and behaviour o F70-F79 Mental retardation o F80-F89 Disorders of psychological development o F90-F98 Behavioural and emotional disorders with onset usually occurring in childhood and adolescence o F99-F99 Unspecified mental disorder - ATC codes for psycholeptics: o N05A Antipsychotics o N05B Anxiolytics o N06A Antidepressants o N06B Psychostimulants, agents used for ADHD and nootropics o N06C Psycholeptics and psychoanaleptics in combination *Note: Not including N05C (Hypnotics and sedatives) or N06D (Anti-dementia drugs) from chapters N05 and N06.* Systemic inflammation: - suPAR and CRP at baseline and follow-up (for Inter99 and Health2006) Covariates: - Sex, age, Charlson score - BMI and smoking (not available for patient cohort)

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

This study will extend our understanding of the biomarker suPAR by investigating its associations with psychopathology five community samples of population-representative young, midlife, and older adults and one large clinical sample of unselected acute medical patients. Notably, the inclusion of three cohorts with multiple assessments of suPAR will allow for analyses of change in those cohorts.

By comparing the widely used inflammation markers CRP and IL-6 with the novel inflammation marker suPAR in these independent population-/patient-based cohorts using both cross-sectional and longitudinal data, we hope to advance our knowledge of the usefulness of these biomarkers to assess psychopathology-related inflammation, by introducing suPAR as a more reliable biomarker of inflammation to a field that has

relied on other inflammation markers like CRP and IL-6.

If elevated suPAR is robustly correlated with mental disorders across these independent cohorts, there are several potential applications for suPAR in the field of psychiatry, including addition of suPAR in basic science studies of inflammation in psychopathology or in intervention studies that seek to reduce psychopathology-related inflammation, as well as clinical assessment of suPAR in patients with mental disorders to assess chronic inflammation level and the risk of comorbidity.

References cited:

1. Upthegrove, R., Corsi-Zuelli, F., Couch, A. C. M., Barnes, N. M. & Vernon, A. C. Current Position and Future Direction of Inflammation in Neuropsychiatric Disorders: A Review. *JAMA Psychiatry* (2025) doi:10.1001/jamapsychiatry.2025.1369.
2. Howren, M. B., Lamkin, D. M. & Suls, J. Associations of depression with C-reactive protein, IL-1, and IL-6: A meta-analysis. *Psychosom. Med.* **71**, 171–186 (2009).
3. Osimo, E. F., Baxter, L. J., Lewis, G., Jones, P. B. & Khandaker, G. M. Prevalence of low-grade inflammation in depression: A systematic review and meta-Analysis of CRP levels. *Psychological Medicine* vol. 49 1958–1970 Preprint at https://doi.org/10.1017/S0033291719001454 (2019).
4. Miller, A. H. Beyond depression: the expanding role of inflammation in psychiatric disorders. *World Psychiatry* **19**, 108–109 (2020).
5. Yuan, N., Chen, Y., Xia, Y., Dai, J. & Liu, C. Inflammation-related biomarkers in major psychiatric disorders: a cross-disorder assessment of reproducibility and specificity in 43 meta-analyses. *Transl. Psychiatry* **9**, 233 (2019).
6. Speer, K., Upton, D., Semple, S. & McKune, A. Systemic low-grade inflammation in post-traumatic stress disorder: a systematic review. *J. Inflamm. Res.* **Volume 11**, 111–121 (2018).
7. Osimo, E. F. *et al.* Inflammatory markers in depression: A meta-analysis of mean differences and variability in 5,166 patients and 5,083 controls. *Brain. Behav. Immun.* **87**, 901–909 (2020).
8. 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).
9. Rasmussen, L. J. H., Petersen, J. E. V. & Eugen-Olsen, J. Soluble Urokinase Plasminogen Activator Receptor (suPAR) as a Biomarker of Systemic Chronic Inflammation. *Front. Immunol.* **12**, 780641 (2021).
10. 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).
11. Rasmussen, L. J. H. *et al.* Association Between Elevated suPAR, a New Biomarker of Inflammation, and Accelerated Aging. *J. Gerontol. Ser. A* **76**, 318–327 (2021).
12. Shell, A., Vize, C., Gianaros, P., Rasmussen, L. J. H. & Marsland, A. L. Executive function and soluble urokinase-type plasminogen activator receptor (suPAR): a longitudinal study of midlife adults. *Brain. Behav. Immun.* **129**, 537–546 (2025).
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. Bahrami, H. S. Z. *et al.* Soluble urokinase plasminogen activator receptor and interleukin-6 improves prediction of all-cause mortality and major adverse cardiovascular events in Type 1 diabetes. *J. Intern. Med.* joim.20108 (2025) doi:10.1111/joim.20108.
15. Yadalam, A. K. *et al.* Proteomics-Based Soluble Urokinase Plasminogen Activator Receptor Levels and Long-Term Cardiovascular Outcomes in Survivors of Breast Cancer: A UK Biobank Study. *J. Am. Heart Assoc.* **14**, e039728 (2025).
16. Guthoff, M. *et al.* Soluble urokinase receptor (suPAR) predicts microalbuminuria in patients at risk for type 2 diabetes mellitus. *Sci. Rep.* **7**, 40627 (2017).
17. Theilade, S. *et al.* Soluble urokinase plasminogen activator receptor levels are elevated and associated with complications in patients with type 1 diabetes. *J. Intern. Med.* **277**, 362–371 (2015).
18. Guthoff, M. *et al.* Soluble urokinase receptor (suPAR) predicts microalbuminuria in patients at risk for type 2 diabetes mellitus. *Sci. Rep.* **7**, 40627 (2017).
19. Loosen, S. H. *et al.* High baseline soluble urokinase plasminogen activator receptor (suPAR) serum levels indicate adverse outcome after resection of pancreatic adenocarcinoma. *Carcinogenesis* 1–9 (2019) doi:10.1093/carcin/bgz033.
20. Tarpgaard, L. S. *et al.* Intact and cleaved plasma soluble urokinase receptor in patients with metastatic colorectal cancer treated with oxaliplatin with or without cetuximab. *Int. J. Cancer* **137**, 2470–7 (2015).
21. Hayek, S. S. *et al.* Soluble Urokinase Receptor and Acute Kidney Injury. *N. Engl. J. Med.* **382**, 416–426 (2020).
22. Hayek, S. S. *et al.* Soluble Urokinase Receptor and Chronic Kidney Disease. *N. Engl. J. Med.* **373**, 1916–1925 (2015).
23. Iversen, E. *et al.* Elevated suPAR Is an Independent Risk Marker for Incident Kidney Disease in Acute Medical Patients. *Front. Cell Dev. Biol.* **8**, 339 (2020).
24. Donadello, K., Scolletta, S., Covajes, C. & Vincent, J. L. suPAR as a prognostic biomarker in sepsis. *BMC Med.* **10**, 2 (2012).
25. Rovina, N. *et al.* Soluble urokinase plasminogen activator receptor (suPAR) as an early predictor of severe respiratory failure in patients with COVID-19 pneumonia. *Crit. Care* **24**, 4–6 (2020).
26. Bourassa, K. J. *et al.* Linking stressful life events and chronic inflammation using suPAR (soluble urokinase plasminogen

activator receptor). *Brain. Behav. Immun.* **97**, 79–88 (2021).
27. Rasmussen, L. J. H. *et al.* Association of Adverse Experiences and Exposure to Violence in Childhood and Adolescence With Inflammatory Burden in Young People. *JAMA Pediatr.* **174**, 38 (2020).
28. Murphy, J. *et al.* Developmental stage of childhood trauma exposure and markers of inflammation at age 24. *Brain. Behav. Immun.* **126**, 225–234 (2025).
29. Rasmussen, L. J. H. *et al.* Cumulative childhood risk is associated with a new measure of chronic inflammation in adulthood. *J. Child Psychol. Psychiatry* **60**, 199–208 (2019).
30. Matthews, T. *et al.* Social isolation, loneliness, and inflammation: A multi-cohort investigation in early and mid-adulthood. *Brain. Behav. Immun.* **115**, 727–736 (2024).
31. Ventorp, F., Gustafsson, A., Träskman-Bendz, L., Westrin, Å. & Ljunggren, L. Increased Soluble Urokinase-Type Plasminogen Activator Receptor (suPAR) Levels in Plasma of Suicide Attempters. *PLOS ONE* **10**, e0140052 (2015).
32. Gustafsson, A. *et al.* Effects of Acute Exercise on Circulating Soluble Form of the Urokinase Receptor in Patients With Major Depressive Disorder. *Biomark. Insights* **12**, 117727191770419 (2017).
33. Mongan, D. *et al.* Associations between plasma inflammatory markers and psychotic disorder, depressive disorder and generalised anxiety disorder in early adulthood: A nested case-control study. *Brain. Behav. Immun.* **111**, 90–100 (2023).
34. Trotta, A. *et al.* Associations between childhood victimization, inflammatory biomarkers and psychotic phenomena in adolescence: A longitudinal cohort study. *Brain. Behav. Immun.* **98**, 74–85 (2021).
35. Nielsen, J. *et al.* Soluble Urokinase-Type Plasminogen Activator Receptor Levels in Patients With Schizophrenia. *Schizophr. Bull.* **41**, 764–771 (2015).
36. Bigseth, T. T. *et al.* Elevated levels of soluble urokinase plasminogen activator receptor as a low-grade inflammation marker in schizophrenia: A case-control study. *Schizophr. Res.* **228**, 190–192 (2021).
37. Haastrup, E. *et al.* Soluble Urokinase Plasminogen Activator Receptor as a Marker for Use of Antidepressants. *PLoS ONE* **9**, e110555 (2014).
38. Murphy, J. *et al.* Associations between soluble urokinase plasminogen activator receptor (suPAR) concentration and psychiatric disorders – A systematic review and meta-analysis. *Brain. Behav. Immun.* **120**, 327–338 (2024).
39. Genc, A. *et al.* Serum soluble urokinase-type plasminogen activator receptor levels in male patients with acute exacerbation of schizophrenia. *Psychiatry Res.* **236**, 179–181 (2016).
40. Ozpercin, P. U. *et al.* Decreased circulating urokinase plasminogen activator receptor (uPAR) concentration in acute episodes of bipolar disorder; could it be a reflection of axonal injury? *Psychoneuroendocrinology* **90**, 122–126 (2018).