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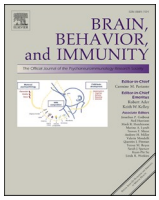

PTSD and suPAR: A multicohort investigation of chronic inflammation

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ABSTRACT

Posttraumatic stress disorder (PTSD) is associated with poor health. Prior research has shown stressful events are associated with inflammatory biomarkers, such as soluble urokinase plasminogen activator receptor (suPAR), suggesting systemic chronic inflammation could be a mechanism linking adversity to poor health. In this study, we examined associations of PTSD and suPAR in two research cohorts—the E-Risk Study (United Kingdom; n = 1,389) and the Dunedin Multidisciplinary Health and Development Study (New Zealand; n = 927)—and a clinical cohort of medical patients (Denmark; n = 29,285). We also present results from two commonly assessed inflammatory biomarkers: C-reactive protein (CRP) and interleukin-6 (IL-6). People with a lifetime history of PTSD had higher suPAR at age 18 in E-Risk ($\beta = 0.21$, $p = 0.046$) and age 38 in the Dunedin Study ($\beta = 0.23$, $p = 0.025$), but not age 45 in the Dunedin Study ($\beta = 0.18$, $p = 0.050$). Individuals who developed PTSD in the year prior to age 45 in Dunedin had significant increases in suPAR from age 38 to 45 ($\beta = 0.45$, $p = 0.034$). Danish patients with a recent diagnosis of PTSD or a stress-related psychiatric disorder had higher levels of suPAR compared to propensity score-matched patients without such diagnoses ($0.10 < \beta s < 0.24$, $ps < 0.05$). CRP and IL-6 did not show consistent associations with PTSD. These results suggest that PTSD is associated with suPAR and that systemic chronic inflammation could help explain how trauma and PTSD might result in poor health.

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1. Introduction

The experience of stress and adversity is associated with poor health (Cohen et al., 2007; Richardson et al., 2012), chronic disease, and premature mortality (Bourassa, 2021; Glaser et al., 1999; Phillips et al., 2001). These associations extend to particularly challenging stressors, such as exposure to trauma and the development of posttraumatic stress disorder (PTSD; Boscarino, 2008; Nilaweera et al., 2023). Numerous physiological mechanisms that have been shown to link adversity and ill health, including cardiovascular functioning (Beristianos et al., 2016; Bourassa et al., 2021a; Ebrahimi et al., 2021; Padhi et al., 2024; Rosenbaum et al., 2015), biological aging (Bourassa et al., 2024; Bourassa et al., 2023; Wolf & Morrison, 2017), and systemic inflammation (Bourassa et al., 2021b; Marsland et al., 2017; Passos et al., 2015; Peruzzolo et al., 2022; Yang & Jiang, 2020). Characterizing the contributions of the pathways that link PTSD to poor health would provide targets to improve outcomes for people who experience adversity (Bourassa & Sbarra, 2024).

Systemic inflammation is hypothesized to be a particularly relevant pathway linking trauma and PTSD to health (Marsland et al., 2017; Sapolsky et al., 2000; Wirtz, & von Känel, 2017). The experience of chronic psychological stress is thought to promote inflammatory profiles through dysregulation of the hypothalamic–pituitary–adrenal (HPA) axis (Guilliams and Edwards, 2010). For example, stress and adversity could impact glucocorticoids or cortisol production (Castro-Vale et al., 2016; Pan et al., 2018; Szeszko et al., 2018) or receptor sensitivity with downstream impacts on immune function. Chronic stress has also been linked to sympathetic nervous system changes relevant to future diseases (Heidt et al., 2014). This physiological dysregulation could extend to PTSD (Jones & Moller, 2011; Sarapultsev et al., 2020) and account, at least in part, for associations between PTSD and cardiovascular disease (Wirtz, & von Känel, 2017). PTSD is also associated with changes in health behaviors such as smoking, diet, and physical activity that could impact inflammation (van den Berk-Clark et al., 2018). Alternatively, it is possible that increased inflammation reflects genetic predisposition to PTSD present among individuals who develop PTSD after experiencing trauma (Katrinli et al., 2022).

Although PTSD has been linked to systemic inflammation (Jones & Moller, 2011; Sarapultsev et al., 2020), there are many biomarkers that can be used to assess systemic inflammation, each with their own strengths and weaknesses. For example, C-reactive protein (CRP) and interleukin-6 (IL-6) have been used in a number of studies linking adversity and inflammation, though these markers can be affected by acute health conditions, which could obscure associations with chronic stress. For example, two recent studies did not find consistent associations of IL-6 nor CRP with stressful life events (Bourassa et al., 2021b) or social isolation (Matthews et al., 2024). However, these studies did find associations with a relatively novel biomarker of chronic systemic inflammation, soluble urokinase plasminogen activator receptor (suPAR). suPAR is the soluble form of the membrane-bound receptor uPAR, which is cleaved from the surface of immune cells and other cell types during immune activation and states of inflammation and released to the bloodstream (Rasmussen et al., 2021b). Compared to biomarkers like CRP and IL-6, suPAR is less reactive to acute infections and conditions (Desmedt et al., 2017; Lyngbæk et al., 2013; Rasmussen et al., 2021b). For example, suPAR has a lower diagnostic value than CRP for predicting sepsis, but a stronger prognostic value for predicting mortality among sepsis patients (Donadello et al., 2014). Similarly, suPAR shows less dramatic increases to acute inflammatory stimuli such as myocardial infarction, knee surgery, or traumatic injury (Langkilde et al., 2017; Lyngbæk et al., 2012; Timmermans et al., 2015) compared to other inflammation markers (e.g., IL-6, IL-10, and CRP). The practical availability of suPAR (it can be measured in plasma or serum using standard immunoassays) along with its stability may be useful when testing associations with psychological trauma or PTSD, where associations for inflammatory markers more sensitive to acute health conditions might be obscured, particularly in patient populations at risk of poor health. To our knowledge, however, no studies have extended recent findings linking adversity to suPAR (Bourassa et al; 2021b; Matthews et al., 2024) to study PTSD.

1.1. Present Study

In the current study, we tested whether PTSD was associated with greater systemic chronic inflammation using suPAR in two research cohorts—the Environmental Risk (E-Risk) Longitudinal Twin Study (n = 1,389) and the Dunedin Multidisciplinary Health and Development Study (Dunedin Study; n = 927)—and a clinical cohort of medical patients from Hvidovre Hospital (n = 29,285). Models included associations at age 18 in E-Risk, age 38 and 45 in the Dunedin Study, and changes in inflammation from age 38 to 45 in the Dunedin Study. We then examined associations among patients from the Hvidovre Hospital cohort based on the presence of a PTSD or stress-related psychiatric diagnosis using a propensity score matching approach. We also investigated associations for CRP and IL-6 in the E-Risk and Dunedin studies, and CRP in the Hvidovre Hospital cohort.

2. Methods

2.1. Participants

Participants were members of the E-Risk Study (n = 1,389), Dunedin Study (n = 927), or Hvidovre Hospital cohort (n = 29,285).

2.1.1. E-risk Study

The E-Risk Longitudinal Twin Study has tracked the development of a 1994–95 birth cohort of 2,232 British children (Moffitt & E-Risk Study Team, 2002). Briefly, the E-Risk sample was constructed in 1999–2000, when 1,116 families (93 % of those eligible) with same-sex 5-year-old twins participated in home-visit assessments. This sample comprised 56 % monozygotic (MZ) and 44 % dizygotic (DZ) twin pairs; sex was evenly distributed within zygosity (49 % male). The sample represents socioeconomic conditions in Great Britain (Odgers et al., 2012). Assessments were performed during five home visits from age 5 to 18 years. The Joint South London and Maudsley and the Institute of Psychiatry Research Ethics Committee approved each phase of the Study. Parents gave informed consent and twins gave assent between 5–12 years and informed consent at age 18. Venous blood was collected with EDTA tubes. Tubes were spun at 2500 x g for 10 min, and plasma samples obtained. Samples were stored at − 80 °C until batch analysis after inclusion of all participants. Our study included participants who had plasma assayed for suPAR and had been assessed for PTSD at age 18 (n = 1,389).

2.1.2. Dunedin longitudinal Study

The Dunedin Study is an ongoing longitudinal investigation of health and behavior in a birth cohort with the most recent study occasion at age 45. The cohort comprised all individuals born between April 1, 1972, and March 31, 1973, in Dunedin, New Zealand, who were eligible based on residence in the province of Otago and participation in the first assessment at 3 years of age (Poulton et al., 2022). Study participants are primarily of New Zealand European ethnicity; 8.6 % reported Māori ethnicity at age 45. Assessments were performed at fourteen visits from birth to age 45. Informed consent was obtained from participants, and protocols were approved by the Health and Disability Ethics Committee at the New Zealand Ministry of Health and Duke University Institutional Review Board. Venous blood was collected with EDTA or serum separator tubes. Tubes were spun at 3500 RPM for 10 min, and plasma or serum samples obtained, respectively. Samples were stored at − 80 °C until batch analysis. Our study included participants who had plasma assayed for suPAR and had PTSD measured at age 38 or 45 (n = 927).

2.1.3. Hvidovre Hospital cohort

The Hvidovre Hospital Cohort (also known as the suPAR-29 K Cohort) is a retrospective, observational, registry-based cohort of all patients (n = 29,285, average age = 59.9 years) who were admitted to the Acute Medical Unit of the Emergency Department, Copenhagen University Hospital Hvidovre between 18 November 2013 and 17 March 2017 and had suPAR measured at admission as part of routine blood-work analyzed in fresh plasma samples (Bengaard et al. 2022; Iversen et al. 2020). The Emergency Department received unselected, adult internal medicine patients of all specialties, except for patients suspected of gastroenterological diseases and obstetric patients. The index admission was defined as the first recorded admission with a suPAR measurement available. Data on suPAR and CRP were extracted from the electronic hospital database LABKA via the Department of Clinical Biochemistry. ICD-10 codes from the decade prior to the index admission were extracted from the Danish National Patient Registry, including primary cause of admission, comorbid conditions, and past diagnoses from both somatic and psychiatric visits. The study was approved by the Danish Data Protection Agency (ref. HVH-2014–018, 02767) and the Danish Health and Medicines Authority (ref. 3–3013-1061/1).

2.2. Measures

2.2.1. Inflammation

2.2.1.1. suPAR (ng/mL). Plasma suPAR was analyzed at age 18 in E-Risk, at age 38 and 45 in the Dunedin Study, and at admission as part of routine analysis in the Hvidovre Hospital Cohort, using the suPARnostic AUTO Flex ELISA (ViroGates A/S, Birkerød, Denmark) according to the manufacturer's instructions as previously described (Iversen et al. 2020; Rasmussen et al., 2020; Rasmussen et al., 2021b). The lower detection limit of the assay was 0.1 ng/mL. Two values in Dunedin at age 45 were excluded due to suPAR values > 9 SD above the mean, likely as these participants had kidney disease and were receiving dialysis treatment (Rasmussen et al., 2021a). In E-Risk, both the inter- and intra-assay coefficient of variation (CV) were 6 %. In the Dunedin Study, the intra-assay correlation of repeat measurements of the same sample was $r = 0.98$ and CV = 2.4 %, and the inter-assay correlation was $r = 0.81$ and CV = 12.8 %. In the Hvidovre Hospital cohort, the inter-assay CV was 5.1 %. suPAR values were log2-transformed in the Hvidovre Hospital cohort to account for skewness.

2.2.1.2. High-sensitivity CRP (hsCRP; mg/L). In E-Risk, plasma high-sensitivity CRP (hsCRP) was measured using Quantikine ELISA Kit DCRP00 (R&D Systems, Minneapolis, MN) following the manufacturer's instructions. Both the inter- and intra-assay CVs were 5.6 %, and the mean minimum detectable dose was 0.010 ng/mL. In the Dunedin Study, serum hsCRP was measured on a Modular P analyzer (Roche Diagnostics GmbH, Mannheim, Germany) at age 38 and on a Cobas c 702 analyzer (Roche Diagnostics GmbH) at age 45, using particle-enhanced immunoturbidimetric assays. The intra- and inter-assay CVs reported by the manufacturer were 0.28–1.34 % and 2.51–5.70 %, respectively, and the lower detection limit of the assay was 0.3 mg/L. In the Hvidovre Hospital cohort, plasma hsCRP was routinely analyzed at the Department of Clinical Biochemistry, Copenhagen University Hospital Hvidovre, using a Cobas 6000 analyzer (Roche Diagnostics GmbH, Mannheim, Germany). The lower detection limit of the assay was 0.3 mg/L. CRP scores were log transformed within each cohort and assessment to account for skew.

2.2.1.3. IL-6 (pg/mL). In E-Risk, plasma IL-6 was measured using Quantikine HS ELISA Kit HS600C (R&D Systems) following the manufacturer's instructions. The CV was 12.6 %, and the mean minimum detectable dose of the ELISA kit was 0.031 pg/mL. In the Dunedin Study at age 38, plasma IL-6 was measured on a Molecular Devices (Sunnyvale, CA) SpectraMax plus 384 plate reader using R&D Systems (Minneapolis, MN) Quantikine High-sensitivity ELISA kit HS600B according to the manufacturer's instructions. The mean intra- and inter-assay CVs reported by the manufacturer were 7.4 % and 7.8 %, respectively, and the mean minimum detectable dose was 0.039 pg/mL. At age 45, serum IL-6 was measured on a Cobas e 602 analyzer (Roche Diagnostics GmbH), using an electrochemiluminescence immunoassay. The intra- and inter-assay CVs reported by the manufacturer were 2.5–6.0 % and 2.9–8.5 %, respectively, and the lower detection limit of the assay was 1.5 pg/mL. IL-6 scores were log transformed within each cohort and assessment to account for skew. The Hvidovre Hospital Cohort did not assess IL-6.

2.2.2. Posttraumatic stress disorder (PTSD)

In the E-Risk and Dunedin studies, lifetime PTSD was ascertained using the Diagnostic Interview Schedule (Robins, Cottler, Bucholz, & Compton, 1995) administered by staff who underwent 2 weeks of training: health professionals and clinical psychology students, as previously described (Caspi et al., 2024; Schaefer et al., 2018)." DSM diagnoses were based on symptom algorithms and impairment ratings, but also incorporated standardized teacher, parent, or informant reports as developmentally appropriate; psychiatrists' review of interviewers' case notes; pharmacists' medication review; and staff ratings of symptoms observed. In E-Risk, clinical interviews used DSM-5 diagnostic criteria. In the Dunedin Study, PTSD was assessed at age 38 according to then current versions of DSM-IV and at age 45 according to the DSM-5. E-Risk data also included diagnoses using DSM-IV criteria; sensitivity analyses using these criteria are presented in Supplemental Analysis 1. In both studies, participants were first asked whether they experienced a trauma and were interviewed on their symptoms related to the traumatic experience that most affected them since the last assessment. In the Hvidovre Hospital Cohort, presence of PTSD and stress-related psychiatric diagnoses were ascertained using ICD-10 codes (F43.1 and F43.X, respectively) over two timespans: one year and five years prior to admission.

2.2.3. Trauma exposure

In E-Risk, participants' report of lifetime trauma exposure was assessed at age 18 as part of the PTSD assessment. In Dunedin, trauma exposure was assessed using participants' recall of prior traumatic experiences reported at age 38 and 45 during the PTSD assessment. These reports were used to code participants as having been exposed to trauma across the lifetime. The Hvidovre Hospital Cohort did not assess trauma exposure.

2.2.4. Study covariates

A number of covariates were included in our models.

2.2.4.1. Demographics. Participants' parents reported their sex at birth in the E-Risk and Dunedin cohorts. In the Hvidovre Hospital Cohort, information on sex and age were obtained from the Danish Civil Registration System.

2.2.4.2. Smoking. In the E-Risk and the Dunedin Studies, participants' self-reported current and past daily smoking status was used to create a measure of smoking behavior (0 = current smoking, 1 = past smoking, or 2 = never smoked). The Hvidovre Hospital Cohort did not assess smoking.

2.2.4.3. Body mass index (BMI). In the E-Risk and Dunedin studies, body mass index (kg/m^2) was assessed using the standard formula applied to height and weight. The Hvidovre Hospital Cohort did not assess BMI.

2.2.4.4. Anti-inflammatory medication. In the E-Risk (at age 18) and Dunedin studies (age 38 and 45), participants were assessed for recent

anti-inflammatory medications use, including non-steroidal anti-inflammatory drugs (NSAIDs), anti-gout medication, corticosteroids (respiratory, systemic), anti-rheumatics, prophylactic aspirin, and statins. The Hvidovre Hospital Cohort did not assess anti-inflammatory medication use.

2.2.4.5. Medical covariates. The Hvidovre Hospital Cohort included two medical covariates: Charlson Comorbidity Index (CCI) and presence of a recent infection during index admission. The CCI was used to create a score of disease burden due to medical comorbidities, based on concurrent ICD-10 diagnoses on a per-patient basis, with updated weights as defined by Quan and colleagues (2011). All primary and secondary diagnoses registered in the National Patient Registry for the past 10 years before and including the index admission were used to calculate the score. Infection during index admission was identified as primary or secondary infection diagnoses (see Supplemental Text 1 for ICD-10 codes used to indicate infection; Yang et al., 2020) during the index admission.

2.3. Data analysis

We first tested the cross-sectional associations between lifetime PTSD and suPAR in the two research cohorts—at age 18 in E-Risk and at age 38 and 45 in the Dunedin Study. We also examined whether suPAR increased from age 38 to 45 among Dunedin Study participants who received a PTSD diagnosis using a residualized regression approach. Models in both studies used robust maximum likelihood (MLR) estimation. We next examined suPAR levels in the individuals with PTSD and stress-related psychiatric disorders diagnoses (over the last year and last 5 years) in the Hvidovre Hospital clinical cohort using propensity score-matched samples to account for differences in the age based on PTSD status. Propensity scoring was conducted using the *matchit* function in R with nearest neighbor matching and a 1 case (PTSD [F43.1] or stress-related diagnostic code [F43.X]) to 3 controls ratio (no PTSD or stress-related diagnostic code) accounting for age and sex. This resulted in 4 sub-cohorts (individuals with: 1.) PTSD in the last year, 2.) PTSD in the last 5 years, 3.) stress-related diagnosis in the last year, 4.) stress-related diagnosis in the last 5 years, each matched to controls in a 3:1 ratio). Similar approaches were used to assess CRP in all three cohorts. E-Risk and Dunedin Study models also tested IL-6 as an outcome, examined associations for lifetime trauma exposure, and tested differences between current and lifetime PTSD using multiple regression.

Models in E-Risk and the Dunedin Study were adjusted for sex, BMI, smoking, and anti-inflammatory medications. E-Risk models also controlled for zygosity by accounting for shared variance in twins using a sandwich estimator. Hvidovre Hospital Cohort models adjusted for sex, age, Charlson score, and infection status at admission, and confidence intervals were estimated using nonparametric bootstrapping with 10,000 repetitions. Estimates are reported as standardized β values to allow comparisons of effect sizes for the individual inflammatory biomarkers. Models using E-Risk and the Dunedin Study data were run in MPLUS version 8.3, whereas Hvidovre Hospital Cohort data were run in R Studio version 2023.12.1. All analyses were checked for reproducibility by independent data analysts, who used the manuscript to recreate the statistical code and applied it to a fresh copy of each dataset.

3. Results

We examined associations between PTSD and systemic chronic inflammation in the E-Risk (age 18) and Dunedin (age 38 and 45) studies, as well as in the Hvidovre Hospital using propensity scoring. Supplemental Tables 1 and 2 present demographic characteristics for the three cohorts and the propensity score-matched subsamples in the Hvidovre Hospital cohort.

3.1. Research Cohorts: E-risk and Dunedin Study

3.1.1. E-risk Study (Age 18)

In the E-Risk Study, young adults who had a lifetime history of PTSD showed higher levels of suPAR at age 18 (β = 0.21, 95 % CI [0.00, 0.39], $p = 0.046$; Table 1).

3.1.2. Dunedin Study (Age 38 and 45)

In the Dunedin study, adults with a lifetime history of PTSD showed higher suPAR levels (Fig. 2) at age 38 (β = 0.23, 95 % CI [0.02, 0.45], $p = 0.025$), but not at age 45 (β = 0.18, 95 % CI [-0.00, 0.37], $p = 0.050$).

3.1.3. Dunedin Study: Change in suPAR from age 38 to 45

People diagnosed with PTSD in the year prior to the age 45 assessment showed a significant increase in their suPAR between age 38 and 45 (β = 0.45, 95 % CI [0.04, 0.85], $p = 0.034$). This association was not significant when including participants who developed PTSD in the period between age 38 and 45, but did not meet criteria for PTSD in the past year (β = 0.26, 95 % CI [-0.04, 0.57], $p = 0.096$). Both models accounted for lifetime history of PTSD prior to age 38 and suPAR levels at age 38.

3.2. Clinical Cohort: Acutely admitted medical patients from Hvidovre Hospital

We next investigated suPAR levels among acutely admitted medical patients at the Emergency Department at Hvidovre Hospital in Denmark. Patients with a PTSD or stress-related diagnosis were compared to patients without those diagnoses using propensity score matching (1:3 matching on age and sex). Patients with a diagnosis of PTSD in the last year (β = 0.24, 95 % CI [0.01, 0.47], $p = 0.040$) and five years (β = 0.15, 95 % CI [0.00, 0.30], $p = 0.042$) had higher levels of suPAR. Patients also had higher levels of suPAR if they had a stress-related psychiatric diagnosis in the last year (β = 0.10, 95 % CI [0.01,

Table 1
Association of suPAR with trauma and PTSD.

Associations with suPAR	Diagnostic status		Bivariate association		Accounting for covariates	
	PTSD	No PTSD	β	95 % CI	β	95 % CI
E-Risk Study cohort						
PTSD (age 18)	*n* = 113	*n* = 1,276	0.51**	[0.27, 0.74]	0.21*	[0.00, 0.42]
Dunedin Study cohort						
PTSD (age 38)	*n* = 145	*n* = 782	0.44**	[0.20, 0.68]	0.23*	[0.02, 0.45]
PTSD (age 45)	*n* = 170	*n* = 757	0.39**	[0.18, 0.59]	0.18	[-0.00, 0.37]
Hvidovre Hospital cohort						
PTSD, past year	*n* = 79	*n* = 237	0.24	[-0.01, 0.50]	0.24*	[0.01, 0.47]
PTSD, past 5 years	*n* = 199	*n* = 597	0.15	[-0.01, 0.31]	0.15*	[0.00, 0.30]
Stress-related Dx, past year	*n* = 559	*n* = 1,677	0.07	[-0.02, 0.17]	0.10*	[0.01, 0.18]
Stress-related Dx, past 5 years	*n* = 1,385	*n* = 4,155	0.12**	[0.06, 0.18]	0.14**	[0.08, 0.19]

Note: E-risk and Dunedin Study models adjusted for demographic covariates included sex, body mass index, anti-inflammatory medication use, and smoking status. E-Risk models also accounted for zygosity and used a sandwich estimator to adjust for shared variance among twin pairs. Hvidovre Hospital cohort models adjusted for sex, age, Charlson comorbidity index scores, and infection status. CI = confidence interval; Dx = diagnosis; PTSD = posttraumatic stress disorder; suPAR = soluble urokinase plasminogen activator receptor. * $p < 0.05$. ** $p < 0.01$.

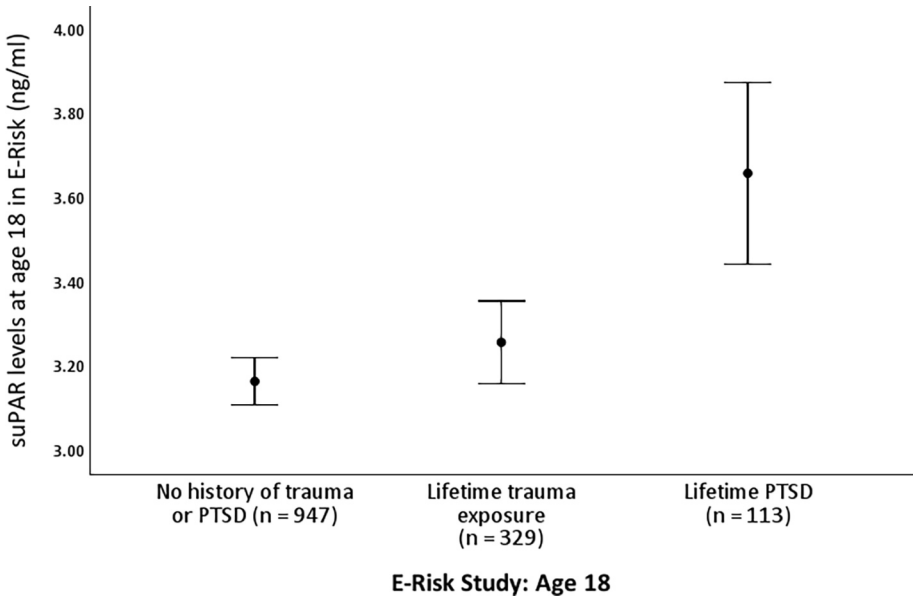

Fig. 1. Mean levels of suPAR by trauma and PTSD status at age 18 in the E-Risk Study. PTSD = posttraumatic stress disorder; suPAR = soluble urokinase plasminogen activator receptor. Bars represent 95 % confidence intervals.

0.18], $p = 0.023$) or five years (β = 0.14, 95 % CI [0.08, 0.19], $p < 0.001$). Results from the full cohort are presented in Supplemental **Analysis 2**.

3.3. Analyses with CRP and IL-6

When examining the associations with CRP and IL-6, neither inflammatory biomarker was consistently associated with PTSD in the E-Risk and Dunedin cohorts. PTSD was significantly associated with CRP at age 38 in the Dunedin Study, but no association was present at age 45 in Dunedin or in E-Risk at age 18. No statistically significant associations were observed for IL-6. PTSD between ages 38 and 45 also was not associated with changes in CRP or IL-6 in the Dunedin Study. In the Hvidovre Hospital Cohort, no statistically significant associations were observed between CRP and PTSD. CRP was associated with stress-related psychiatric diagnoses, however, associations were in the opposite direction of what would be expected—patients with a stress-related psychiatric diagnosis had *lower* CRP levels, though the associations were no longer significant after adjusting for chronic disease burden and infection status. Supplemental Table 3 presents the full results for CRP and IL-6.

3.4. Secondary Analysis: Associations with trauma in the e-risk and Dunedin studies

In the E-Risk Study, young adults who had a lifetime history of trauma did not have significantly higher levels of suPAR at age 18 (β = 0.09, 95 % CI [-0.02, 0.19], $p = 0.099$). In the Dunedin study, adults with a lifetime history of trauma had significantly higher suPAR at age 38 (β = 0.17, 95 % CI [0.05, 0.28], $p = 0.003$), but not at age 45 (β = 0.09, 95 % CI [-0.03, 0.19], $p = 0.125$). Full results for trauma exposure are presented in Supplemental Table 4. suPAR levels are illustrated for individuals with trauma and PTSD in E-Risk (Fig. 1) and the Dunedin Study (Fig. 2). Boxplots are presented in Supplemental Fig. 1.

3.5. Secondary Analysis: Comparing current and lifetime PTSD in the e-risk and Dunedin studies

When comparing current and past PTSD diagnoses, there was no significant difference in suPAR at age 18 in the E-Risk study or age 38 in the Dunedin Study. However, individuals with PTSD in the last year in the Dunedin Study had significantly higher suPAR compared to individuals with PTSD in the past (β = 0.61, 95 % CI [0.24, 1.15], $p = 0.003$). Full results are included in Supplemental **Analysis 3.**

4. Discussion

Across three independent cohorts, we found that people with a history of PTSD had higher levels of systemic chronic inflammation, as assessed by suPAR. This included young adults from England and Wales at age 18, New Zealanders assessed in midlife at ages 38 and 45, and a clinical sample of Danish patients admitted to an emergency hospital setting. These associations were largely robust to adjustments for demographic and clinical covariates and had notably similar magnitudes of associations across the three cohorts (Fig. 3). Beyond cross-sectional associations, we also found a longitudinal association in the Dunedin Study—individuals who met criteria for recent PTSD (i.e., within the past year) showed increased levels of suPAR from age 38 to 45, though this association was not significant when including all individuals who met criteria for PTSD since age 38. We did not observed consistent associations between PTSD and two other commonly assessed inflammatory biomarkers, CRP and IL-6. Our findings align with prior studies linking suPAR—but not CRP or IL-6—to stressful life events (Bourassa et al., 2021b) and loneliness (Matthews et al., 2024) and provide further evidence that suPAR is a useful marker of chronic inflammation when testing associations with adversity.

These findings have theoretical and practical implications. In terms of theory, our results suggest that systemic chronic inflammation is higher among individuals who develop PTSD across the adult lifespan. If maintained over time, high levels of systemic inflammation can result in worsening health, including increased risk for the onset of chronic diseases (Pawelec, Goldeck, & Derhovanessian, 2014), cancer (Nøst et al., 2021), and cardiovascular disease (Henein et al., 2022). Similarly, extensive associations have been reported between higher suPAR and risk for adverse health events, including specific chronic diseases and severe illness (Hayek et al., 2015; Yadalam et al., 2025), as well as hospital readmission and premature mortality (Bahrami et al., 2025; Haupt et al., 2012; Montecillo et al., 2024; Rasmussen et al., 2016). It is possible that suPAR, whether used independently or in concert with other inflammatory measures, could be useful in indexing the future

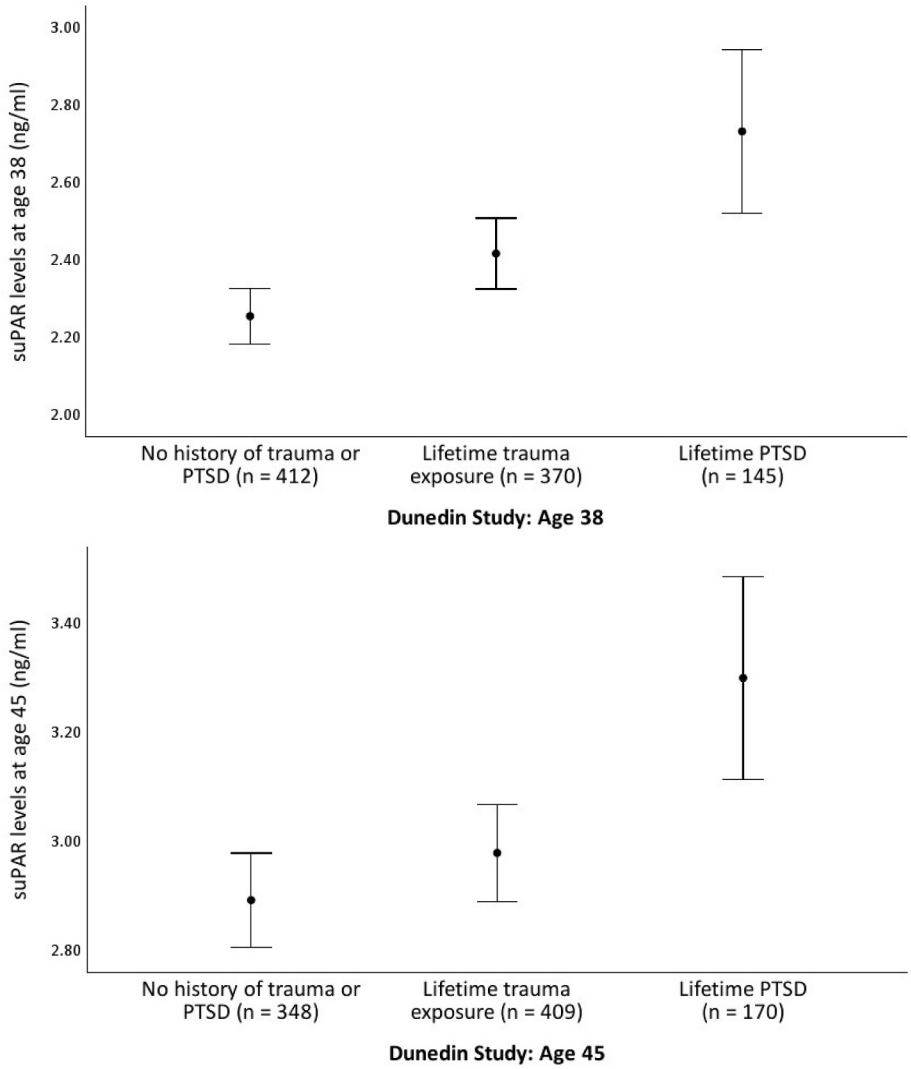

Fig. 2. Mean suPAR (ng/ml) by trauma and PTSD status at age 38 and 45 in the Dunedin Study. PTSD = posttraumatic stress disorder; suPAR = soluble urokinase plasminogen activator receptor. Bars represent 95 % confidence intervals.

disease risk among individuals with PTSD. Future research should extend associations between suPAR and PTSD to clinical outcomes.

Beyond disease-specific pathways, a number of recent studies have linked trauma and PTSD to measures of accelerated epigenetic aging (Bourassa et al., 2024; Wolf & Morrison, 2017), which predict the onset of chronic diseases and mortality in turn (Bourassa et al., 2025). Chronic inflammation was recently added as a hallmark of aging (López-Otín et al., 2023) to reflect consistent associations between advancing chronological age and heightened inflammation (i.e., "inflammaging;" Baechle et al., 2023; Ferrucci and Fabbri, 2018; López-Otín et al., 2023). Importantly, inflammation is both a process of aging and consequence of aging, making inflammatory biomarkers particularly useful when investigating PTSD, accelerated aging, and poor health. In short, systemic chronic inflammation appears to be a plausible physiological mechanism that could link PTSD and poor health. Future studies should examine how higher levels of suPAR and different rates of epigenetic aging might interact to explain this association.

Our findings have practical implications related to the assessment of chronic inflammation in patient populations and for interventions that could reduce risk for poor health among individuals with PTSD. In terms of clinical assessment, the results from the Hvidovre Hospital cohort suggest that traditional measures like CRP may be less useful in testing associations between PTSD and inflammation. In an acute medical context, we found patients with a recent stress-related psychiatric disorder actually had lower CRP—likely due to their younger age, lower rate of systemic infection, and health status. Even in models using a propensity score matching approach to address these differences, CRP was not associated with PTSD or stress-related psychiatric diagnoses, standing in contrast to significant positive associations for suPAR. Although IL-6 was not assessed in the Hvidovre Hospital cohort, IL-6 is generally thought to be more responsive to acute infection than CRP (Slaats et al., 2016) and would have likely shown similar issues in a medically complex population. Our results stand in contrast to other recent *meta*-analyses that have found associations between CRP, IL-6, and PTSD (Passos et al., 2015; Peruzzolo et al., 2022; Yang & Jiang, 2020), though the most recent meta-analysis did not find an association between hsCRP (used in this study) and PTSD (Peruzzolo et al., 2022). Our results suggest further need for comparisons of suPAR, CRP, and IL-6 for people who have mental health diagnoses, particularly in patient populations.

Finally, our findings suggest systemic inflammation could be a modifiable target to reduce risk for poor health among people with PTSD. Anti-inflammatory treatments are being developed and tested with the goal of slowing aging and improving health (López-Otín et al., 2023). Interventions that reduce systemic inflammation would be particularly valuable in populations with high levels of trauma and

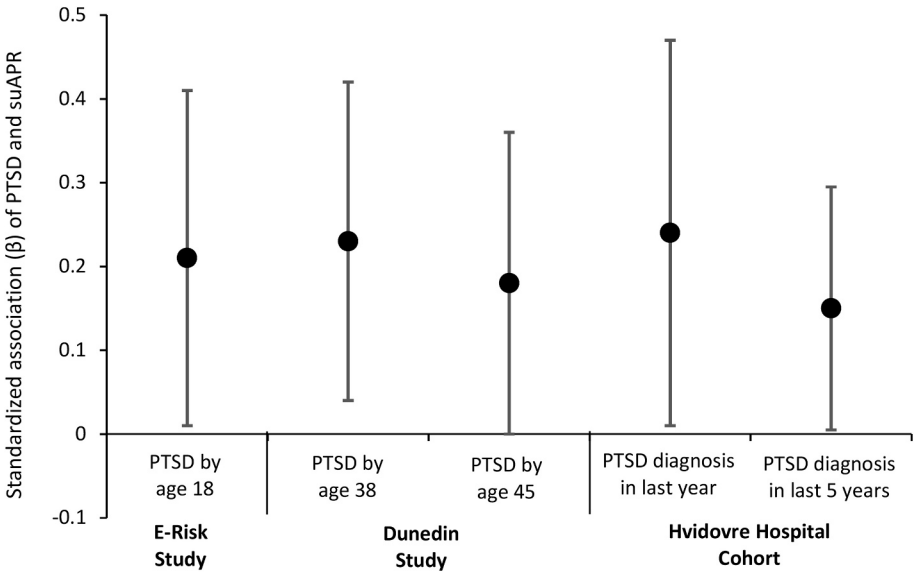

Fig. 3. Size of the unstandardized associations between PTSD diagnosis status (yes or no) and suPAR across cohorts, adjusted for relevant covariates. Associations are with lifetime PTSD diagnosis in the E-Risk Study at age 18 (n = 113) and the Dunedin Study at age 38 (n = 145) and age 45 (n = 170), as well as diagnosis within the last year (n = 79) and 5 years (n = 199) in the Hvidovre Hospital Cohort. PTSD = posttraumatic stress disorder; suPAR = soluble urokinase plasminogen activator receptor. Bars represent 95 % confidence intervals.

PTSD, such as military veterans and first responders. However, most anti-inflammatory treatments, such as canakinumab (López-Otín et al., 2023; Ridker et al., 2017), have not been tested on suPAR. Future research would benefit from clinical trials testing whether anti-inflammatory interventions reduce suPAR and, most critically, whether lowering suPAR levels can improve health by reducing risk for the onset of chronic disease and premature mortality.

This study has limitations relevant to interpreting the results. First, associations in E-Risk and the Hvidovre Hospital cohort were cross-sectional—only Dunedin included multiple assessments of suPAR allowing an assessment of longitudinal change. Future studies would benefit from modeling change in suPAR in other populations. Second, the Hvidovre Hospital cohort had limitations due to its clinical composition, including selection based on consecutive hospital admissions, lack of smoking and BMI covariates, and use of hospital records that—despite using two registry sources capturing both inpatient and outpatient diagnostic codes—may not fully capture PTSD status. Similarly, the acute nature of the admissions could have impacted our observed results. However, it is notable that we detected associations in a clinical cohort with these limitations, which could reflect the generalizability of the associations observed, particularly in real-world medical settings. Third, the assessment of PTSD was limited to the presence or absence of the disorder. Future studies would benefit from adding measures of PTSD symptom severity, medication use, PTSD chronicity, or trauma types, which might capture additional variance in suPAR. Similarly, age 38 in the Dunedin Study used DSM-IV criteria, whereas age 45 used DSM-5 criteria. Fourth, different assay platforms and laboratories were used to derive the measures in each study and the studies varied based on their ages and contexts (research cohorts, clinical setting). Although we consider this heterogeneity a strength given the consistency of the results for suPAR within each study and across samples, we also note these differences might have impacted the observed findings. Fifth, although the E-Risk and Dunedin Study models controlled for body mass index, it is possible other health conditions impacted the results. Future studies should aim to disentangle the associations between PTSD, inflammation, and chronic disease onset over time. Finally, this study only assessed associations with PTSD and stress-related psychiatric disorders. Future studies would benefit from investigating associations between suPAR and other psychiatric disorders.

4.1. Conclusions

Using data from two research cohorts and a third clinical cohort of hospital patients, we found PTSD was associated with higher levels of systemic chronic inflammation, as assessed by suPAR. This included longitudinal increases in suPAR over seven years in the Dunedin Study among individuals with recent PTSD. We did not observe consistent associations with either CRP or IL-6 across cohorts. These findings suggest that higher levels of systemic chronic inflammation might be a physiological mechanism that helps explain why people with PTSD are at greater risk of poor health.

CRediT authorship contribution statement

Kyle J. Bourassa: Writing – original draft, Methodology, Formal analysis, Conceptualization. **Terrie E. Moffitt:** Writing – review & editing, Supervision, Funding acquisition, Conceptualization. **Louise Arseneault:** Writing – review & editing, Project administration. **Ashleigh Barrett-Young:** Writing – review & editing. **Andrea Danese:** Writing – review & editing, Project administration, Funding acquisition. **Melanie E. Garrett:** Writing – review & editing. **Renate Houts:** Writing – review & editing, Formal analysis. **Timothy Matthews:** Writing – original draft, Investigation, Data curation. **Richie G. Poulton:** Project administration, Funding acquisition. **Sandhya Ramrakha:** Writing – review & editing, Project administration. **Stefan Sprinckmoller:** Writing – review & editing, Project administration. **Karen Sugden:** Writing – review & editing, Methodology, Data curation. **Benjamin Williams:** Project administration, Methodology, Data curation. **Jean C. Beckham:** Writing – review & editing, Supervision. **Allison E. Ashley-Koch:** Writing – review & editing, Formal analysis, Conceptualization. **Nathan A. Kimbrel:** Writing – review & editing, Supervision, Conceptualization. **Helen L. Fisher:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition. **Reremoana F. Theodore:** Writing – review & editing, Supervision, Project administration, Methodology, Investigation, Funding acquisition. **Avshalom Caspi:** Writing – review & editing, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Line J.H. Rasmussen:** Writing – review & editing, Writing – original draft, Supervision, Methodology, Investigation, Formal analysis, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbi.2025.106159.

Data availability

The authors do not have permission to share data.

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