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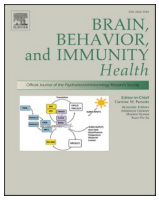

SuPAR in major depression: Association with 26 weeks antidepressant response and 10-year depression outcomes

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ABSTRACT

Introduction: Inflammation has been associated with depression and differential antidepressant (AD) treatment response. Soluble urokinase plasminogen activator receptor (suPAR) is a novel measure of chronic inflammation. We investigated whether suPAR is associated with depression severity and AD response.

Methods: We included 90 patients with major depressive disorder (MDD) who participated in a part-randomized clinical trial of 26 weeks of treatment with escitalopram or nortriptyline. suPAR levels were measured in serum samples collected at baseline and after 8, 12 and 26 weeks. Mixed effects models for the association between suPAR levels and AD response were performed. By merging with Danish nationwide registers, we included information on psychiatric hospital contacts during ten years after the GENDEP trial. Cox regression analyses calculated the hazard rate ratios between suPAR levels and subsequent hospitalizations.

Results: At baseline, higher suPAR levels were not associated with overall depression severity but with greater severity of neurovegetative depressive symptoms, specifically appetite and weight changes. 57 (63.3%) patients responded positively to treatment. Among 57 (63.3%) patients who achieved response, those who responded had significantly higher baseline suPAR levels levels, and response was associated with a significant decrease in suPAR during AD treatment. Remitters decreased from 3.1 ng/ml at baseline to 2.8 ng/ml after 26 weeks ($p = 0.003$) and responders from 3.0 to 2.8 ng/ml ($p = 0.02$), whereas non-remitters and non-responders showed unchanged suPAR levels. We found no correlation between a change in suPAR and a change in MADRS, but a lowering of suPAR correlated with a decrease in neurovegetative symptoms. We found no association between suPAR levels and 10-year risk for hospitalizations.

Discussion: The present study suggests that an elevated level of chronic inflammation, measured as the suPAR level, is associated with better response to AD treatment.

1. Introduction

Major depressive disorder (MDD) is a common, chronic-recurring disease characterized by markedly depressed mood, decreased energy and interest, and several accessory symptoms depending on severity. MDD is associated with considerable morbidity, mortality, and is a leading cause of disability world-wide (James et al., 2018). The etiology of MDD is multifactorial including genetic and environmental influences (Sullivan et al., 2000). Antidepressants (ADs) are first-line pharmacological treatment of MDD. However, effect sizes of AD treatment are modest and induce remission only in approximately 60-70% of cases after time-consuming trial and error treatment attempts, and relapse rates are high (Rush et al., 2006; Cipriani et al., 2018). While there is some evidence that severe depressions with melancholia/somatic syndrome are more responsive to AD treatment (Yang et al., 2013; Fournier et al., 2010), further elucidation of the mechanisms behind AD treatment response and lack thereof are urgently needed to improve treatment.

In recent years, accumulating evidence show an association between MDD and inflammation (Valkanova et al., 2013; Khandaker et al., 2014; Benros et al., 2013). During episodes of MDD, elevated levels of several pro-inflammatory biomarkers such as C-reactive protein (CRP),

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interleukin-6 (IL-6), and tumor necrosis factor α (TNF-α) have been consistently demonstrated (Howren et al., 2009; Dahl et al., 2014; Dowlati et al., 2010). Further, treatment of hepatitis C with interferon-α (IFN-α) induce depressive symptoms in 80% of patients (Reichenberg et al., 2005), and MDD is a common comorbidity to chronic medical conditions (Gold et al., 2020). Based on this potential correlation between inflammation and depression, a recent meta-analysis suggested proof-of-concept evidence for immunosuppressive therapies for MDD (Köhler et al., 2014), with large trials further investigating whether specific groups of patients may benefit of anti-inflammatory add-on (Otte et al., 2020). Large population studies have demonstrated an association between IL-6, CRP and specific depressive symptom as well as coheritability between CRP and depressive symptoms (Kappelmann et al., 2021; Milaneschi et al., 2021). Taken together, there is mounting evidence for a bidirectional relationship between systemic inflammation and MDD, but there is a need for further studies on specific inflammatory biomarkers during episodes of MDD treated with ADs. A recent meta-analysis suggest that while ADs reduce levels of IL-4, IL-6, and IL-10, CRP is unchanged (Więdłocha et al., 2018).

Soluble urokinase plasminogen activator receptor (suPAR) is a soluble form of uPAR, a glycophosphatidylinositol-anchored (GPI) receptor expressed on various immune cells and on endothelium, especially when affected by trauma, hypoxia or noxious agents (Plesner et al., 1997; Graham et al., 1998; Barchowsky et al., 1997). suPAR can be measured in plasma and serum, with the molecule being highly stable both in vivo (Andersen et al., 2008) and in vitro (Kofoed et al., 2006). Elevated suPAR levels are associated with increased mortality and adverse outcomes in conditions such as sepsis (Casagranda et al., 2015) and cancer (Stephens et al., 1999), as well as in cohorts of acutely admitted medical patients (Rasmussen et al., 2016) and in the general population (Eugen-Olsen et al., 2010; Langkilde et al., 2011). Importantly, suPAR's association with mortality, diabetes, cancer and cardiovascular disease is independent from CRP (Rasmussen et al., 2016; Eugen-Olsen et al., 2010; Langkilde et al., 2011), and lifestyle interventions decrease suPAR as well as mortality (Haupt et al., 2019), suggesting that suPAR is a more specific biomarker of chronic inflammation (Rasmussen et al., 2021). In a study of more than 9000 blood donors, suPAR was positively associated with the future purchase of ADs. Among healthy young adults, adverse childhood experiences (ACEs) were associated with increased suPAR levels at 18 years in a dose-dependent manner (Rasmussen et al., 2016). ACEs are associated with the development of MDD (Yazawa et al., 2022). Thus, current evidence suggests a bidirectional relationship between suPAR and MDD similar to that demonstrated for IL-6 and CRP. However, no studies have investigated the relationship between severity of MDD or the response to AD treatment. We hypothesized that serum suPAR levels are associated with depression severity, with response to AD treatment, and with long-term outcomes of MDD.

1.1. Aims

In a clinical trial on patients with MDD conducted between 2004 and 2007, we measured suPAR levels before and during 26 weeks of antidepressant treatment with escitalopram or nortriptyline. By merging with Danish nationwide registers, we included ten years of follow-up regarding long-term outcomes.

We aimed to investigate the correlation between baseline and change in suPAR levels with the following outcomes:

1) Overall and symptom-specific depression severity at baseline,
2) Overall and symptom-specific antidepressant treatment response during the 26 weeks of the clinical trial as measured with clinical rating scales,
3) 10-year depression outcomes as measured with hospitalization rates.

2. Methods

2.1. Setting and design

The present study represents secondary analyses and is based on the Genome Based Therapeutic Drugs for Depression (GENDEP) study, a multicenter open-label partially randomized trial conducted from 2004 to 2007. A subset of Danish participants was included since serum samples and follow-up data were available for these participants, as has been used in previous studies (Kofod et al., 2022; Gasse et al., 2022). The study was approved by the research ethics boards of all the participating centers, and participants provided informed written consent.

The study design has been described in detail elsewhere (Uher et al., 2008, 2009). In brief, GENDEP included individuals aged ≥18 years and diagnosed with MDD of at least moderate severity according to the Schedules for Clinical Assessment in Neuropsychiatry (SCAN) interview version 2.1. Exclusion criteria were any first-degree relative with bipolar affective disorder or schizophrenia, a history of hypomanic or manic episodes, psychotic depression with mood incongruent psychotic symptoms, primary substance misuse or primary organic disease, current treatment with an antipsychotic drug or a mood stabilizer, and pregnancy or lactation. Participants were randomly allocated to treatment with either escitalopram or nortriptyline. However, participants with any contraindications, a history of adverse effects, or non-response to escitalopram or nortriptyline were allocated to the other drug. Escitalopram was initiated at 10 mg daily with a target dose of 15 mg daily and the possibility to increase the dose to 30 mg daily if necessary. Nortriptyline was initiated at 50 mg daily with a target dose of 100 mg daily and the possibility to increase the dose to 200 mg.

2.2. Linkage with nationwide registers

All Danish residents receive a unique personal registration number (Pedersen, 2011), enabling linkage with information from nationwide registers. Information from the Danish civil registry and the Danish Psychiatric Central Research Register until December 31st, 2018 was used to assess the outcomes after participation in the GENDEP trial (Supplementary Fig. 1). The linkage with and usage of the register-based information has been approved by Statistics Denmark and the Danish Data Protection Agency.

2.3. Serum SuPAR levels

Morning blood samples were collected by venipuncture before treatment initiation and after 8, 12 and 26 weeks of antidepressant treatment, respectively (Supplementary Fig. 1). Samples were centrifuged (1550g, 10 min, 4 °C), aliquoted, immediately stored at -80 °C, and were re-thawed in September 2020 to analyze suPAR levels. suPAR levels are stable during freeze-thaw cycles (Riisbro et al., 2001). All samples were analyzed at the same time using the suPARnostic flex enzyme-linked immunosorbent assay (ELISA) (ViroGates, Copenhagen, Denmark). The standards (ranging from 0.7 to 14.3 ng/ml) and the samples were run in singlets. The curve control included on the plate was within the expected range (2.0-3.4 ng/ml) with 2.44 ng/ml.

2.4. Clinical outcomes: depression symptom ratings

Three depression rating scales were used: the 17-item Hamilton Depression Rating Scale (HAMD) and Montgomery-Åsberg Depression Rating Scale (MADRS), including the self-reported Beck Depression Inventory (BDI). The ratings were performed weekly for the first 12 weeks with another visit after 26 weeks. Intra-class correlation was 0.90 to 0.92, indicating high inter-rater reliability (Uher et al., 2008). The MADRS was used as the primary outcome measure (Uher et al., 2008, 2009). Response was defined as >50% reduction on the MADRS score, and remission was defined as a MADRS<10.

In addition, we used the following symptom dimensions, which were identified in previous item-response analyses on the GENDEP (Uher et al., 2008, 2009): "observed mood and anxiety", "cognitive", "neuro-vegetative" (including a specific appetite-weight score), and "suicidal ideation".

2.5. Register-based outcomes: psychiatric hospital contact

All participants were followed for ten years after their last visit in the GENDEP trial to ensure the same follow-up time for all participants. We investigated the following outcomes:

1) Psychiatric hospital contacts due to any mental disorder (International Classification of Diseases, 10th edition (ICD-10): F00-99) after a contact (inpatient, outpatient, or emergency department) with a psychiatric hospital department in Denmark, a surrogate marker for a worsening of the mental health state. The data was extracted from the Danish Psychiatric Central Research Register (Cipriani et al., 2018), that contains electronic records of all psychiatric diagnoses assigned at psychiatric hospital departments in Denmark since 1969 including all outpatient and emergency room contacts since 1995.
2) Psychiatric hospital contacts due to depression specifically (ICD-10: F32-33) (Cipriani et al., 2018).

2.6. Covariates

We included information on the following covariates at treatment initiation (Table 1): age, sex, CRP, BMI, smoking status, and previous depressive episodes.

2.7. Statistical analyses

Data on suPAR and MADRS at baseline were rather normally distributed (Supplementary Figs. 2A and 2C), with log-transformation showing a slightly better distribution for suPAR (Supplementary Fig. 2B). Hence, the analyses were performed on original suPAR values, and all analyses were also performed on log-transformed suPAR values, with all analyses showing similar results.

Descriptive statistics present baseline characteristics of the participants including suPAR levels as means or medians with standard deviations (SD) or interquartile ranges (IQR).

First, we performed analyses during the clinical trial. To evaluate a correlation between baseline suPAR levels and baseline severity on the overall MADRS and the specific symptom dimensions, we performed Pearson correlation analyses. T-tests were performed to compare differences between specific groups at specific time-points, e.g., differences in baseline suPAR levels between responders and non-responders.

To study the change in SuPAR during the 26-week study period, we performed mixed effects models. Mixed models prevent patients with missing data from being excluded from analysis. Furthermore, we performed mixed effects analyses with interactions to compare the following groups: 1) responders versus non-responders, 2) remitters versus non-remitters, and 3) those treated with escitalopram versus nortriptyline. An interaction analysis was also performed between the change in suPAR and the change in MADRS scores to study whether a change in depression symptom severity correlated with a change in SuPAR levels during the study period. The same analysis was performed between the change in suPAR and the change in severity on the specific symptom dimensions.

Secondly, we investigated the register-based outcomes during the ten years after the GENDEP trial. We performed Cox regression analyses to calculate the risk between 1) baseline levels of suPAR and 2) the last suPAR measurement during the GENDEP trial with the risk for a psychiatric hospital contact during ten years of follow-up.

All analyses were adjusted for age, sex, smoking status, and baseline suPAR levels.

Table 1
Baseline characteristics of the 90 patients with MDD from the GENDEP trial stratified according to median suPAR levels. Abbreviations: MDD: Major depressive disorder; HAMD: Hamilton Depression Rating Scale; MADRS: Montgomery Aasberg Depression Rating Scale; BDI: Beck Depression Inventory; CRP: C-reactive protein; BMI: Body mass index; IQR: Interquartile range; suPAR: soluble urokinase plasminogen activator receptor.

	All	Above median OF SUPARR	below median OF SuPAR	p-value[1]
FEMALE SEX, N (%)	63 (70.8)	29 (64.4)	34 (77.3)	0.19
MEAN AGE ± SD (RANGE)	37.7 ± 10.7 (20-59)	40.7 ± 10.4 (24-59)	34.8 ± 10.3 (20-57)	**0.01**
BMI BASELINE, MEAN ± SD (RANGE)	25.3 ± 5.0 (20-49)	26.2 ± 4.7 (20-41)	24.7 ± 5.1 (20-49)	0.23
TREATMENT, N (%)				
NORTRIPTYLINE	50 (55.6)	25 (55.6)	25 (55.6)	
ESCITALOPRAM	40 (44.4)	20 (44.4)	20 (44.4)	0.93
CRP, MEAN MG/L ± SD (RANGE)	2.5 ± 4.0 (0-19)	3.4 ± 4.4 (0-16)	1.9 ± 3.7 (0-19)	0.21
SMOKER, N (%)	28 (31.1)	15 (33.3)	13 (28.9)	0.45
NUMBER OF DEPRESSIVE EPISODES, N (%)				0.60
rowhead		18 (40.0)	19 (43.2)	
1 rowhead	37 (41.1)	21 (46.7)	22 (47.7)	
2 rowhead	43 (47.8)	6 (13.3)	4 (9.1)	
3+ rowhead	10 (11.1)			
BASELINE DEPRESSION SCORE				0.32
HAMD, MEAN ± SD (RANGE)	23.0 ± 3.7 (16-33)	23.4 ± 4.2 (18-33)	22.6 ± 3.2 (16-32)	0.62
MADRS, MEAN ± SD (RANGE)	28.6 ± 5.0 (18-46)	28.9 ± 5.4 (21-46)	28.3 ± 4.7 (18-40)	0.90
BDI, MEAN ± SD (RANGE)	31.5 ± 7.6 (14-48)	31.6 ± 8.3 (14-57)	31.8 ± 6.9 (19-47)	
SUPAR LEVELS BASELINE, MEDIAN NG/ML (IQR)	2.71 (1.33-5.06)	3.48 (2.73-5.06)	2.20 (1.33-2.71)	**<0.001**

[1] T-tests indicating differences between those above versus those below the median suPAR levels, with $p < 0.05$ indicating a significant difference.

All statistical work was performed with STATA version 16.0. Tests were two-tailed, and a P-value of 0.05 was considered significant.

3. Results

3.1. Characteristics

The cohort consisted of 90 Danish patients with MDD, whereof 71% were women and with a mean age of 38 years (Table 1). A total of 41% had their first depressive episode and the patients had a mean baseline depression severity corresponding to a moderate depression. The mean CRP at baseline was 2.5 mg/L, while the mean and median suPAR values were 2.81 (SD = 0.83) ng/mL and 2.71 ng/mL. When compared to the rest of the GENDEP sample, Danish participants were slightly younger and therefore more often randomized to nortriptyline (Supplementary Table 1).

When comparing those with baseline suPAR levels above the median to those below the median suPAR, we found no differences in baseline characteristics except for that those with higher suPAR levels were older (Table 1). Although those with suPAR levels above the median had nominally higher CRP levels (mean 3.4 versus 1.9 mg/L), we found no correlation between higher CRP and higher suPAR at baseline in logistic regression analyses ($p = 0.30$). When instead stratifying participants according to AD response, we found no statistically significant differences in baseline characteristics (Supplementary Table 2).

We had valid suPAR measurements for 85 participants at baseline, for 84 at week 8, for 73 at week 12, and for 54 at week 26.

3.2. Baseline correlation between suPAR and depression severity and symptom dimensions

Pearson correlation analyses showed a significant positive association between higher suPAR levels and a higher severity on the neurovegetative dimension and specifically on the appetite-weight dimension, but not on the overall MADRS or the other symptom dimensions (Table 2). The findings were similar on log-transformed suPAR levels (Supplementary Table 3).

3.3. Correlation between change in suPAR and 26-week antidepressant response

In the entire sample, suPAR levels decreased during the 26 weeks of the trial from a baseline mean of 2.81 ng/ml (SD = 0.83; IQR = 2.17-3.41) to 2.71 ng/ml (SD = 0.79; IQR = 2.28-3.11) at week 26 (Table 3). When comparing the change in suPAR levels depending on AD treatment response (Table 3 and Fig. 1A and B), we found higher baseline suPAR levels among remitters and responders, compared to non-remitters and non-responders, respectively (all $p<0.05$ for difference between groups). The suPAR levels were similar during the 26 weeks among non-remitters and non-responders, and we found a significant decrease in suPAR among remitters (mean 3.1 ± 0.9 ng/ml to 2.8 ± 0.8 ng/ml, $p = 0.03$) and responders (mean 3.0 ± 0.8 ng/ml to 2.8 ± 0.7 ng/ml, $p = 0.02$). At week 12 and 26, we found no significant difference in suPAR levels between remitters and non-remitters respectively responders and non-responders. There was no significant correlation between changes in suPAR levels and MADRS scores at week 8 or week 12 (Fig. 1C and D). However, mixed effects interaction analyses indicated that remitters showed a trend towards a greater decrease in suPAR compared to non-remitters (coefficient = -0.012, $p = 0.057$ for interaction), and responders showed a greater decrease in suPAR compared to non-responders (coefficient = -0.014, $p = 0.049$ for interaction). Baseline characteristics for remitters and non-remitters are presented in Supplementary Table 2. All results were similar when using log-transformed suPAR levels (Supplementary Table 4).

We found no differences in suPAR levels between those treated with nortriptyline and those treated with escitalopram (Table 3).

When studying the correlation between a decrease in suPAR and AD response on the specific symptom dimensions (Supplementary Fig. 3), mixed effects analyses only indicated a significant correlation between a decrease in suPAR and a significant improvement in neurovegetative dimension and specifically in the appetite-weight dimension scores (Supplementary Table 5). Of note, the decrease in the appetite-weight dimension scores was only significant among remitters but not among non-remitters. All results were similar on log-transformed data (results not shown).

Table 2
Pearson correlation analyses between baseline suPAR levels with overall MADRS symptom severity and severity on the specific symptom dimensions.

SYMPTOM SCALE	CORRELATION COEFFICIENT[1]
MADRS	0.03
MOOD AND ANXIETY DIMENSION	0.03
COGNITIVE DIMENSION	0.001
NEUROVEGETATIVE DIMENSION	**0.28***
APPETITE-WEIGHT DIMENSION	**0.35***
SUICIDAL IDEATION	0.04

* Indicates a p-value <0.05.
[1] The numbers represent the pearson correlation coefficient, measuring the association between the symptom score and the suPAR level. A positive coefficient indicates a higher symptom score depending on higher suPAR levels.

3.4. Correlation between suPAR levels and 10-year depression outcomes

By merging with the Danish nationwide registers, we included information on hospital contacts during the ten years after the GENDEP trial. A total of 27 (30.0%) of the GENDEP participants had any psychiatric hospital contact, and 22 (24.4%) had a hospital contact specifically due to depression (Table 4). Those who experienced a psychiatric hospital contact during follow-up had nominally lower suPAR levels at baseline and at the last visit of the GENDEP trial, but adjusted cox regression analyses showed no association between higher suPAR levels at baseline or higher suPAR levels at the last visit in the GENDEP trial with a differential risk for psychiatric hospitalizations.

4. Discussion

In this secondary analysis of a part-randomized clinical trial of 90 patients with MDD treated with either escitalopram or nortriptyline, we found that suPAR at baseline was not associated with overall depression severity, but with the neurovegetative dimension of MADRS, and specifically with the appetite-weight item. AD responders had higher baseline suPAR levels which decreased significantly during AD treatment. There was no correlation between changes in MADRS and suPAR during treatment, but a decrease in suPAR correlated with a decrease in neurovegetative symptoms.

suPAR was positively associated with the neurovegetative scale and specifically the appetite-weight item of MADRS. Two large general population studies from Sweden and Denmark, respectively, showed that obesity as well as underweight as measured by BMI were associated with slightly increased suPAR levels (Haupt et al., 2014; Borné et al., 2014). In a trial investigating the effect of interval training and caloric restriction in 55 participants with obesity and pre-diabetes, there was a significant decrease in suPAR after 1 year in the group assigned to both interval training and caloric restriction. (Pedersen et al., 2019). In a study of 32 patients undergoing bariatric surgery, weight loss at 1 year follow-up was associated with a marked decline in plasma high sensitivity-CRP, while suPAR decreased only slightly (Kokkinos et al., 2021). Taken together, previous studies suggest that weight changes in either direction increases suPAR, which might explain the association between suPAR and the appetite-weight item.

When stratifying participants according to AD response, remitters and responders had significantly higher baseline suPAR levels than non-remitters and non-responders, respectively. Additionally, suPAR levels among AD responders decreased significantly more during treatment than among non-responders. To our knowledge, this is the first study demonstrating that AD treatment response is associated with increased serum suPAR levels which are reduced by remission. The absolute suPAR differences at baseline and changes during AD treatment were small (in the 0.2–0.5 ng/ml range), indicating that serum suPAR levels alone cannot predict AD treatment response. However, given the lack of reliable biomarkers for AD treatment response, suPAR's association with treatment response is of interest. Also, a large general population study of 3000 individuals showed that a suPAR reduction after 5 years of lifestyle changes is associated with a lower risk of mortality, suggesting that even small decreases in suPAR may decrease subsequent mortality (Haupt et al., 2019). Previous studies on suPAR and MDD show that both current and future MDD is associated with increased suPAR levels (Gustafsson et al., 2017; Haastrup et al., 2014). A study of 73 patients with MDD, 54 of whom attempted suicide, and 19 healthy controls, showed increased plasma suPAR levels in MDD compared with healthy controls, and even higher levels in the group that attempted suicide (Ventorp et al., 2015). Together with the current observation that suPAR levels are significantly higher among AD responders, but not associated with MADRS or HAMD, it is possible that low-grade inflammation as measured by suPAR reflects aspects of MDD severity not encapsulated by rating scales.

suPAR was not associated with future hospital contacts for MDD.

Table 3
Mixed effects models evaluating changes in mean suPAR levels during 26 weeks of antidepressant treatment depending on response and antidepressant drug. 1 The models are based on N = 84 complete cases at week 0, N = 76 complete cases at week 8, N = 65 complete cases at week 12, and N = 50 complete cases at week 26.^ suPAR levels are shown as mean ng/mL ± standard deviation.

	N (%)	Week 0^	week 8^	week 12^	week 26^	coefficient	p-value
SUPAR^	90 (100)	2.8 ± 0.8	2.9 ± 1.2	2.8 ± 0.9	2.7 ± 0.8	-0.007	**0.045**
REMITTERS[A,B]	43 (47.8)	3.1 ± 0.9*	3.2 ± 1.4*	2.9 ± 0.9	2.8 ± 0.8	-0.13	**0.03**
NON-REMITTERS[A,B]	47 (52.8)	2.6 ± 0.7*	2.6 ± 0.9*	2.6 ± 0.8	2.6 ± 0.8	0.0001	0.97
RESPONDERS[C,D]	57 (63.3)	3.0 ± 0.8*	3.0 ± 1.3	2.8 ± 0.9	2.8 ± 0.7	-0.11	**0.02**
NON-RESPONDERS[C,D]	33 (36.7)	2.5 ± 0.7*	2.6 ± 1.0	2.7 ± 0.9	2.6 ± 1.0	0.003	0.44
NORTRIPTYLINE	50 (55.6)	2.9 ± 0.8	3.1 ± 1.4	3.0 ± 1.0	2.7 ± 0.8	-0.007	0.20
ESCITALOPRAM	40 (44.4)	2.7 ± 0.9	2.6 ± 0.8	2.6 ± 0.7	2.7 ± 0.8	-0.006	0.07

* T-tests indicating a significant difference (i.e. p<0.05) comparing remitters with non-remitters respectively responders with non-responders at the specific time points.

[a] Defined as MADRS<10.

[b] Mixed effects interaction analyses indicate that remitters show a trend towards a greater decrease in suPAR compared to non-remitters (coefficient -0.012, p = 0.057).

[c] Defined as >50% improvement in MADRS score.

[d] Mixed effects interaction analyses indicate that responders show a trend towards a greater decrease in suPAR compared to non-responders (coefficient -0.014, p = 0.049).

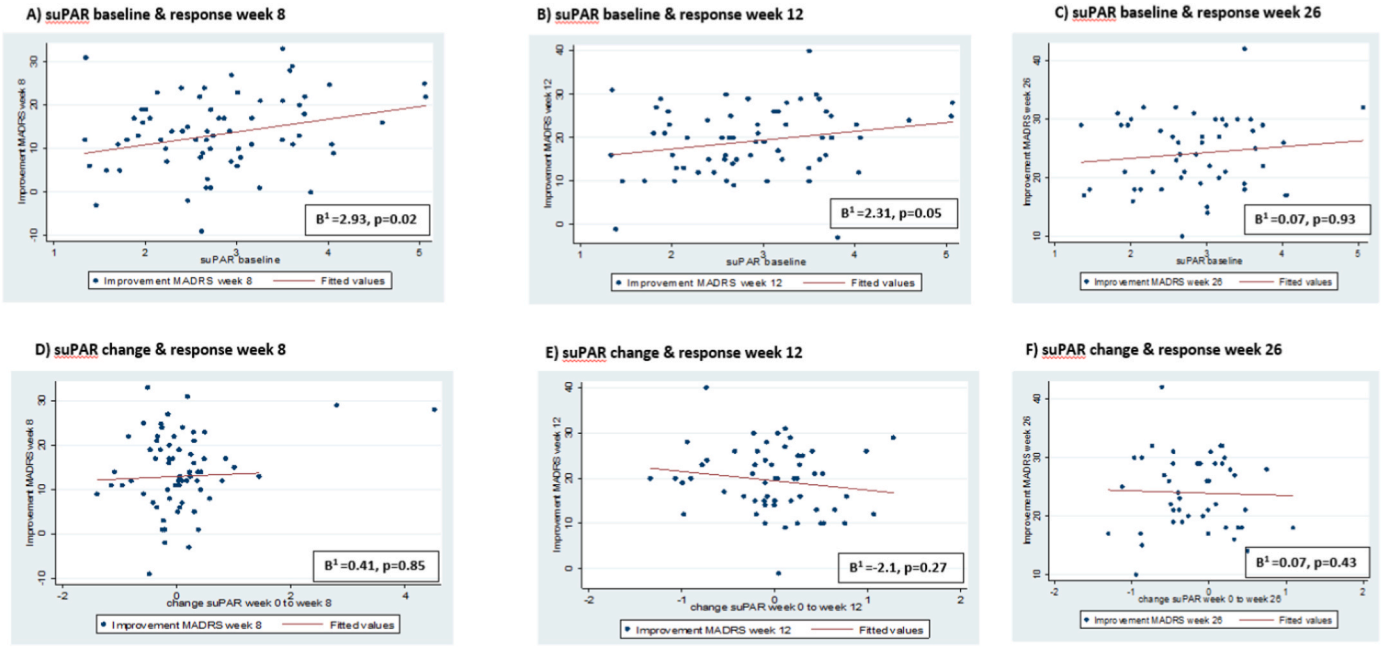

Fig. 1. Among patients with depression treated with escitalopram or nortriptyline, illustrating the correlation between suPAR baseline levels and change in MADRS from baseline to week 8 (A), week 12 (B) or week 26 (C) and the correlation between a change in suPAR and a change in MADRS at week 8 (D), week 12 (D) or week 26 (E).
[1]Beta-coefficient based on linear regression analyses adjusted for age and sex, with the improvement in MADRS being the dependent variable and the change in cholesterol level the independent variable.

This is somewhat surprising since suPAR is strongly associated with mortality and moderately associated with readmission among medical patients (Rasmussen et al., 2016; Haupt et al., 2012). We suspect that our sample size was too small to detect an association. Moreover, the association with readmission in cohorts of medical patients was within a 30-day period, not 10 years.

This study has several strengths. Firstly, the study population was a homogenous sample of patients aged 18 to 65 years, of white European ancestry without psychotic, bipolar or drug dependency disorders. Secondly, suPAR was measured before, during and after AD treatment. Regarding the weaknesses, the present analyses represent secondary analyses that were defined after the GENDEP trial has been conducted. Participants with inflammation-associated diagnoses (e.g. rheumatoid arthritis) were not excluded. suPAR was measured in serum stored for more than 10 years. suPAR is a highly stable molecule over time, but it is likely that absolute suPAR levels were systematically over-estimated due to sublimation of fluids from the samples. The number of participants was probably too low to detect an association between suPAR levels and readmission for depression. Further studies with greater sample size are needed to investigate if suPAR levels are associated with adverse psychiatric outcomes.

In conclusion, in a study of MDD, serum suPAR levels were associated with neurovegetative symptoms, but not with overall MDD severity. Higher suPAR levels at baseline were associated with subsequent response to AD treatment with escitalopram and nortriptyline. suPAR levels decreased during treatment only among responders and remitters.

Table 4
Association between suPAR levels among patients with MDD in the GENDEP trial with psychiatric outcomes[1] during the subsequent ten years of follow-up.

	N (%)	FIRST SUPAR[2], MEAN ± SD	HRR (95% CI)[3]	LAST SUPAR[2], MEAN ± SD	OR (95% CI)[3]
NO PSYCHIATRIC HOSPITAL CONTACT[1]	63 (70.0)	2.83 ± 0.87	1.0 (ref.)	2.77 ± 0.90	1.0 (ref.)
ANY PSYCHIATRIC HOSPITAL CONTACT[1]	27 (30.0)	2.72 ± 0.74	0.82 (0.46-1.45)	2.52 ± 0.66	0. 77 (0.41-1.43)
NO DEPRESSION HOSPITAL CONTACT[1]	68 (75.6)	2.82 ± 0.85	1.0 (ref.)	2.74 ± 0.87	1.0 (ref.)
DEPRESSION HOSPITAL CONTACT[1]	22 (24.4)	2.70 ± 0.79	0.81 (0.45-1.45)	2.55 ± 0.71	0.76 (0.41-1.40)

Abbreviations: suPAR = soluble urokinase plasminogen activator receptor; MDD = Major Depressive Disorder.

[1] The outcomes are based on information from Danish nationwide registers. A psychiatric hospital contact refers to a hospital contact at a psychiatric hospital for any cause (ICD-10: F00-99), whereas a hospital contact with depression refers to depression specifically (ICD-10: F32-33).

[2] First SuPAR levels (i.e. at baseline) and last suPAR levels (i.e. at the last visit in the trial where suPAR was measured).

[3] Cox regression analyses calculating the hazard rate ratio (HRR) including 95% confidence intervals (95%CI) for the specific outcomes based on first and last suPAR levels. The HRRs indicate a change in risk depending on a higher suPAR level.

Declaration of competing interest

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: Jesper Eugen-Olsen is chief scientific officer, co-founder, and shareholder in ViroGates. Jesper Eugen-Olsen is named inventor on patents on suPAR owned by Copenhagen University Hospital Hvidovre, Denmark. Ole Köhler-Forsberg reports honoraria for lectures for Lundbeck Pharma A/S and consultant work for WCG Clinical. The other authors declare no competing interests.

Data availability

The authors do not have permission to share data.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.bbih.2023.100685.

References

Andersen, O., Eugen-Olsen, J., Kofoed, K., Iversen, J., Haugaard, S.B., 2008. Soluble urokinase plasminogen activator receptor is a marker of dysmetabolism in HIV-infected patients receiving highly active antiretroviral therapy. J. Med. Virol. 80, 209–216.

Barchowsky, A., Lannon, B.M., Elmore, L.C., Treadwell, M.D., 1997. Increased focal adhesion kinase- and urokinase-type plasminogen activator receptor-associated cell signaling in endothelial cells exposed to asbestos. Environ. Health Perspect. 105 (Suppl. 5), 1131–1137.

Benros, M.E., et al., 2013. Autoimmune diseases and severe infections as risk factors for mood disorders: a nationwide study. JAMA Psychiatr. 70, 812–820.

Borné, Y., Persson, M., Melander, O., Smith, J.G., Engström, G., 2014. Increased plasma level of soluble urokinase plasminogen activator receptor is associated with incidence of heart failure but not atrial fibrillation. Eur. J. Heart Fail. 16, 377–383.

Casagranda, I., et al., 2015. Usefulness of suPAR in the risk stratification of patients with sepsis admitted to the emergency department. Intern. Emerg. Med. 10, 725–730.

Cipriani, A., et al., 2018. Comparative efficacy and acceptability of 21 antidepressant drugs for the acute treatment of adults with major depressive disorder: a systematic review and network meta-analysis. Lancet 391, 1357–1366.

Dahl, J., et al., 2014. The plasma levels of various cytokines are increased during ongoing depression and are reduced to normal levels after recovery. Psychoneuroendocrinology 45, 77–86.

Dowlati, Y., et al., 2010. A meta-analysis of cytokines in major depression. Biol. Psychiatr. 67, 446–457.

Eugen-Olsen, J., et al., 2010. Circulating soluble urokinase plasminogen activator receptor predicts cancer, cardiovascular disease, diabetes and mortality in the general population. J. Intern. Med. 268, 296–308.

Fournier, J.C., et al., 2010. Antidepressant drug effects and depression severity: a patient-level meta-analysis. JAMA 303, 47–53.

Gasse, C., et al., 2022. Association between cholesterol and response to escitalopram and nortriptyline in patients with major depression: study combining clinical and register-based information. Biomark. Neuropsychiatry 7, 100057.

Gold, S.M., et al., 2020. Comorbid depression in medical diseases. Nat. Rev. Dis. Prim. 6, 69.

Graham, C.H., Fitzpatrick, T.E., McCrae, K.R., 1998. Hypoxia stimulates urokinase receptor expression through a heme protein-dependent pathway. Blood 91, 3300–3307.

Gustafsson, A., et al., 2017. Effects of acute exercise on circulating soluble form of the urokinase receptor in patients with major depressive disorder. Biomark. Insights 12, 1177271917704193.

Haastrup, E., et al., 2014. Soluble urokinase plasminogen activator receptor as a marker for use of antidepressants. PLoS One 9, e110555.

Haupt, T.H., et al., 2012. Plasma suPAR levels are associated with mortality, admission time, and Charlson Comorbidity Index in the acutely admitted medical patient: a prospective observational study. Crit. Care Lond. Engl. 16, R130.

Haupt, T.H., et al., 2014. Risk factors associated with serum levels of the inflammatory biomarker soluble urokinase plasminogen activator receptor in a general population. Biomark. Insights 9, 91–100.

Haupt, T.H., et al., 2019. Healthy lifestyles reduce suPAR and mortality in a Danish general population study. Immun. Ageing 16, 1.

Howren, M.B., Lamkin, D.M., Suls, J., 2009. Associations of depression with C-reactive protein, IL-1, and IL-6: a meta-analysis. Psychosom. Med. 71, 171–186.

James, S.L., et al., 2018. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 392, 1789–1858.

Kappelmann, N., et al., 2021. Dissecting the association between inflammation, metabolic dysregulation, and specific depressive symptoms: a genetic correlation and 2-sample mendelian randomization study. JAMA Psychiatr. 78, 161–170.

Khandaker, G.M., Pearson, R.M., Zammit, S., Lewis, G., Jones, P.B., 2014. Association of serum interleukin 6 and C-reactive protein in childhood with depression and psychosis in young adult life: a population-based longitudinal study. JAMA Psychiatr. 71, 1121–1128.

Kofod, J., Elfving, B., Nielsen, E.H., Mors, O., Köhler-Forsberg, O., 2022. Depression and inflammation: correlation between changes in inflammatory markers with antidepressant response and long-term prognosis. Eur. Neuropsychopharmacol 54, 116–125.

Kofoed, K., Schneider, U.V., Scheel, T., Andersen, O., Eugen-Olsen, J., 2006. Development and validation of a multiplex add-on assay for sepsis biomarkers using xMAP technology. Clin. Chem. 52, 1284–1293.

Köhler, O., et al., 2014. Effect of anti-inflammatory treatment on depression, depressive symptoms, and adverse effects: a systematic review and meta-analysis of randomized clinical trials. JAMA Psychiatr. 71, 1381–1391.

Kokkinos, A., et al., 2021. Plasma levels of soluble urokinase plasminogen activator receptor (suPAR) and high-sensitivity C-reactive protein after Roux-en-Y gastric bypass or sleeve gastrectomy: a 1-year prospective observational study. J. Endocrinol. Invest. 44, 599–608.

Langkilde, A., et al., 2011. Increased plasma soluble uPAR level is a risk marker of respiratory cancer in initially cancer-free individuals. Cancer Epidemiol. Biomark. Prev. Publ. Am. Assoc. Cancer Res. Cosponsored Am. Soc. Prev. Oncol. 20, 609–618.

Milaneschi, Y., et al., 2021. Association of inflammation with depression and anxiety: evidence for symptom-specificity and potential causality from UK Biobank and NESDA cohorts. Mol. Psychiatr. 26, 7393–7402.

Otte, C., et al., 2020. Simvastatin add-on to escitalopram in patients with comorbid obesity and major depression (SIMCODE): study protocol of a multicentre, randomised, double-blind, placebo-controlled trial. BMJ Open 10, e040119.

Pedersen, C.B., 2011. The Danish civil registration system. Scand. J. Publ. Health 39, 22–25.

Pedersen, L.R., et al., 2019. Effects of 1 year of exercise training versus combined exercise training and weight loss on body composition, low-grade inflammation and lipids in overweight patients with coronary artery disease: a randomized trial. Cardiovasc. Diabetol. 18, 127.

Plesner, T., Behrendt, N., Ploug, M., 1997. Structure, function and expression on blood and bone marrow cells of the urokinase-type plasminogen activator receptor, uPAR. Stem Cells Dayt. Ohio 15, 398–408.

Rasmussen, L.J.H., et al., 2016. 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. EMJ. https://doi.org/10.1136/emermed-2015-205444.

Rasmussen, L.J.H., Petersen, J.E.V., Eugen-Olsen, J., 2021. Soluble urokinase plasminogen activator receptor (suPAR) as a biomarker of systemic chronic inflammation. Front. Immunol. 12, 780641.

Reichenberg, A., Gorman, J.M., Dieterich, D.T., 2005. Interferon-induced depression and cognitive impairment in hepatitis C virus patients: a 72 week prospective study. AIDS Lond. Engl. 19 (Suppl. 3), S174–S178.

Riisbro, R., Christensen, I.J., Høgdall, C., Brünner, N., Høgdall, E., 2001. Soluble urokinase plasminogen activator receptor measurements: influence of sample handling. Int. J. Biol. Markers 16, 233–239.

Rush, A.J., et al., 2006. Acute and longer-term outcomes in depressed outpatients requiring one or several treatment steps: a STAR*D report. Am. J. Psychiatr. 163, 1905–1917.

Stephens, R.W., et al., 1999. Plasma urokinase receptor levels in patients with colorectal cancer: relationship to prognosis. J. Natl. Cancer Inst. 91, 869–874.

Sullivan, P.F., Neale, M.C., Kendler, K.S., 2000. Genetic epidemiology of major depression: review and meta-analysis. Am. J. Psychiatr. 157, 1552–1562.

Uher, R., et al., 2008. Measuring depression: comparison and integration of three scales in the GENDEP study. Psychol. Med. 38, 289–300.

Uher, R., et al., 2009. Differential efficacy of escitalopram and nortriptyline on dimensional measures of depression. Br. J. Psychiatry J. Ment. Sci. 194, 252–259.

Valkanova, V., Ebmeier, K.P., Allan, C.L.C.R.P., 2013. IL-6 and depression: a systematic review and meta-analysis of longitudinal studies. J. Affect. Disord. 150, 736–744.

Ventorp, F., Gustafsson, A., Träskman-Bendz, L., Westrin, Å., Ljunggren, L., 2015. Increased soluble urokinase-type plasminogen activator receptor (suPAR) levels in plasma of suicide attempters. PLoS One 10, e0140052.

Więdłocha, M., et al., 2018. Effect of antidepressant treatment on peripheral inflammation markers - a meta-analysis. Prog. Neuro-Psychopharmacol. Biol. Psychiatry 80, 217–226.

Yang, S.-J., et al., 2013. Response to antidepressants in major depressive disorder with melancholic features: the CRESCEND study. J. Affect. Disord. 144, 42–50.

Yazawa, A., et al., 2022. Early childhood adversity and late-life depressive symptoms: unpacking mediation and interaction by adult socioeconomic status. Soc. Psychiatr. Psychiatr. Epidemiol. 57, 1147–1156.