Soluble Urokinase-Type Plasminogen Activator Receptor Levels in Patients With Schizophrenia

Jimmi Nielsen*,1,3, Rasmus Røge1,4, Sofie Gry Pristed1, Anne Grethe Viuff5, Henrik Ullum6, Lise Wegner Thørner6, Thomas Werge7, and Torkel Vang1,3

1Department of Psychiatry, Aalborg University Hospital, Aalborg, Denmark; 2Department of Clinical Medicine, Aalborg University, Aalborg, Denmark; 3Psychiatry in Vestfold, Tønsberg, Norway; 4Institute of Pathology, Aalborg University Hospital, Aalborg, Denmark; 5Regional Psychiatric Services West, Herning, Denmark; 6Department of Clinical Immunology, Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; 7Institute of Biological Psychiatry, Copenhagen Mental Health Services; Department of Clinical Medicine, University of Copenhagen; The Lundbeck Foundation Initiative for Integrative Psychiatric Research, iPSYCH, Copenhagen, Denmark

*To whom correspondence should be addressed; Centre for Schizophrenia, Aalborg University Hospital, Brandevej 5, 9210 Aalborg Ø, Denmark; tel: +4597643565; fax: +4597643566; e-mail: jin@rn.dk

Background: The etiology of schizophrenia remains largely unknown but alterations in the immune system may be involved. In addition to the psychiatric symptoms, schizophrenia is also associated with up to 20 years reduction in life span. Soluble urokinase-type plasminogen activator receptor (suPAR) is a protein that can be measured in blood samples and reflects the levels of inflammatory activity. It has been associated with mortality and the development of type 2 diabetes and cardiovascular disease. Methods: suPAR levels in patients with schizophrenia were compared to healthy controls from the Danish Blood Donor Study. SuPAR levels were dichotomized at >4.0 ng/ml, which is considered the threshold for low grade inflammation. A multiple logistic regression model was used and adjusted for age, sex, and current smoking. Results: In total we included 1009 subjects, 105 cases with schizophrenia (10.4%) and 904 controls (89.6%). The mean suPAR values were 4.01 ng/ml (SD = 1.43) for the cases vs 1.91 ng/ml (SD = 1.35) for the controls (P < .001). Multiple logistic regression with odds ratio (OR) for suPAR levels >4.0 ng/ml yielded: schizophrenia, OR: 46.15 95% CI 22.69–93.87, P < .001; age, OR: 1.02 95% CI 0.99–1.02, P = .15; male sex, OR: 0.70 95% CI 0.35–1.36, P = .29; and current smoking, OR: 3.51 95% CI 1.78–6.94, P < .001. Conclusions: Patients with schizophrenia had significantly higher suPAR levels than healthy controls. Further studies are warranted to clarify if elevated suPAR levels are involved in the pathophysiology of schizophrenia and/or the increased mortality found in patients with schizophrenia.

Key words: immunology/inflammatory/psychosis/mortality/cardiovascular/low grade

Introduction

Schizophrenia affects approximately 0.7% of the population and is in many cases a chronic disease. For instance, 10% of the patients are institutionalized and 90% receive early retirement pension. The overall prognosis is also relatively poor; data indicate up to 20 years reduction in lifespan compared to the background population. Along these lines, schizophrenia is associated with several somatic comorbidities, most importantly increased prevalence of cardiovascular disease. Metabolic syndrome is more common in this patient group and is present in one-third to half of the patients, depending on the chronicity of the patient population. Both the schizophrenia disease itself and the antipsychotic treatment increase the risk of type 2 diabetes. Patients with schizophrenia are less physically active and their eating habits are often poor with high rates of saturated fats and carbohydrates. Although schizophrenia patients are more prone to physical comorbidities, they are less likely to have timely and proper health care. Recent studies have shown that the mortality gap between patients with schizophrenia and the background population has increased during the last decades. This suggests that patients with schizophrenia do not receive the benefits of the improvement achieved by the discipline of medicine in the same period. With these hard figures, it becomes evident that the underrecognition and undertreatment of somatic diseases in patients with schizophrenia are a significant health care problem.

The etiology of schizophrenia is largely genetic with estimates of heritability approaching 0.80, and recent findings by international genomic consortia strongly implicate the immune system in the disorder.
of the immune system in the development of schizophrenia is further supported by converging evidence from a diverse range of biomedical studies. Approximately one-third of schizophrenia patients display an overt immunological abnormality. Furthermore, Benros et al found that prior infections or a diagnosis of autoimmune disease was a risk factor for later developing schizophrenia. A meta-analysis by Miller et al found that cytokine levels were altered for patients with schizophrenia compared to healthy controls. Interleukin (IL)-12, interferon-γ (IFN-γ), tumor necrosis factor-α (TNF-α), and soluble IL-2 receptor (sIL-2R) appeared to be trait markers, as levels were elevated compared to controls and unaffected by antipsychotic treatment. In contrast, IL-1β, IL-6, and transforming growth factor-β (TGF-β) appeared to be state markers as they decreased to normal levels during antipsychotic treatment.

In addition to these findings, add-on treatment with nonsteroidal antiinflammatory drugs (NSAID) such as celecoxib and aspirin, has in recent, double blinded studies been found to reduce the positive symptoms of schizophrenia. Clozapine, the most effective antipsychotic drug, has also been shown to have immunomodulatory effects.

Although the exact mechanisms or involvement of the immune system in schizophrenia remains largely unknown, it may be a part of a low grade inflammation (LGI) process. LGI is a subclinical chronic inflammatory state and is thought to play a role in several diseases, such as type 2 diabetes, cardiovascular disease, and Alzheimer’s disease. In patients with schizophrenia elevated serum levels of C-reactive protein (CRP), measured with a high sensitivity test referred to as HS-CRP) are correlated with more severe psychopathology. However, CRP is an acute phase reactant and to a large degree influenced by current infections. Therefore, it may not be optimal as a biomarker for LGI.

The urokinase-type plasminogen activator receptor (uPAR, also known as CD87) is a glycosylphosphatidylinositol (GPI)anchored protein found on the cell surface and is foremost expressed in endothelial cells and various hematopoietic cells such as neutrophils, monocytes, and activated T cells. At the molecular level, uPAR is a high-affinity receptor for the serine protease urokinase-type plasminogen activator (uPA), but it can also serve as a ligand for several integrins. As a consequence, uPAR is involved in focused proteolysis and cellular adhesion/migration. At the systemic level, the importance of uPA/uPAR is exemplified by the fact that mice deficient in either uPA or uPAR succumb to infections due to defective recruitment of monocytes/T cells or neutrophils, respectively. Interestingly, uPAR is released from cells to generate soluble uPAR (suPAR), which can be measured in the blood. suPAR is an emerging inflammatory marker which, in contrast to many other inflammatory markers, is physiologically stable over time making it a good biomarker of chronic inflammatory conditions, contrary to CRP and can withstand several freezing and thawing cycles. SuPAR levels are considered to reflect the inflammatory state in the body, and suPAR levels are positively correlated with proinflammatory biomarkers such as leukocyte counts and levels of TNF-α and CRP. Besides, high suPAR levels have been associated with short-term mortality and poor prognosis in several diseases, such as HIV, tuberculosis, and malaria.

SuPAR correlates with the Charlson Comorbidity Index, admission time and 90-day mortality in acutely admitted medical patients. The predictive value of suPAR as regards to mortality in these conditions is less affected by current infections, and when adjusting for CRP the suPAR value remained predictive. In a study investigating CRP and suPAR in patients with systemic inflammatory response syndrome (SIRS), CRP was predictive of whether SIRS was of bacterial origin while suPAR was not. In contrast, suPAR but not CRP was predictive of 30-day mortality.

Elevated suPAR levels predict an increased risk of developing cardiovascular disease, cancer, and mortality. SuPAR values of less than 4.0 ng/ml are considered normal or termed as a low-inflammatory state. Values 6–10 ng/ml may indicate a 10-year risk of development of diabetes, cancer, or mortality whereas values above 10 ng/ml are associated with current critical illness, such as sepsis, tuberculosis, and HIV.

Because of the solid evidence for an immunological involvement in schizophrenia and the increased mortality associated with this disease, we hypothesized that suPAR may be elevated either as a reflection of the causes of disease or even part of the disease mechanism, or that suPAR elevation is secondary to the disease and a marker related to early death of patients with schizophrenia. We conducted a cross-sectional study of suPAR levels in patients with schizophrenia and compared them with healthy controls from the Danish Blood Donor Study. In addition, we sought to identify predictors of increased suPAR levels within the schizophrenia population.

**Methods**

**Sample**

Only patients with a life time diagnosis of ICD-10 F20 schizophrenia were included as cases in this study. Patients were recruited from 3 psychiatric hospitals in Denmark; Herning, Aalborg and Brønderslev. Patients were recruited from outpatient clinics. The study was conducted under the auspices of the research program Danish Psychiatric Biobank and is approved by the Regional Scientific Ethical Committee and the Danish Data Protection Agency. Cases were recruited in the period March 22, 2012–July 20, 2013.
Data and blood samples from healthy controls were achieved from the Danish Blood Donor Study which is approved for biomedical research independently of this study (M-20090237). As controls were included the first 904 participants recruited from Copenhagen in the Danish Blood Donor Study. Blood donors represent a healthy subset of the general population, and the Danish Blood Donor Study has contributed significantly to biomedical research. 40 Donating blood in Denmark is voluntarily and donors do not receive any payment. Reasons for donations in the Scandinavian countries is considered to be altruism and the donors are often of middle- to high- socioeconomic status. 41 Apparent behavioral abnormality is an exclusion criterion for donation and all individuals stated that they felt completely healthy with a possibility to discuss any health-related issues with a physician. Blood donors are screened for various diseases, such as hepatitis, HIV and fulfill a health questionnaire before each donation (see reference for further description). 41 Age, sex, and current smoking status (yes/no) were registered for cases and controls.

At the time of the blood sampling, cases and controls had no signs of infection or any acute disease.

Blood specimens were centrifuged within 6 hours after sampling, and collected plasma was stored at minimum −25°C. Samples were analyzed within 12 months by Virogates Inc., Birkerød, Denmark, by using ELISA techniques. All samples were analyzed with the same batch in order to avoid analytical biases.

Background information for the cases was found in hospital records. Cancer diagnosis was defined as any kind of previous diagnosis of cancer. Prior cardiovascular disease was defined as any diagnosis of cardiovascular disease within the ICD-10 DI2 chapter.

**Statistics**

Student t-test was used for comparing continuous variables between groups. SuPAR values were not normally distributed in the cases, controls, and total and were logarithmically transformed. Binary variables were compared by using a chi-square test. In cases with less than 5 subjects in one of the 4 cells, Fischer’s exact test was used instead. Percentage of hospitalization was not normally distributed and instead median and 25 and 75 percentiles were provided. Comparison was in this case done by using the Wilcoxon rank sum test.

A multiple linear regression model was initially used to model suPAR levels and the following explanatory variables: case status, sex, age, and current smoking status. The assumptions for the linear regression were tested graphically, and because the residuals were only borderline normally distributed, a logistic regression model was also conducted. The suPAR values were dichotomized on the median in the total, combined sample of cases and controls corresponding to 2 ng/ml.

The same analyses were performed in a cases-only approach in order to identify predictors of high suPAR levels in the schizophrenia patient group. SuPAR levels of the cases were dichotomized at the median, and explanatory variables were first tested in a univariate logistic regression model. Explanatory variables with P value < .1 were subsequently tested in a multivariate logistic regression model adjusted for the variables known to be associated with suPAR levels: age, sex, and current smoking status. The median for the cases only was 4 ng/ml, which is also considered as the cutoff value for LGI.

Besides the above mentioned explanatory variables, the following explanatory variables were included in the logistic regression model: age of onset of schizophrenia, percentage of hospitalization, current antipsychotic treatment, diagnosis of prior cardiovascular disease, and diabetes type 2. Current antipsychotic treatment was divided into: aripiprazole, clozapine, olanzapine, quetiapine, and risperidone. First generation antipsychotics (FGA) were treated as 1 group and included chlorpromazine, fluphenazine, haloperidol, levomepromazine, perphenazine, and zuclopenthixol. If patients received more than 1 antipsychotic drug, they were included in all the respective treatment groups.

Statistical analyses were performed with STATA version 11. All tests were used 2 sided and only P values < .05 were considered statistically significant. Power analysis was not performed because of the novelty of investigating suPAR in this patient group. Numbers of cases were arbitrarily chosen.

**Results**

In total, we included 1009 subjects, 105 cases with schizophrenia (10.4%) and 904 controls (89.6%). The demographics are shown in table 1 and differed significantly between patients and healthy subjects with the exception of gender. The results from the linear regression are

**Table 1. Demographics of schizophrenia cases and healthy controls**

<table>
<thead>
<tr>
<th></th>
<th>Cases (N = 105)</th>
<th>Controls (N = 904)</th>
<th>Total (N = 1009)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age, years (SD)</td>
<td>43.9 (14.3)</td>
<td>39.6 (12.3)</td>
<td>40.0 (12.6)</td>
<td>.0009</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>51 (48.6%)</td>
<td>484 (53.5%)</td>
<td>535 (53.2%)</td>
<td>.3</td>
</tr>
<tr>
<td>Current smoker (0/1)</td>
<td>59 (56.2%)</td>
<td>156 (17.3%)</td>
<td>215 (21.3%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Mean suPAR value, ng/ml (SD)</td>
<td>4.01 (1.43)</td>
<td>1.91 (1.35)</td>
<td>2.07 (1.46)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Persons with &gt;4 ng/ml</td>
<td>51 (48.6%)</td>
<td>12 (1.3%)</td>
<td>63 (6.2%)</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Persons with &gt;10 ng/ml</td>
<td>2 (1.9%)</td>
<td>0 (0.0%)</td>
<td>2 (0.2%)</td>
<td>.011</td>
</tr>
</tbody>
</table>
shown in table 2. In a multiple logistic regression model adjusted for sex/age/smoking, schizophrenia was associated with a 69 times higher risk than controls for suPAR levels higher than 2 ng/ml, as shown in table 3. Similar figures for suPAR levels with cutoff >4 ng/ml yielded OR 46.15, 95% CI: 22.69–93.87, P < .0005.

Females had higher suPAR values than males (2.02 ng/ml 95% CI: 2.13–2.28 vs 1.96 ng/ml 95% CI: 1.90–2.02, P < .001). However, we found no difference in suPAR values between females and males in the schizophrenia sample (4.07 ng/ml 95% CI: 3.68–4.49 vs 3.96 ng/ml 95% CI: 3.58–4.38, P = .71). Among the controls, females had higher levels than males (2.04 ng/ml 95% CI: 1.98–2.09 vs 1.82 ng/ml 95% CI: 1.77–1.87, P < .001).

For smokers, there were significantly higher suPAR values both in schizophrenia and controls. Among the cases smokers vs nonsmokers suPAR levels were 4.35 ng/ml 95% CI: 3.98–4.75 vs 3.62 ng/ml 95% CI: 3.25–4.03, P = .008. Corresponding values for the controls were 2.20 ng/ml 95% CI: 2.08–2.33 vs 1.86 ng/ml 95% CI: 1.83–1.90, P < .001. P values when comparing cases vs controls were <.001 both in among smoker and nonsmokers.

Fifty-one of the cases (48.6%) had values of more than 4.0 ng/ml compared to only 12 (1.3%) in the control group. Demographics and treatment variables of the schizophrenia group are shown in table 4.

Two male patients with schizophrenia had suPAR levels >10 ng/ml, both 10.4 ng/ml. Both of them were current smokers but had no evidence of cancer, diabetes, or cardiovascular disease. The age of the 2 patients was 39 and 52 years. Highest suPAR value for the controls was 4.8 ng/ml.

For patients with schizophrenia with suPAR levels >4 ng/ml, a diagnosis of diabetes type 2 was in the univariate regression borderline significant (OR: 3.02, 95% CI: 0.98–9.29, P = .054), but remained nonsignificant in the adjusted model (OR 2.55, 95% CI: 0.81–8.09, P = .11). Prior cardiovascular disease remained nonsignificant.

Of the schizophrenia severity variables, hebephrenic subtype was in a multiple logistic regression model adjusted for age/sex/current smoking status, associated with a reduced risk of high suPAR values (OR: 0.28, 95% CI: 0.07–1.06, P = .049). Other variables associated with outcome, such as age of onset of schizophrenia and percentage of prior psychiatric hospitalization, were not associated with suPAR levels.

None of the current treatment variables were statistically significant in the regression model. Clozapine was nearest the level of becoming significant; in a univariate logistic regression, suPAR values of >4 were associated with OR 2.6 95% CI: 0.95–4.93, P = .065; when adjusted for age, sex, and current smoking status, the numbers were OR 2.1 95% CI: 0.92–5.00, P = .079.

**Discussion**

This is the first study to investigate suPAR levels in patients with schizophrenia. The major result of this study was that patients with schizophrenia had higher levels of suPAR compared to healthy controls. Almost half of the patients with schizophrenia had suPAR values of more than 4.0 ng/ml, which is considered the threshold for LGI.36

We found that increasing age and smoking were associated with higher values of suPAR, which is in line with previous findings.38 In the control population, we found that females had higher suPAR levels than males, which is also consistent with previous findings.42 Such a difference between the sex was not found in the schizophrenia sample. The reason for this remains unknown.

Two patients with schizophrenia had suPAR concentrations >10 ng/ml. Still, there were apparently no signs or history of serious physical disease. Such high suPAR value is associated with critical illness and high short term mortality. The reason for these high values in these 2 patients remains unknown, but one should suspect unrecognized physical disease and these patients should undergo a thorough physical examination.

Since suPAR is a nonspecific marker for inflammation and correlated to a wide variety of diseases and mortality, it may be useful for screening patients with schizophrenia for physical disease. A recent study found that suPAR levels improved the predictive accuracy of both abnormal ECG findings and of elevated troponin concentrations regarding all-cause mortality in patients admitted with acute chest pain.43 This may be important...
### Table 4: Demographics of schizophrenia patients with normal or elevated suPAR (>4 ng/ml)

<table>
<thead>
<tr>
<th></th>
<th>SuPAR &gt; 4.0 ng/ml (N = 51)</th>
<th>SuPAR ≤ 4 ng/ml (N = 54)</th>
<th>Total (N = 105)</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (SD)</td>
<td>45.6 (15.1)</td>
<td>42.2 (13.3)</td>
<td>43.9 (14.3)</td>
<td>.2</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>24 (47.1%)</td>
<td>27 (50.0%)</td>
<td>51 (48.6%)</td>
<td>.7</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>33 (64.7%)</td>
<td>26 (48.2%)</td>
<td>59 (56.2%)</td>
<td>.09</td>
</tr>
<tr>
<td>Married, n (%)</td>
<td>6 (11.8%)</td>
<td>12 (22.6%)</td>
<td>18 (17.1%)</td>
<td>.9</td>
</tr>
<tr>
<td>Living alone, n (%)</td>
<td>45 (88.5%)</td>
<td>43 (79.6%)</td>
<td>88 (83.8%)</td>
<td>.2</td>
</tr>
<tr>
<td>Living in institution, n (%)</td>
<td>3 (5.9%)</td>
<td>1 (1.9%)</td>
<td>4 (3.8%)</td>
<td>.4</td>
</tr>
<tr>
<td>Receiving early retirement pension, n (%)</td>
<td>39 (76.5%)</td>
<td>44 (81.2%)</td>
<td>83 (79.1%)</td>
<td>.5</td>
</tr>
<tr>
<td>Mean age of onset of schizophrenia diagnosis, years (SD)</td>
<td>25.8 (8.2)</td>
<td>24.7 (8.1)</td>
<td>8.1</td>
<td>.5</td>
</tr>
<tr>
<td>Median percentage of psychiatric hospitalization, median, (25–75 percentiles)</td>
<td>7.4 (3.9–16.5)</td>
<td>6.7 (2.7–13.6)</td>
<td>7.2 (3.2–14.7)</td>
<td>.2</td>
</tr>
<tr>
<td>Hebephrenic schizophrenia</td>
<td>1 (2.0%)</td>
<td>7 (13.0)</td>
<td>8</td>
<td>.06</td>
</tr>
<tr>
<td>Current treatment*</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aripiprazole</td>
<td>12 (23.5%)</td>
<td>11 (20.4%)</td>
<td>23 (21.9%)</td>
<td>.7</td>
</tr>
<tr>
<td>Clozapine</td>
<td>22 (43.1%)</td>
<td>14 (25.9%)</td>
<td>36 (34.3%)</td>
<td>.06</td>
</tr>
<tr>
<td>Olanzapine</td>
<td>7 (13.7%)</td>
<td>13 (24.1%)</td>
<td>20 (19.1%)</td>
<td>.2</td>
</tr>
<tr>
<td>Quetiapine</td>
<td>15 (29.4%)</td>
<td>22 (40.7%)</td>
<td>37 (35.2%)</td>
<td>.2</td>
</tr>
<tr>
<td>Risperidone</td>
<td>8 (15.7%)</td>
<td>8 (14.8%)</td>
<td>16 (15.2%)</td>
<td>.9</td>
</tr>
<tr>
<td>First generation antipsychotics</td>
<td>47 (92.2%)</td>
<td>48 (88.9%)</td>
<td>95 (90.5%)</td>
<td>.6</td>
</tr>
<tr>
<td>Antidepressant</td>
<td>34 (67.3%)</td>
<td>37 (68.5%)</td>
<td>71 (67.2%)</td>
<td>.8</td>
</tr>
<tr>
<td>Somatic</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of cancer</td>
<td>1 (2.0%)</td>
<td>2 (3.7%)</td>
<td>3 (2.9%)</td>
<td>.6</td>
</tr>
<tr>
<td>Diabetes type II</td>
<td>12 (23.5%)</td>
<td>5 (9.3%)</td>
<td>17 (15.2%)</td>
<td>.047</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>6 (11.8%)</td>
<td>3 (5.6%)</td>
<td>9 (8.6%)</td>
<td>.3</td>
</tr>
<tr>
<td>Receiving statins</td>
<td>13 (25.5%)</td>
<td>12 (22.2%)</td>
<td>25 (23.8%)</td>
<td>.7</td>
</tr>
</tbody>
</table>

Note: *Total numbers exceeded total numbers of cases because some were treated with antipsychotic polypharmacy.

in patients with schizophrenia because they often have difficulties in describing their physical symptoms and physical signs may be interpreted in the context of psychotic symptoms, eg, chest pain as radiation from outer space. With a reduced lifespan of 20 years it is highly warranted to identify somatic disease in these patients and institute appropriate treatment. Larger longitudinal studies in patients with schizophrenia should clarify whether suPAR may play a role as a screening tool for somatic disease in this vulnerable patient group.

Several studies suggest an association between schizophrenia and the immune system. As already mentioned, the cytokines IL-1β, IL-6, and TGF-β can serve as state markers in schizophrenia, as their levels correlate with clinical improvement in response to treatment with antipsychotics. Likewise, it would be interesting to determine if the inflammatory marker suPAR can serve as a state marker in schizophrenia. Unfortunately, we did not have access to corresponding levels of suPAR in the cerebrospinal fluid (CSF) in order to determine whether suPAR was of CNS or of peripheral origin. Reference values of CSF suPAR do not exist. However, previous studies have found high CSF levels of suPAR in patients with CNS infections, neoplastic disease, and neurologically comprised HIV patients. In HIV patients, there was no correlation between levels of suPAR and the CSF to serum albumin ratio. This suggests that suPAR does not play an important role in HIV-induced blood-brain barrier disruption. Studies investigating the levels of CSF suPAR in patients with schizophrenia are warranted and may contribute to the understanding of our findings.

Our study was not designed to follow suPAR levels in patients over time and related to severity of psychotic symptoms. Therefore, additional studies are required to clarify these issues. Interestingly, we found that hebephrenic subtype, which is usually associated with a poor outcome of the disease, displayed reduced risk of high suPAR values. Currently, we are not able to explain these findings, but it may be speculated that differential immune involvement in various subtypes of schizophrenia plays a role. However, this issue is complex since it has been suggested that immunomodulation affects positive symptoms to a larger degree than negative symptoms. LGI may be involved in depression and bipolar disorder as well, and it may be of interest to compare levels of suPAR in these groups with what we found in patients with schizophrenia. Although, the univariate regression remained nonsignificant a trend for increased values in clozapine patients was seen. The severe metabolic adverse effects of clozapine may have contributed to this. Interestingly, olanzapine which has a similar adverse effect profile was not associated with high suPAR values. Previous studies have found immunomodulatory effects of clozapine, whether this is responsible for the increased suPAR levels remains unknown. Longitudinal
studies investigating the effect of different antipsychotics on suPAR levels is warranted.

This study should be interpreted within its limitations. The cases and controls came from 2 separate studies which may have caused unknown biases. However, the suPAR shows a high degree of stability preanalytically and postanalytically and all samples were analyzed using the same batch in the laboratory.29,50 The relatively low number of cases made it difficult to identify predictors of high suPAR levels within the patients with schizophrenia. Blood sampling was not performed at the same time of the day but a previous study including 296 patients found that suPAR showed minimal diurnal variation.50

The study design was cross-sectional which makes it impossible to determine any causality. We did not have access to laboratory values or clinical data, such as cholesterol, fasting glucose, body mass index (BMI), waist circumference, and exercise or eating habits. Other inflammatory markers, such as CRP and different interleukines would have contributed to the understanding of our findings. In contrast to CRP, suPAR has been shown not to be correlated to BMI or waist circumference.38 We only had access to current smoking status, and past smoking status may erroneously have caused higher suPAR levels in the nonsmoking group. History of alcohol abuse and liver disease has been associated with higher levels of suPAR.51 These conditions are likely more prevalent in patients with schizophrenia than in healthy controls. Unfortunately, we did not have access to data on these conditions in any of the 2 groups. Screening for illicit drug use may also have influenced the results and was unfortunately not done. We used smoking as a dichotomous variable, and we cannot exclude that schizophrenia patients smoke more which may have caused higher suPAR levels in the schizophrenia group. However, we did a sensitivity analysis in nonsmokers to confirm the increased levels of suPAR in patients with schizophrenia.

We used blood samples from the Danish Blood Donor study which is a healthier control group than the background population, eg, the rate of obesity is 15.3% for men and 13.6% for women in the Danish background population compared with Danish blood donors 10.0% and 9.3%, respectively.40 This may have biased the result and increased the difference between the suPAR levels in the 2 groups. However, with suPAR values more than 2-fold higher in patients with schizophrenia compared to the controls, it is unlikely that this was solely accounted for by a super selection of the control group. This view is further supported by results from the population based cohort study, Malmö Diet and Cancer Study, where the mean suPAR was 3.17 ng/ml (3.05 ng/ml for nonsmokers and 3.39 ng/ml for smokers).29 Interestingly, the mean age in the latter study was 65.6 years which is more than 20 years older than the patients with schizophrenia in our group.

The usefulness of suPAR as a diagnostic or prognostic marker in the general population and especially in patients with severe mental disorders, is far from fully elucidated.36 Patients with schizophrenia have a reduced life span and the diagnoses of somatic diseases are often delayed with a poorer prognosis as a consequence. In conclusion, we found that patients with schizophrenia had significantly higher suPAR levels than healthy controls. Longitudinal studies are highly warranted to determine whether suPAR levels may play a role as a screening tool for somatic disease. Furthermore, larger studies should also clarify whether suPAR may play a role as a state or trait marker in schizophrenia.

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