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Original Article

Similar immune profile in bipolar disorder and schizophrenia: selective increase in soluble tumor necrosis factor receptor I and von Willebrand factor

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Background: Alterations in the inflammatory system have been associated with schizophrenia and major depression, while bipolar disorder has been less studied. Most previous studies examined small samples, and the literature is inconsistent with regard to specific underlying immune mechanisms. In the present study, we examined markers representing different inflammatory pathways, and the aim was to investigate whether the levels of inflammatory parameters in a representative sample of bipolar disorder and schizophrenia are elevated compared to healthy controls, and to investigate whether the inflammatory profile is different between the groups.

Methods: Plasma levels of soluble tumor necrosis factor receptor 1 (sTNF-R1), interleukin-1 receptor antagonist (IL-1Ra), interleukin-6 (IL-6), high-sensitivity CRP (hs-CRP), soluble CD40L ligand (sCD40L), and von Willebrand factor (vWf) were measured with ELISA techniques in a catchment area based sample of consecutively referred patients with severe mental disorders [N = 311, comprising bipolar disorder (n = 125) and schizophrenia (n = 186)] and in healthy volunteers (n = 244).

Results: Plasma levels of sTNF-R1 and vWf were statistically significantly increased in both bipolar disorder and schizophrenia compared to controls ($p < 0.00001$), and were also increased in unmedicated patients, but there were no major differences between the two diagnostic groups. Controlling for age, gender, ethnicity, cardiovascular disorders, kidney and liver function, and other confounders did not affect the results. There were no differences in other inflammation factors between the groups.

Conclusion: The present results indicate specific alterations of endothelium-related inflammation processes in both bipolar disorder and schizophrenia.

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The underlying pathological mechanisms of severe mental disorders are still largely unknown. The disorders are highly heritable (1) and are regarded as complex genetic disorders, involving interplay

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between genetic and environmental factors (2), but the mechanisms involved remain elusive. Several lines of evidence have implicated the immune system in the development of severe psychiatric disorders. Susceptibility genes for severe mental disorders have been associated with immune function (3–6). Immune challenges during fetal and early life are a risk factor for severe psychiatric disorders (7, 8). Proinflammatory factors are involved in the response to mental stress (9, 10), and recently, important roles of inflammatory mediators in neurotransmission and plasticity have been revealed (11–13). While these findings indicate a role of inflammation in general in the pathogenesis of severe mental disorders, the specific inflammatory mechanisms are still unknown.

The role of inflammation is best substantiated in depression, where the macrophage hypotheses of depression (14) have been supported by findings of pathology related to inflammatory processes (11, 15). Several lines of evidence implicate infection and inflammation as possible contributing factors in schizophrenia as well. This has led to the cytokine imbalance hypothesis, which has been investigated with inconsistent results (16–20), but a recent review indicates the presence of an inflammatory syndrome in schizophrenia (21). In bipolar disorders, there are fewer studies, and the role of inflammation is still largely unknown. Recent studies have suggested increased inflammatory responses also in bipolar disorder (5, 22, 23), but further studies are needed.

Many of the studies of immune factors in severe mental disorders are small, and have been performed in selected samples (21). Furthermore, the number of immune factors investigated is often limited, making it difficult to draw conclusions about the immune mechanisms involved. There is also a lack of studies investigating differences between bipolar disorder and schizophrenia in the same study, limiting the possibility to explore whether the alterations are disease specific or common to larger groups of severe mental disorders. Traditionally, bipolar disorder has been considered a clinical entity distinct from schizophrenia. This assumption has been recently challenged by new findings of similar genetic and biological profiles supporting the continuum hypothesis (24–26), suggesting that there also might be similarities in immune abnormalities.

In the present study, we examined several soluble markers of inflammation and immune activation representing different inflammatory pathways in both schizophrenia and bipolar disorder patients, in addition to healthy controls from the same geographical area. The analyses included a general downstream marker of immune activation [high-sensitivity C-reactive protein (hs-CRP)] (27), being the prototypical acute-phase protein, a marker of endothelial cell activation [von Willebrand factor (vWf)] (28), more specific markers of the activity in the upstream inflammatory pathways such as interleukin-6 (IL-6) and the tumor necrosis factor α (TNFα) [i.e., soluble TNF receptor type I (sTNF-RI)] (29), and the interleukin-1 (IL-1) [i.e., IL-1 receptor antagonist (IL-1Ra)] systems, as well as a marker of platelet-mediated inflammation [i.e., soluble CD40 ligand (sCD40L)]. These various cytokines and immune markers reflect distinct, but potentially equally important pathophysiological pathways, and we hypothesize that investigating these various markers will lead to better understanding of specific immune mechanisms underlying severe mental disorders.

The aim of the present study was to investigate whether the levels of inflammatory parameters in a representative sample of bipolar disorder and schizophrenia patients are elevated compared to healthy controls, and to evaluate whether the inflammatory profile is different between bipolar disorder and schizophrenia.

Methods

Subjects

Patients were included through referrals to the ongoing Thematic Organized Psychosis (TOP) research study carried out by the University Hospitals of Oslo, Oslo, Norway [for details, see (30)]. Inclusion criteria were: being registered in the psychiatric services of any one of the four University Hospitals in Oslo; age 18–65 years; meeting DSM-IV criteria for schizophrenia or bipolar spectrum disorders; and being willing and able to give written, informed consent for participation. Exclusion criteria were: history of moderate or severe head injury, neurological disorder, mental retardation, and autoimmune disorders. Included in the current analyses are consecutive referred patients with valid measurements of immunological markers, without any autoimmune disorders or use of nonsteroid anti-inflammatory drugs or statins, consisting of a total of 311 patients, of whom 186 had a DSM-IV schizophrenia spectrum disorder [schizophrenia (n = 142), schizophreniform disorder (n = 11), and schizoaffective disorder (n = 33)] and 125 had a bipolar spectrum disorder [bipolar I disorder (n = 73), bipolar II disorder (n = 44), and bipolar disorder not otherwise specified (n = 8)]. The bipolar disorder patients had a mean Global Assessment of

Functioning Scale (GAF, split version) score of 59 (symptom)/57 (function), and the schizophrenia patients had GAF scores of 42 (symptom)/42 (function).

A representative control group was randomly selected from statistical records from the same catchment area as the patient groups and contacted by letter inviting them to participate. Included in the current analyses are controls without a history of medical problems, severe psychiatric disorders, including drug abuse/dependency, or severe mental disorder reported in close relatives. A total of 244 consecutively recruited healthy controls had valid measurements of immunological parameters.

There were no differences in age and gender between the patient group and the control group, but the control group had a significantly higher participation of persons of European descent (Table 1). The schizophrenia group had a higher proportion of males. At the time of blood sample collection, a total of 29 patients (9.3%) were unmedicated, 15 (12%) in the bipolar disorder group and 14 (7.4%) in the schizophrenia group. Antipsychotic drugs were used by 44% of the bipolar disorder patients and 88% of the schizophrenia patients; mood stabilizers were used by 58% of the bipolar disorder patients and 21% of the schizophrenia patients. Two percent of the patients were treated regularly with medications for somatic disorders (insulin, cetirizin, omeprazol, metoprolol, and diclofenac); no patients used anticoagulants. None of the subjects in the control group received any medications. In the patient group, 55% were current smokers (schizophrenia 58%, bipolar disorder 54%), 4 (0.7%) had diabetes and 11 (1.9%) had cardiovascular disease. We did not have information about smoking habits among the controls. Cortisol levels were measured in 283 patients.

All participants gave written informed consent to participation, and the study was approved by the Regional Committee for Medical Research Ethics and the Norwegian Data Inspectorate.

Assessments

All patients were assessed by trained clinical research personnel (psychiatrists and clinical psychologists). The Structured Clinical Interview for DSM-IV Axis I Disorders (SCID-I) was used for diagnostic purposes, and global symptomatology and functioning was measured by the GAF Scale (split version). Inter-rater reliability was good, with an overall kappa score of 0.77 [95% confidence interval (CI): 0.60–0.94] for diagnoses and an intraclass correlation coefficient (1.1) of 0.86 for both symptom and function GAF scores. Control participants were assessed with a structured interview and screened with the Primary Care Evaluation of Mental Disorders (PRIME-MD) (31). For all participants, the use of alcohol during the two weeks prior to assessment was recorded. Blood samples were drawn shortly after a physical examination, between 08:00 and 17:00 hours. The analysis of clinical chemistry parameters was performed by standard methods at the Department of Clinical Chemistry, Ullevål University Hospital, Oslo, Norway on an Integra 800 from Roche Diagnostics (Basel, Switzerland). For immunological analysis, blood was drawn on EDTA vials, and plasma was extracted the next work day and stored at −80°C.

Immunological measures

Plasma levels of sTNF-RI, IL-1Ra, and IL-6 were measured by enzyme immunoassays (EIA) obtained from R&D Systems (Minneapolis, MN, USA). Plasma levels of sCD40L were measured by

Table 1. Sample description

	Healthy controls	All patients	Schizophrenia	Bipolar disorder
Age, mean (SD)	36 (10)	34 (11)	33 (12)	35 (12)
Female gender, n (%)	137 (56)	154 (50)	78 (42)[d]	76 (62)
European, n (%)	242 (99)	255 (82)[d]	142 (76)[d]	113 (90)[d]
Creatinine (umol/l), mean (SD)[a]	72 (11)	72 (15)	72 (13)	72 (17)
ALAT (U/l), mean (SD)[a]	25 (18)	28 (20)	29 (19)	27 (21)
Diabetes/CVD, n (%)	0 (0)	14 (5)	9 (5)	5 (4)
Alcohol use, mean (SD)[b,c]	9 (10)	9 (19)	7 (17)	13 (23)

ALAT = alanine aminotransferase; CVD = cardiovascular disease.
[a]Missing data for 5 controls, 5–9 schizophrenia subjects, and 6 bipolar disorder subjects.
[b]Missing data for 28 controls, 11 schizophrenia subjects, and 2 bipolar disorder subjects.
[c]Number of alcohol units (10 ml alcohol) during the last two weeks.
[d]$p \leq 0.05$, significantly different compared to controls.

EIA obtained from Bender Medsystems (Vienna, Austria). Plasma concentrations of CRP and vWf were measured by EIAs as described elsewhere (32). In the vWF analyses, levels are given in plasma concentration percent (%), and the standard curve is based on samples from a plasma pool of healthy individuals, where the normal range is arbitrarily set to 70–130%. All intra- and interassay coefficients of variance were less than 10%.

Statistical procedures

All statistical analyses were done using the SPSS software package for Windows, version 15.0 (SPSS, Chicago, IL, USA). All tests are two-sided with a preset level of significance of 0.05. The main part of the immunological parameters was significantly skewed, and was analyzed with nonparametric tests (Spearmans Rho and Kruskal–Wallis test with Mann–Whitney *U*-test for post-hoc analyses; the latter were corrected for multiple testing through an adapted Bonferroni correction). The results were controlled for the possible confounders age, gender, ethnicity, kidney function (creatinine), liver function [alanine aminotransferase (ALAT)], alcohol intake, diabetes, or known cardiovascular disease by using hierarchical multiple linear regression analyses; here, the two diagnostic groups were collapsed into one and the resulting variable (case versus control) was entered into the analysis at the last step. The linear regression did not include cortisol levels or time at blood sampling due to lack of complete information in all subjects.

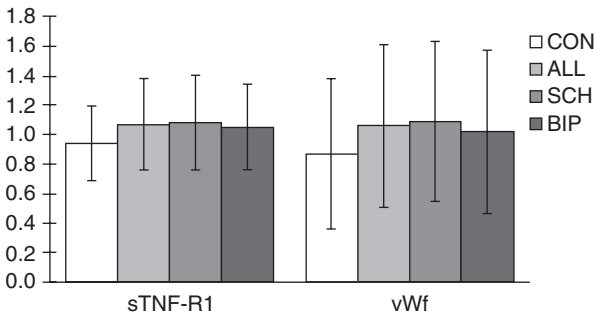


Fig. 1. vWF and sTNF-R1 levels. Mean levels with standard deviations are presented. sTNF-R1 values represent ng/ml; vWf values represent % (1/100). CON = controls; ALL = all patients; SCH = schizophrenia; BIP = bipolar disorder; sTNF-R1 = soluble tumor necrosis factor receptor 1; vWF = von Willebrand factor.

Results

The combined patient group had highly statistically significantly elevated levels of two inflammatory markers, sTNF-RI and vWf, compared to the

Table 2. Levels of inflammatory markers

	Healthy controls n = 244	All patients n = 311	Schizophrenia n = 186	Bipolar disorder n = 125
sTNF-R1				
Median (CI)	0.91 (0.87–0.96)	1.05 (1.01–1.08)[a]	1.05 (1.01–1.10)[a]	1.03 (0.98–1.08)[b]
Mean (SD)	0.94 (0.25)	1.07 (0.31)	1.08 (0.32)	1.05 (0.29)
sCD40L				
Median (CI)	1.65 (1.49–1.76)	1.60 (1.37–1.75)	1.70 (1.48–2.02)	1.42 (1.24–1.66)
Mean (SD)	1.85 (1.23)	1.92 (1.46)	2.00 (1.54)	1.80 (1.33)
IL-1Ra				
Median (CI)	0.33 (0.26–0.42)	0.37 (0.32–0.45)	0.42 (0.34–0.50)	0.31 (0.24–0.45)
Mean (SD)	0.60 (0.87)	0.74 (1.06)	0.85 (1.87)	0.59 (0.81)
vWf				
Median (CI)	77 (69–84)	98 (92–103)[a]	100 (92–107)[a]	95 (82–103)[b]
Mean (SD)	87 (51)	106 (55)	109 (54)	102 (55)
Hs-CRP				
Median (CI)	0.30 (0.20–0.41)	0.37 (0.31–0.41)[c]	0.38 (0.30–0.46)	0.35 (0.28–0.43)
Mean (SD)	0.80 (1.25)	0.95 (1.86)	0.85 (1.30)	1.09 (2.45)
IL-6				
Median (CI)	0.17 (0.15–1.19)	0.18 (0.15–0.21)	0.17 (0.13–0.21)	0.18 (0.15–0.24)
Mean (SD)	0.30 (0.34)	0.36 (0.50)	0.36 (0.47)	0.36 (0.53)

All levels are listed as ng/ml, except vWf is listed as %. Mann–Whitney *U*-test comparing controls to all patients, and Kruskal–Wallis test comparing controls, schizophrenia, and bipolar disorder.

sTNF-R1 = soluble tumor necrosis factor receptor 1; sCD40L = soluble CD40 ligand; IL-1Ra = interleukin-1 receptor antagonist; vWF = von Willebrand factor; hs-CRP = high-sensitivity CRP; IL-6 = interleukin-6; CI = 95% confidence interval; SD = standard deviation.

[a]$p < 0.000005$; [b]$p < 0.005$; [c]$p = 0.01$.

healthy control group, reflecting activation of the TNFα system and endothelial cells, respectively ($p < 0.000002$ for both) (Table 2 and Fig. 1). The increase was 17% for sTNF-RI and 27% for vWf (Table 2). By contrast, there was no significant difference in the levels of IL-6, sCD40L, or IL-1Ra between the patients and the controls, but hs-CRP was significantly elevated ($p = 0.02$). Also in unmedicated patients, there was a significant increase in plasma levels of sTNF-R1 (1.09 versus 0.91 ng/ml, $p < 0.001$) and vWF (101 versus 77%, $p < 0.007$) as compared with concentrations in healthy controls. These elevations also remained significant after controlling for possible confounders. There were no significant differences in any inflammatory parameters between patients that were medicated or unmedicated.

As shown in Table 2, bipolar disorder and schizophrenia had the same inflammatory profile, with no significant differences in levels of any inflammation markers between the two diagnostic groups. Both diagnostic groups showed highly significant elevations of sTNF-RI ($p < 0.001$) and vWf ($p < 0.005$) (Table 2). There was a difference in hs-CRP which did not remain significant when the patient group was divided into schizophrenia and bipolar disorder, due to loss of statistical power.

The impact of case control status on the level of sTNF-RI and vWf after controlling for possible confounders was explored in two linear regression analyses (Tables 3 and 4). Adding information on differences in age, gender, ethnicity, liver function (ALAT), kidney function (creatinine), cardiovascular disease, diabetes, and alcohol intake did not affect the results. Also after controlling for hs-CRP, the levels of sTNFR1 and vWf remained statistically significantly elevated in the patients. Limiting the analysis to patients with strict schizophrenia and bipolar I disorder (i.e., excluding patients with schizoaffective disorder, schizophreniform disorder, bipolar disorder II, and bipolar disorder not otherwise specified), the immune profile was still similar and the elevations remained statistically significant (data not shown).

Table 3. Linear regression with possible confounders of the correlation between sTNF-R1 and group, patient, or control

	B	SE	*t*	p value
Constant	0.5	0.1	3.8	0.0002
Age	0.001	0.001	0.7	0.5
Gender	0.09	0.03	2.9	0.004
European	0.001	0.01	0.1	0.9
Creatinine	0.007	0.001	3.8	0.0000
ALAT	0.000	0.001	0.7	0.5
Diabetes/CVD	0.2	0.08	2.3	0.02
Alcohol use[a]	0.000	0.001	−0.3	0.8
hs-CRP	0.04	0.008	4.8	0.0000
Group (patient or control)	−0.095	0.03	−3.6	0.0004

N = 489. Adjusted R^2 for the total model ≈0.14. *F* for the total model = 9.5, $p < 0.001$.
sTNF-R1 = soluble tumor necrosis factor receptor 1; SE = standard error; ALAT = alanine aminotransferase; CVD = cardiovascular disease; hs-CRP = high-sensitivity C reactive protein.
[a]Last two weeks.

Table 4. Linear regression with possible confounders of the correlation between vWf and group, patient, or control

	B	SE	*t*	p value
vWf (dependent)	81	23	3.6	0.0004
Age	0.4	0.2	2.0	0.05
Gender	−2.9	5.7	−0.51	0.0004
European	3.7	1.9	2.0	0.05
Creatinine	0.26	0.20	1.3	0.2
ALAT	0.09	0.13	0.7	0.5
Diabetes/CVD	−1.3	15	−0.09	0.9
Alcohol use[a]	0.083	0.15	0.56	0.0004
hs-CRP	2.7	1.4	3.6	0.05
Group (patient or control)	−17	5.0	−3.3	0.0009

N = 489. Adjusted R^2 for the total model ≈0.05. *F* for the total model = 3.59, $p < 0.001$.
vWf = von Willebrand factor; SE = standard error; ALAT = alanine aminotransferase; CVD = cardiovascular disease; hs-CRP = high-sensitivity C-reactive protein.
[a]Last two weeks.

In the total sample, STNF-R1 correlated significantly with all other immune factors, with *r* values from 0.28 for vWf and 0.20 for hs-CRP ($p < 0.00001$). VWf correlated significantly only with sTNF-R1and IL-1Ra ($r = 0.15$, $p < 0.0005$). The strongest correlation was seen between IL-6 and hs-CRP ($r = 0.48$, $p < 0.00001$). Smoking habits among the patients did not have any significant correlation with either sTNF-RI, vWf, or hs-CRP. The inflammatory cytokines were not correlated to the cortisol levels in patients, except for hs-CRP, which had a small positive Pearson correlation coefficient with cortisol of 0.12 ($p = 0.04$).

Since there are some indications of diurnal variation in inflammatory levels (33, 34), we analyzed the correlation of immune parameters with the time of blood sampling, and did not find any significant correlations except for IL-1Ra, which was weakly correlated ($r = 0.13$, $p = 0.03$ in patients and $r = 0.14$, $p = 0.06$ in controls). We then compared levels of IL-1Ra in patients with time-matched controls, and IL-1Ra was significantly elevated ($p = 0.007$). However, when controlled for possible confounders, the difference was not significant ($p = 0.17$).

Discussion

The main finding of the present study was a specific and highly significant increase in plasma levels of sTNF-RI and vWf in patients with both bipolar disorder and schizophrenia compared to healthy controls, with no clear differences between the two diagnostic groups. This is the first time this has been studied in a large group of patients comprising the diagnoses of both schizophrenia and bipolar disorder. These findings add to previous findings that have suggested an association between inflammation and severe mental disorders by indicating that this association may involve certain inflammatory pathways, such as activation of the TNF system and endothelial cell activation.

In a recent review regarding schizophrenia, Potvin and colleagues (21) found evidence supporting inflammatory cytokine alterations, with increased levels of IL-1Ra, sIL-2R, and IL-6, and a decrease in IL-2. In contrast, our current study did not find statistically significant alterations of IL-6, and weak changes in IL-1Ra. A possible explanation could be that the meta-analysis included several studies with small samples, different methods, and variety of disease stages, and did not control for confounders. Our results are in agreement with a recent study which also failed to find IL-6 elevations (16). Furthermore, sTNF-RI, a stable and reliable marker of the activity in the TNFα system, was not included in the meta-analysis. Moreover, the advantage of the current study is the large sample size of relatively young subjects, with little or no comorbidity, recruited from a catchment area.

Immune factors in bipolar disorders have received less attention. Most research in mood disorders has involved unipolar depression, where immune alterations have been shown (15, 35, 36). The present study suggests that certain inflammatory pathways (i.e., activation of the TNFα system and endothelial cell activation) are activated in bipolar disorder to the same extent as in schizophrenia. This may reflect similarities in disease mechanisms, as suggested in the continuum hypothesis (24–26). Alternatively, inflammation can be a common epiphenomenon induced by disease-related behavior or lifestyle, which must be investigated further.

To the best of our knowledge, no article (in English) has been published regarding levels of vWF, a reliable marker of endothelial cell activation, in schizophrenia or bipolar disorder. One study of psychotic disorders reported association and genetic linkage between bipolar I disorder and the vWF gene (37). Our findings in the current study of elevated levels of vWf suggest that endothelial cell activation is of importance in both schizophrenia and bipolar disorder, consistent with new findings of endothelial dysfunction in schizophrenia (38).

The highly significant elevation of sTNF-RI and vWf with no differences in other immune markers—with the possible exception of a more minor elevation of hs-CRP and IL-1Ra—may indicate a specific immune-related aberration related to the endothelium in severe mental disorders, as TNFα also is associated with endothelial leakage and endothelial cell activation (39, 40). The combined elevation of TNFα and vWf may suggest that endothelial-related inflammation could be operating in both bipolar disorder and schizophrenia.

It is also of interest that recent studies have implicated a role of TNFα and other cytokines in neurotransmission and other aspects of neuronal function (41–44) independent of inflammation processes. The sTNF-RI pathway is implicated in a wide spectrum of diseases (45), and was recently reported to be required for TNFα-induced sickness behavior (46). TNFα is involved in neurotoxity and neuroplasticity (13, 41, 47–50), and TNFα interacts with both dopaminergic and serotonergic systems (51–54), which are main targets of antipsychotic and mood-stabilizing agents. TNFα is also associated with a general negative effect on emotions and cognition (55, 56), which are the core symptoms of schizophrenia and bipolar disorder. Our results are in agreement with recent findings of upregulated TNFα genes in the brains of schizophrenia patients and association of TNFα polymorphisms with schizophrenia (6, 57).

However, the underlying pathological mechanism related to our findings is uncertain, and we cannot rule out alterations outside of the central nervous system. Endothelial dysfunction as well as TNFα activation could play a role in development of insulin resistance and type 2 diabetes (58–62), which are known to be increased in severe mental disorders. Thus, the pathophysiology of insulin resistance, metabolic syndrome, and severe mental disorders may share inflammatory basis as a common denominator involving enhanced activation of endothelial cells and TNFα.

Earlier studies have indicated an association between blood brain barrier (BBB) pathology and schizophrenia (63). It could be speculated that alterations in endothelial function, with consequent BBB dysfunction (63), might induce toxic neuronal effects leading to alterations in brain structure associated with severe mental disorders (64). Interestingly, treatment with a cyclo-oxygenase inhibitor, an anti-inflammatory agent that also

has endothelium-related effects (65), has been found to be effective as adjunctive medication in the treatment of schizophrenia (66). However, although a dysregulation of endothelial-related vWf has been linked to impaired BBB, the relationship between the raised plasma levels of vWf in patients with severe mental disorders and BBB function in these individuals is not known.

The present study is cross-sectional, as are most studies in the field of immunology in psychiatry, which limits the discussion of causality. Although we controlled for many important confounders, we cannot rule out that other confounders are present. Smoking could confound the findings, but we did not find any significant correlation between smoking and the inflammation markers, and we have recently shown that smoking cessation does not change the levels of sTNF-RI or vWf (67). Antipsychotics have been found to be associated with both inflammatory and anti-inflammatory effects (68, 69), and we cannot completely rule out that the medication is a confounder. This is less likely, however, since the levels of the immune markers were also significantly elevated in nonmedicated patients. Furthermore, despite different drug regimens, the two diagnostic groups showed similar profiles of inflammatory parameters.

To conclude, the main result of the present study is a significant increase in sTNF-RI and vWf in both schizophrenia and bipolar disorders, present also after controlling for confounders. These findings may indicate an association between severe mental illness and abnormal endothelial-related inflammation.

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