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Inflammation in Schizophrenia: Cytokine Levels and Their Relationships to Demographic and Clinical Variables

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Abstract

Objective—Inflammation may play a role in the accelerated physical aging reported in schizophrenia though biomarker findings and associations with demographic and clinical factors are inconsistent.

Design—Cross-sectional, case-control design

Setting—Community-dwelling participants tested in an academic laboratory.

Participants—95 outpatients with schizophrenia (mean age ± SD: 48.1 ± 10.2 yrs) and 95 demographically-comparable healthy comparison subjects (HCs) (mean age ± SD: 48.1 ± 12.1 yrs)

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Contributors

Ellen E. Lee conducted literature reviews, data interpretation, data analyses, and manuscript preparation.
Suzi Hong was involved in data interpretation and manuscript preparation.
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Lisa T. Eyler conducted data analyses, data interpretation, and manuscript preparation.
Dilip V. Jeste designed the study and was involved in manuscript preparation.
All the authors contributed to manuscript preparation.

Conflicts of Interest

The authors declare no relevant conflicts of interest.

Measurements—Sociodemographic and clinical data were collected, and plasma levels of tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interferon-γ (IFN-γ) were assayed. We compared cytokine levels, examined demographic and clinical associations. and adjusted for relevant variables with linear models.

Results—Individuals with schizophrenia had higher levels of TNF-α and IL-6, but not IFN-γ, than HCs. Age was not related to cytokine levels, and age relationships did not differ between diagnostic groups. Women had higher levels of IL-6. TNF-α and IL-6 levels were significantly correlated with depressive symptoms, and adjustment for depression reduced the group effect for both. Within the HCs, TNF-α levels were associated with physical comorbidity and body mass index (BMI). IL-6 levels were significantly correlated with BMI, and within schizophrenia patients, with worse mental and physical well-being. Accounting for physical morbidity and mental well-being reduced group differences in TNF-α and IL-6 levels, respectively. Worse positive symptoms were associated with higher IL-6 levels.

Conclusions—Higher TNF-α and IL-6 levels in schizophrenia patients were associated with depression, physical comorbidity, and mental well-being. Further longitudinal studies are warranted to assess inflammation as a potential treatment target for a subgroup of schizophrenia.

Keywords

TNF-α; IL-6; IFN-γ; schizophrenia; inflammation; cytokines

Objective

Schizophrenia, a serious mental illness, is also associated with increased physical morbidity and premature mortality (1–8), possibly suggesting accelerated biological aging (9). This may stem from dysregulated inflammatory processes (10, 11). There is a large, but inconsistent, literature examining inflammatory blood-based markers in schizophrenia, including high-sensitivity C-reactive protein (hs-CRP), interleukin-6 (IL-6), IL-6 receptor and soluble IL-2 receptor (12–18).

The present study focused on three inflammatory cytokines with well-characterized immunological functions and evidence of a role in the central nervous system (CNS): TNF-α, IL-6, and IFN-γ. TNF-α has important roles in neurogenesis, neuronal cell death, and innate and adaptive immune response (19). Studies on TNF-α vary from higher levels (15, 20–29), no difference (30–40), and lower levels in schizophrenia (41–45). IL-6 has pro-inflammatory and, under certain conditions, anti-inflammatory effects (46), and was elevated in nearly two-thirds of the published reports (15, 22, 24, 28, 29, 35–39, 44, 47–62), no different in a third (20, 21, 23, 26, 30–32, 34, 45, 63–67), and lower in schizophrenia in one study (68). IFN-γ is involved in lymphocyte activation and the kynurenine pathway of tryptophan metabolism, which may link inflammatory processes with glutamatergic and dopaminergic systems. Nine studies of IFN-γ reported lower levels (24, 44, 69–75), four found higher levels (29, 37, 76, 77), and six showed no difference in levels (38, 67, 78–81).

Age is a crucial factor since chronic elevation of inflammatory cytokine levels may indicate immunosenescence, as highly differentiated (“aged”) immune cells readily produce

inflammatory molecules. Normal aging affects CNS regeneration and repair processes, including dysregulation of TNF-α and IL-6 (82). TNF-α, IL-6 and IFN-γ blood levels have been shown to vary with age in healthy samples (24, 61, 81, 83), though findings in schizophrenia are mixed; with only one study of TNF-α levels(81), tree studies of IL-6 (24, 61, 81, 83), and one study of IFN-γ (15, 21, 39, 44, 45, 47, 52, 55) finding significant correlations between age and cytokine levels only in persons with schizophrenia. Although these findings are somewhat suggestive of a stronger correlation of age with cytokine levels in persons with schizophrenia than healthy comparison subjects, none of these studies directly compared the magnitude and direction of the correlations between those groups. It is important to compare the apparent rate of aging between patients and HCs to understand if there is an accelerated trajectory of inflammatory aging. In a cross-sectional study, one possible indication of this would be a statistically stronger association with age in persons with schizophrenia compared to the HC group, previously not shown for these three cytokines.

Gender is another potentially important factor in understanding group differences in cytokine levels. TNF-α levels have been reported to be higher in women, compared to men, both in the general population (84) and in schizophrenia (85). IL-6 levels (84, 86) have been reported to be higher in women compared to men, in the general population, though the opposite relationship was seen in persons with schizophrenia (61). Due to the unclear relationship between gender, diagnosis and cytokine levels, careful gender matching is needed when examining diagnostic group differences, and it is important to explore further possible interactions between gender and diagnosis. Finally, studies in persons with cardiovascular disease have demonstrated that cytokine levels (specifically, IL-6) vary significantly by race (61, 84), suggesting the need for well-matched samples based on racial / ethnic composition.

Previous studies are inconsistent in the degree to which patient groups are matched on demographic factors, the exploration of possible associations with age and gender and examination if such associations differ among people with schizophrenia. Furthermore, there is often little consideration of whether group differences in inflammatory markers persist after adjusting for the myriad of potentially related factors (e.g., BMI, smoking, depression, physical illnesses, anti-inflammatory medication) that often differ between persons with schizophrenia and HCs. In most cases, it is not possible to create matched groups for a long list of covariates without severely limiting the generalizability of the sample. One can explore whether adjusting for them reduces the magnitude of the diagnostic difference in cytokine levels. In the current analysis, we defined potential confounds as those variables that 1) differed significantly between persons with schizophrenia and HCs in our sample, and 2) were correlated with either cytokine level in either group. We then examined for each potential confounder whether group differences in cytokine levels persisted after statistically adjusting for them. Finally, studies have only infrequently examined how schizophrenia-specific factors (e.g duration of illness, positive and negative symptoms, and antipsychotic medication dosage) relate to inflammation. For this class of schizophrenia-specific variables, we examined their relationships to cytokine levels only in the patient group in order to further characterize patients with the greatest inflammation.

We hypothesized that cytokine levels would be elevated in persons with schizophrenia compared to the demographically-comparable HCs. We also hypothesized that cytokine levels would be higher in older participants, and that this age relationship would be stronger among persons with schizophrenia. Inflammation was expected to be greater among women, although whether this gender effect would vary by diagnosis was unclear based on the prior literature. We expected to find several potential confounding variables (i.e., that were different between groups and related to cytokine levels in either group), but that group differences in cytokine levels would persist after adjusting for these. Finally, we expected that individuals with schizophrenia who had a more severe clinical profile (e.g., greater symptom severity and chronicity) would show the greatest inflammatory marker elevations.

Methods

Study participants

All participants spoke English and were recruited from the greater San Diego area. Schizophrenia diagnosis was based on the Structured Clinical Interview for the DSM-IV-TR (SCID) (87). HCs were recruited via multiple methods including from an ongoing survey study of successful aging in healthy adults, recruitment flyers in the community, ResearchMatch.org, and word-of-mouth. They were screened with the Mini-International Neuropsychiatric Interview (MINI) (88) and excluded from the study if they had a past or present diagnosis of a major neuropsychiatric illness. Subjects were excluded for the following: 1) other current DSM-IV-TR Axis I diagnoses; 2) alcohol or other non-tobacco substance abuse or dependence within 3 prior months; 3) diagnosis of dementia, intellectual disability disorder, or a major neurological disorder; 4) medical disability affecting a subject's ability to complete study procedures. The UC San Diego Human Research Protections Program reviewed and approved the study protocol. All subjects were consented prior to their participation.

The total study sample included 113 HCs and 133 subjects with schizophrenia, in whom we had data on levels of the three cytokines on which the present report was focused. These groups were comparable in mean age, but differed significantly in race/ethnicity distribution and nearly significantly in gender. Therefore, using the case-control matching procedure in SPSS (Version 23.0, Armonk, NY, IBM Corp), we formed two subgroups of gender- and race–matched subjects (N = 95 in each group).

Sociodemographic and clinical characteristics

Subjects were interviewed by trained study staff and completed the following standardized assessments for: mental health (Short Form Health Survey - Mental), psychopathology (Patient Health Questionnaire-9 for depression, Scale for the Assessment of Positive Symptoms, Scale for the Assessment of Negative Symptoms), physical health (Short Form Health Survey - Physical), and medical co-morbidity (Cumulative Illness Rating Scale) (89–94). Subjects were interviewed about their current medications, smoking habits, history of arthritis and sleep. BMI was calculated from the participant's measured height and weight. Cognitive assessments included measures of executive functioning (95, 96), incorporating three subtests from the Delis-Kaplan Executive Function System (97).

Cytokine Assays

Participants had a fasting blood draw, where 65 mL of blood were drawn for testing various biomarkers.

Plasma TNF-α, IL-6 and IFN-γ levels were quantified using Meso Scale Discovery (MSD) MULTI-SPOT® Assay System and analyzed on a SECTOR Imager 2400 instrument (Rockville, MD, USA). Using MSD Discovery Workbench® analysis software, standard curves were formed by fitting electrochemiluminescence signal from calibrators to a 4-parameter logistic model with a 1/y2 weighting. Samples were run in duplicates, using V-PLEX Human Biomarker panels (Catalog # K151A0H-2) to measure the cytokines. V-PLEX kits are fully validated according to fit-for-purpose principles and the FDA's analytical validation guidelines according to the manufacturer (MSD). The laboratory technician performing the assays was "blind" to the subject's diagnosis. Intra-assay variability was <10% and inter-assay variability was <5% for all three assays. The lowest detected levels for cytokines were: 0.06 pg/mL (TNF-α), 0.05 pg/mL (IL-6), and 0.28 pg/mL (IFN-γ). No sample showed cytokine levels below the detection limits.

Plasma hs-CRP levels were measured with a commercially available (MSD, Rockville, MD) enzyme-linked immunosorbent assay (ELISA) at the CTRI lab. Intra- and inter-assay coefficients were <5%.

Statistical Analyses

Analyses presented below are based on the two subgroups obtained through the case-control matching, described in the *Participants* section; data on the full sample are available upon request. Intra-class correlations (ICCs) of the cytokines were very low (TNF-α: ICC(3,1)=0.112, IL-6: ICC(3,1) = 0.041, IFN-γ: ICC (3,1) = 0.124), so we used independent samples analyses rather than paired samples analyses.

Variables were assessed for violation of distribution assumptions and were log-transformed as necessary, and adjusted for unequal variances (Levene's test) if necessary. TNF-α, IL-6, and IFN-γ levels were log-transformed for all analyses. Independent sample t-tests or chi-square tests were used to assess differences in sample characteristics between the schizophrenia and HC groups. We also used an independent samples t-test to compare cytokine levels. Since our samples were comparable on age, gender, and race, observed group differences in cytokine levels can be interpreted as independent of any cytokine relationships with those demographics.

Two linear models examined the relationship of age and gender to cytokine levels and whether there were differential relationships between the schizophrenia and HC groups. Specifically, we conducted a linear model with group, age, and a group x age interaction, and a linear model with group, gender, and a group x gender interaction.

Spearman's correlations were examined between log-transformed cytokine levels and other relevant variables in both groupsi. Variables that 1) were significantly different between diagnostic groups, and 2) showed significant correlations with cytokine levels in either group were examined further with univariate linear models to assess whether group

differences in cytokine levels persisted after adjusting for the potential confound. For each of these models, main effects of diagnosis and the potential confounding variable as well as an interaction of diagnosis and the potential confound were included, and we compared the effect size for diagnosis in the adjusted model to that seen without adjustment. Finally, within persons with schizophrenia, we used Spearman's correlations to examine the relationship of cytokine levels to schizophrenia-specific variables.

We presented effect sizes and p-values for all of these statistical tests, and interpreted greater than medium effect sizes (i.e., Cohen's d > .45) as meaningful.

Results

Schizophrenia and HC Sample Characteristics

The patient group included 60 persons diagnosed with schizophrenia and 35 people diagnosed with schizoaffective disorder. These two patient subgroups did not differ significantly on demographic variables, cytokines, or clinical variables (except for depressive symptoms). Therefore, we combined them for subsequent analyses and refer to the group as "schizophrenia".

The schizophrenia and HC groups were not significantly different in age, gender, or racial composition (Table 1). Subjects with schizophrenia had fewer years of education, worse scores of physical and mental well-being, greater physical co-morbidity, including arthritis, were more likely to be taking anti-inflammatory medications, and had poorer executive function, higher BMI and greater smoking. In the current sample, 48.4% of the people with schizophrenia and 28.4% of the HC group had hs-CRP levels > 3 mg/L, indicating high cardiovascular risk based on the American Heart Association guidelines (98).

Plasma Cytokine Levels

TNF-α and IL-6 levels were significantly higher in the participants with schizophrenia compared to the demographically-comparable HC group with medium effect sizes. There was no significant difference in IFN-γ levels between the diagnostic groups; therefore, we focused on TNF-α and IL-6 for examination of age and gender relationships, correlation analyses, and linear modeling.

Relationship to Age and Possible Differential Age Associations by Diagnostic Group

A general linear model of TNF-α levels that included age, diagnosis, and an age x diagnosis interaction was significant with good model fit ($F(3, 186) = 6.39$, $p<0.001$, $R^2 = 0.093$), and revealed a main effect of diagnosis ($F(1,186) = 15.4$, $p<0.001$, Cohen's $d = 0.57$), but no age effect ($F(1,186) = 3.5$, $p = 0.064$, Cohen's $d = 0.27$) or age-by-diagnosis interaction ($F(1,186) = 0.07$, $p = 0.80$, Cohen's $d < 0.06$).

The same general linear model with IL-6 levels as the dependent variable was significant with good model fit ($F(3, 186) = 4.5$, $p = 0.004$, $R^2 = 0.065$) and revealed a main effect of diagnosis ($F(1,186) = 13.0$, $p<0.001$, Cohen's $d = 0.53$). There was no main effect of age ($F(1,186) = 0.46$, $p = 0.50$, Cohen's $d = 0.06$) or age-by-diagnosis interaction ($F(1, 186) = 0.24$, $p = 0.62$, Cohen's $d = 0.06$).

Relationship to Gender and Possible Differential Gender Associations by Diagnostic Group

A general linear model of TNF-α levels with gender, diagnosis, and gender x diagnosis interactions was significant with good model fit ($F(3,186)=5.22$, $p=0.002$, $R^2 = 0.078$). There was a main effect of diagnosis ($F(1,186) = 15.2$, $p<0.001$, Cohen's $d = 0.57$), with schizophrenia levels being higher than those in the HC group. There was no meaningful effect of gender ($F(1, 186) = 0.47$, $p = 0.49$, Cohen's $d = 0.11$) or gender-by-diagnosis interaction ($F(1,186) = 0.10$, $p = 0.80$, Cohen's $d =0.06$). A similar model for IL-6 was significant with good model fit ($F(3, 186)=7.14$, $p<0.001$, $R^2 = 0.103$) with a main effect of diagnosis ($F(1,186) = 13.8$, $p<0.001$, Cohen's $d = 0.54$) and gender ($F(1,186) = 5.4$, $p =0.02$, Cohen's $d = 0.34$), such that levels were higher in persons with schizophrenia and among women. There was no meaningful gender-by-diagnosis interaction ($F(1, 186) = 2.5$, $p = 0.11$, Cohen's $d = 0.23$).

Correlations with TNF-α and IL-6 Levels in Schizophrenia and HC Groups

TNF-α levels were significantly correlated with severity of depressive symptoms in both groups (Table 2). In the HCs, TNF-α levels were also higher among those individuals with more physical co-morbidities, with arthritic disease, taking anti-inflammatory medications and with higher BMI.

Across both groups, IL-6 levels were significantly higher among women, individuals with more depressive symptoms and higher BMI. Among persons with schizophrenia, IL-6 levels were also significantly correlated with taking anti-inflammatory medications and worse mental and physical well-being.

Role of Potential Confounds in Group Differences in Cytokine Levels

The following variables met our criteria for potential confounds (i.e., significantly different between groups and related to cytokine levels in either group): depressive symptoms, mental and physical well-being, physical co-morbidities, taking anti-inflammatory medications and BMI. Using general linear models (Table 3), these group differences were reduced for TNF-α after adjustment for depressive symptom severity, physical co-morbidity, and anti-inflammatory medications; in both cases decreasing to a small, non-significant effect. For IL-6, group differences were smaller but still significant after adjustment for most potential confounds; however, adjustment for depression symptom severity and mental well-being greatly reduced the group effect size and the difference was no longer significant. Examination of a subset of non-depressed people with schizophrenia (n=63) compared to non-depressed HCs (n=63) showed significant diagnostic group differences in cytokine levels (TNF-α: $t(169) = -2.82$, $p = 0.005$; IL-6: $t(169) = -2.41$, $p = 0.017$).

Correlations of Cytokine Levels to Schizophrenia-Specific Variables

Duration of illness, antipsychotic medication burden, and negative symptom severity were not related to levels of either cytokine (Table 2). Subjects with more severe positive symptoms had higher IL-6 levels, but no such relationship was seen for TNF-α.

Conclusions

The strengths of our study included a large sample size, demographically matched HCs, and comprehensive evaluation of several relevant covariates (age, gender, BMI, clinical variables, etc.). Our findings of elevated levels of TNF-α and IL-6 in schizophrenia are consistent with some studies, (15, 20–29, 35–39, 44, 47–62), but not others (20, 21, 23, 26, 30–45, 63–68, 78–81). We did not find a significant difference in IFN-γ levels between schizophrenia and HC groups, similar to several published studies (38, 67, 78–81). Only one study that reported lower IFN-γ levels in persons with schizophrenia than in HCs had more than 50 subjects in each group, but had limited generalizability as all the study participants were men and smoked fewer than 5 cigarettes per day (44).

In general, we did not see age effects for TNF-α or IL-6, which was consistent with a number of studies (15, 21, 30, 31, 39, 44, 45, 52, 55), though not with others (24, 61, 83). We examined potentially differential relationships of cytokine levels with age between the two groups, in spite of the lacking evidence for accelerated age-related inflammation in persons with schizophrenia compared to those free of mental illness. However, interpretation of this negative finding is limited by the cross-sectional design, potential non-linear trajectory of cytokine levels with age within the age range studied (26–65 years), and the relatively chronic course of schizophrenia in our patient group. As predicted, we did find higher IL-6, but not TNF-α levels among women. There was no interaction with diagnosis for either cytokine.

Of the potential confounds that we identified, severity of depressive symptoms was strongly related to TNF-α and IL-6 levels and, when accounted for statistically, reduced group differences in both cytokines to small, non-significant effects. The literature supports findings of increased inflammation in people with major depression (99, 100). Recent studies of cytokines have not differentiated between a depressive component of the schizophrenia pathology and a secondary depressive disorder (101). Nota et al. found elevated systemic TNF-α and IL-4 levels in patients with first episode psychosis and depressive symptoms, compared to non-depressed psychotic patients (102). Smagula et al. found peripheral inflammatory biomarkers, including TNF-α levels to be associated with brain structure in patients with late-life depression (103). Depressive symptoms and accompanying inflammation may characterize a subset of schizophrenia patients with somewhat distinct pathophysiology. Furthermore, peripheral inflammation from medications or psychosocial stressors has been found to cause depressive symptoms (104). Treatment-resistant depressed patients were found to have higher baseline levels of inflammatory markers (105). In our study of schizophrenia, we did not find a significant association with antipsychotic mediation response. Altogether, the moderating effects of depression in inflammatory markers in schizophrenia may offer an opportunity for a targeted therapeutics for a subset of patients.

The association between increased inflammation and greater physical co-morbidity has been described in the literature, often in the context of aging, when both inflammation and comorbidities increase (106). The reduction of the main group effect for TNF-α with the addition of physical comorbidity may indicate that, independent of diagnostic group,

physical illness contributes to TNF-α levels. Similarly, mental well-being may also be intrinsically tied to IL-6 related inflammatory pathways, however this relationship may be difficult to extricate from having a severe mental illness such as schizophrenia (107). The main effect of diagnostic group on TNF-α levels decreased significantly with the consideration of anti-inflammatory medications. Treatment with anti-inflammatory medications could reflect increased systemic inflammation that may be related to having schizophrenia. A large main effect of both group and anti-inflammatory medications were found for IL-6 levels. Group differences in IL-6 were somewhat reduced after adjusting for BMI, but TNF-α elevations remained strong, suggesting that some degree of inflammation in schizophrenia is independent of known associations with BMI. The linear model results differ between TNF-α and IL-6 for a number of covariates, possibly reflecting the different roles of each cytokine within inflammation processes and schizophrenia psychopathology.

Of note, we did not find associations between smoking and elevated cytokine levels across the diagnostic groups. Despite multiple investigations showing that cigarette smoking increases cytokine abnormalities in humans *in vivo* (108–112) and *in vitro* (113–116), our findings are consistent with three studies in schizophrenia that did not find any difference in cytokine levels between the smokers and non-smokers (24, 39, 45). Thus, we postulate that the increased inflammation found in persons with schizophrenia compared to HCs is attributable to factors beyond unhealthy behaviors such as smoking.

Our results must be interpreted cautiously, given several limitations. The temporality of the relationship between the inflammatory markers and clinical symptoms cannot be determined in a cross-sectional study design. The schizophrenia group included outpatients with a chronic and relatively stable course of mental illness. These results may not generalize to medication-naïve, acutely ill, and treatment-resistant patients with schizophrenia. We used case-control matching, and the ICCs were very low. The paired t-test for IFN-γ showed no significant differences ($t(94) = 0.164$, $p = 0.87$, $d = 0.022$), though the ICC was not negligible (ICC = 0.124). We did not conduct further analyses on IFN-γ levels as we found no diagnostic group differences. Additionally, certain variables may be an integral part of having schizophrenia (e.g. mental well-being), and separating their influence on cytokine levels from the diagnostic group effect may not be clinically meaningful (117, 118). We only looked at potential confounds individually, though they have the potential to interact with each other. Despite our large sample size, we were not able to conduct multivariate models with adequate power.

Future studies should explore the longitudinal trajectory of cytokine levels in people with schizophrenia, compared to an HC group. Within-individual inflammatory changes with aging may differ between the diagnostic groups. Understanding the temporal interplay between cytokine levels, depression, physical co-morbidity, and mental well-being would help clarify how to intervene to reduce morbidity and mortality and increase quality of life in patients with schizophrenia. The potential role for anti-inflammatory agents in the treatment of depressive symptoms in schizophrenia should be studied (119).

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Table 1

Comparison of Study Participants With and Without Schizophrenia[¥]

	Schizophrenia			Healthy Comparison						
	N	**Mean / %**	**Std Dev**	**N**	**Mean / %**	**Std Dev**	***t***	***df***	***p***	***Cohen's d***
Sociodemographic Factors										
Age (years)	95	48.1	10.2	95	48.1	12.1	0.019	182.9	0.99	<0.06
Gender (% women)	95	48.4		95	48.4		NA			
Race (%)	95			95			NA			
Caucasian		57.8			57.8					
African-American		15.8			15.8					
Hispanic		23.2			23.2					
Asian		3.2			3.2					
Education (years)	95	12.4	1.9	95	14.6	2.2	7.48	183.3	<0.001	−1.07
Current smoker? (% yes)	95	53.6		95	6.3		50.7[†]	1	<0.001	0.52[‡]
Mental Wellness and Cognitive Factors										
Depressive symptom severity[1]	93	7.04	5.9	92	1.73	2.9	−7.8	133.6	<0.001	1.14
Mental well-being[2]	94	45.1	10.9	92	54.7	5.6	7.54	140.4	<0.001	−1.11
Executive function	95	−0.52	0.7	95	0.43	0.6	10.1	182.0	<0.001	−1.47
Physical Factors										
Physical well-being[3]	94	43.5	10.0	92	51.6	9.3	5.75	183.7	<0.001	−0.84
Physical comorbidity[4]	95	6.71	4.7	95	2.68	3.2	−6.89	166.6	<0.001	−1.00
Arthritis (% yes)	76	27.6		45	28.6		0.43[†]	1	0.51	0.06[‡]
Taking anti-inflammatory medication (% yes)	95	35.8		95	16.8		8.79[†]	1	0.003	0.22[‡]
BMI (kg/m^2)	94	32.2	7.7	92	28.5	7.5	−3.31	184.0	0.001	0.49
Schizophrenia-specific Factors										
Duration of illness (years)	94	25.4	11.1							
Antipsychotic dose[6]	95	1.81	1.4							
Positive symptoms[7]	95	6.39	4.2							
Negative symptoms[8]	95	7.06	4.5							

	Schizophrenia			Healthy Comparison						
	N	Mean / %	Std Dev	N	Mean / %	Std Dev	*t*	*df*	*p*	*Cohen's d*
Cytokines										
TNF-α (pg/mL)	95	3.06	1.1	95	2.51	0.8	−3.90	187.9	<0.001	0.57
IL-6 (pg/mL)	95	1.16	1.0	95	0.94	1.6	−3.61	187.5	<0.001	0.53
IFN-γ (pg/mL)	95	8.97	17.1	95	8.24	13.6	−0.153	187.6	0.88	0.02

¥ Independent samples t-tests or Pearson's Chi-square test

† χ^2 value

ǂ Cramer's V

1 As rated on the PHQ-9 = patient health questionnaire

2 As assessed by the Short Form Health Survey (SF-36) Mental Composite score

3 As assessed by the Short Form Health Survey (SF-36) Physical Composite score

4 As assessed by the Cumulative Illness Rating total score.

6 Antipsychotic medication daily dosages were converted to WHO average daily doses based on published standards (120, 121)

7 As assessed by the Scale for the Assessment of Positive Symptoms (SAPS) total score

8 As assessed by the Scale for the Assessment of Negative Symptoms (SANS) total score

NA = Not applicable as the groups were matched on gender and race.

BMI = body mass index

hs-CRP = high sensitivity C-Reactive

Protein TNF = Tumor Necrosis Factor

IL = interleukin

IFN = Interferon

pg/mL = picograms per milliliter

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Table 2

Correlations between Key Demographic and Clinical Variables and TNF-α and IL-6 Levels in Study Participants With and Without Schizophrenia[¥]

	TNF-α				IL-6			
	Schizophrenia		Healthy Comparison		Schizophrenia		Healthy Comparison	
	N	*r or t*	N	*r or t*	N	*r or t*	N	*r or t*
Sociodemographic Factors								
Age (years)	95	0.11	95	0.17	95	0.12	95	0.11
Gender (women vs men)	95	0.70	95	0.27	95	2.91*	95	0.50
Race (Non-Caucasian vs Caucasian)	95	−0.51	95	−1.26	95	0.74	95	1.44
Education (years)	95	−0.05	95	−0.05	95	−0.03	95	−0.07
Current smoker (no vs yes)	95	1.13	95	−0.64	95	0.14	95	0.03
Mental Wellness & Cognitive Factors								
Depressive symptom severity[1]	93	0.23*	92	0.28**	93	0.40**	92	0.22*
Mental well-being[2]	94	−0.14	92	0.06	94	−0.26*	92	−0.17
Executive function	95	−0.19	95	−0.03	95	−0.19	95	−0.11
Physical Factors								
Physical well-being[3]	94	−0.09	92	−0.16	94	−0.30**	92	−0.19
Physical comorbidity[4]	95	0.14	95	0.30**	95	0.19	95	0.15
Arthritis (no vs yes)	76	0.42	45	−2.6*	76	−1.9	45	−0.11
Taking anti-inflammatory medication (no vs yes)	95	−0.72	95	−3.5**	95	−2.0*	95	−0.55
BMI	94	0.16	92	0.25*	94	0.45**	92	0.38**
Schizophrenia-specific Factors								
Duration of illness (years)	94	0.14	--	--	94	0.10	--	--
Antipsychotic dose[5]	95	−0.10	--	--	95	−0.10	--	--
Positive symptoms[6]	95	0.10	--	--	95	0.21*	--	--
Negative symptoms[7]	95	0.09	--	--	95	0.19	--	--

[¥] Spearman's bivariate correlation or independent samples t-tests.

[1] As rated on the PHQ-9 = patient health questionnaire

[2] As assessed by the Short Form Health Survey (SF-36) Mental Composite score

[3] As assessed by the Short Form Health Survey (SF-36) Physical Composite score

[4] As assessed by the Cumulative Illness Rating total score.

[5] Antipsychotic medication daily dosages were converted to WHO average daily doses based on published standards (120, 121)

[6] As assessed by the Scale for the Assessment of Positive Symptoms (SAPS) total score

[7] As assessed by the Scale for the Assessment of Negative Symptoms (SANS) total score

BMI = body mass index

TNF = Tumor Necrosis Factor

IL = interleukin

hs-CRP = high sensitivity C-Reactive Protein

**; and *. Significant 2-tailed correlation coefficients at the 0.01 and 0.05 levels, respectively

Table 3

General linear models testing group effect with depression, mental and physical health, BMI as covariates[†]

	TNF-α								IL-6							
	Full Model		Group		Covariate		Interaction		Full Model		Group		Covariate		Interaction	
	F	d[¥]	F	d	F	d	F	d	F	d	F	d	F	d	F	d
No Covariate	--	--	15.2	0.57	--	--	--	--	--	--	13.0	0.53	--	--	--	--
Clinical Covariate																
Depressive symptom severity[1]	7.3**	0.70	2.8	0.25	5.4*	0.35	0.09	<0.06	13.5**	0.95	0.74	0.13	13.7**	0.55	0.2	0.06
Mental well-being[2]	5.3*	0.59	9.4*	0.45	0.01	<0.06	1.1	0.16	9.1**	0.78	1.4	0.18	11.0**	0.49	0.4	0.09
Physical well-being[3]	6.3**	0.64	7.4*	0.40	3.8	0.29	0.9	0.14	7.5**	0.70	5.9*	0.36	6.1*	0.36	2.4	0.23
Physical comorbidity[4]	10.4**	0.82	3.0	0.26	15.0**	0.57	2.6	0.24	8.4**	0.74	5.0*	0.33	4.8*	0.32	2.7	0.24
Taking anti-inflammatory medication (no vs yes)	9.2**	0.78	3.0	0.26	9.4*	0.45	4.7*	0.31	5.8**	0.61	9.5*	0.45	2.7*	0.24	0.56	0.11
BMI[‡]	8.0**	0.73	10.2*	0.47	7.2*	0.40	1.58	0.20	20.1**	1.2	6.3*	0.37	40.3**	0.94	2.2	0.22

[†] Degrees of freedom = 3, 186 for the full model and 1, 186 for each covariate except when indicated.

[‡] Degrees of freedom = 3, 182 for the full model and 1, 182 for each covariate except when indicated.

[¥] Cohen's d

[1] As rated on the PHQ-9 = patient health questionnaire

[2] As assessed by the Short Form Health Survey (SF-36) Mental Composite score

[3] As assessed by the Short Form Health Survey (SF-36) Physical Composite score

[4] As assessed by the Cumulative Illness Rating total score.

TNF = Tumor Necrosis Factor

IL = interleukin

BMI = body mass index

** , and * Significant 2-tailed correlation coefficients at the 0.01 and 0.05 levels, respectively