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

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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.* **Methods:** *In a cross-sectional, case-control design, 95 outpatients with schizophrenia (mean age ± SD: 48.1 ± 10.2 years) and 95 demographically comparable healthy comparison subjects (HCs) (mean age ± SD: 48.1 ± 12.1 years) were studied. 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. The authors 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. IL-6 levels were significantly correlated with body mass index 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.* **Conclusion:** *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.* (Am J Geriatr Psychiatry 2017; 25:50–61)

Key Words: TNF-α, IL-6, IFN-γ, schizophrenia, inflammation, cytokines

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INTRODUCTION

Schizophrenia, a serious mental illness, is also associated with increased physical morbidity and premature mortality,[1–7] possibly suggesting accelerated biologic aging.[8] This may stem from dysregulated inflammatory processes.[9,10] There is a large, but inconsistent, literature examining inflammatory blood-based markers in schizophrenia, including high-sensitivity C-reactive protein, interleukin-6 (IL-6), IL-6 receptor, and soluble IL-2 receptor.[11–17]

The present study focused on three inflammatory cytokines with well-characterized immunologic functions and evidence of a role in the central nervous system: tumor necrosis factor (TNF)-α, IL-6, and interferon (IFN)-γ. TNF-α has important roles in neurogenesis, neuronal cell death, and innate and adaptive immune response.[18] Studies on TNF-α vary from higher levels,[14,19–28] no difference,[29–39] to lower levels in schizophrenia.[40–44] IL-6 has proinflammatory and, under certain conditions, anti-inflammatory effects[45] and was elevated in nearly two-thirds of published reports,[14,21,23,27,28,34–38,43,46–61] no different in one-third,[19,20,22,25,29–31,33,44,62–66] and lower in schizophrenia in one study.[67] 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,[23,43,68–74] four found higher levels,[28,36,75,76] and six showed no difference in levels.[37,66,77–80]

Age is a crucial factor because chronic elevation of inflammatory cytokine levels may indicate immunosenescence, because highly differentiated ("aged") immune cells readily produce inflammatory molecules. Normal aging affects central nervous system regeneration and repair processes, including dysregulation of TNF-α and IL-6.[81] TNF-α, IL-6, and IFN-γ blood levels have been shown to vary with age in healthy samples,[23,60,80,82] although findings in schizophrenia are mixed; with only one study of TNF-α levels,[80] three studies of IL-6,[23,60,80,82] and one study of IFN-γ[14,20,38,43,44,46,51,54] 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 (HCs), 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 with 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 than in men, both in the general population[83] and in schizophrenia.[84] IL-6 levels[83,85] have been reported to be higher in women compared with men in the general population, although the opposite relationship was seen in persons with schizophrenia.[60] Because of 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,[60,83] 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 of whether 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., body mass index [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 statisti-

cally 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 to further characterize patients with the greatest inflammation.

We hypothesized that cytokine levels would be elevated in persons with schizophrenia compared with 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 *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision*.[86] HCs were recruited via multiple methods, including from an ongoing survey study of successful aging in healthy adults, recruitment flyers in the community, www.ResearchMatch.org, and word-of-mouth. They were screened with the Mini-International Neuropsychiatric Interview[87] and excluded from the study if they had a past or present diagnosis of a major neuropsychiatric illness. Subjects were also excluded for the following: (1) other current *Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, Text Revision* 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 neurologic disorder; and (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 before 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 IBM SPSS Statistics for Windows (Version 23.0, Armonk, NY: IBM Corp), we formed two subgroups of gender- and race-matched subjects (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 comorbidity (Cumulative Illness Rating Scale).[88–93] Subjects were interviewed about their current medications, smoking habits, history of arthritis, and sleep. BMI was calculated from the participants' measured height and weight. Cognitive assessments included measures of executive functioning,[94,95] incorporating three subtests from the Delis-Kaplan Executive Function System.[96]

Cytokine Assays

Participants had a fasting blood draw, where 65 mL blood were drawn for testing various biomarkers. Plasma TNF-α, IL-6, and IFN-γ levels were quantified using the Multi-Spot Assay System and analyzed on a Sector Imager 2400 instrument (Meso Scale Discovery, Rockville, MD). Using Meso Scale Discovery Workbench analysis software, standard curves were formed by fitting the electrochemiluminescence signal from calibrators to a four-parameter logistic model with a 1/y2 weighting. Samples were run in duplicates, using V-PLEX Human Biomarker panels (Catalog no.

K151A0H-2; Meso Scale Discovery) to measure the cytokines. V-PLEX kits are fully validated according to fit-for-purpose principles and the U.S. Food and Drug Administration's analytical validation guidelines according to the manufacturer. The laboratory technician performing the assays was "blind" to the subject's diagnosis. Intra-assay variability was <10% and interassay variability <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 high-sensitivity C-reactive protein levels were measured with a commercially available (Meso Scale Discovery) enzyme-linked immunosorbent assay at the Clinical and Translational Research Institute lab (La Jolla, CA). Intra- and interassay coefficients were <5%.

Statistical Analyses

Analyses presented below are based on the two subgroups obtained through the case-control matching (described above in *Participants*); data on the full sample are available upon request. Intraclass 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 χ^2 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. Because 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 × age interaction and a linear model with group, gender, and a group × gender interaction.

Spearman's correlations were examined between log-transformed cytokine levels and other relevant variables in both groups. Variables that were significantly different between diagnostic groups and 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 model, 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 statistical tests and interpreted greater than medium effect sizes (i.e., Cohen's $d \geq 0.45$) 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, cytokine levels 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 comorbidity, 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 high-sensitivity C-reactive protein levels >3 mg/L, indicating high cardiovascular risk based on American Heart Association guidelines.[97]

Plasma Cytokine Levels

TNF-α and IL-6 levels were significantly higher in the participants with schizophrenia compared with the

TABLE 1. Comparison of Study Participants with and Without Schizophrenia[a]

	Schizophrenia			HC						
	N	Mean/%	SD	N	Mean/%	SD	t	df	p	Cohen's d
Sociodemographic factors										
Age, yr	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			
White		57.8			57.8					
African American		15.8			15.8					
Hispanic		23.2			23.2					
Asian		3.2			3.2					
Education, yr	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[b]	1	<0.001	0.52[c]
Mental wellness and cognitive factors										
Depressive symptom severity[d]	93	7.04	5.9	92	1.73	2.9	−7.8	133.6	<0.001	1.14
Mental well-being[e]	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[f]	94	43.5	10.0	92	51.6	9.3	5.75	183.7	<0.001	−0.84
Physical comorbidity[g]	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[b]	1	0.51	0.06[c]
Taking anti-inflammatory medication (% yes)	95	35.8		95	16.8		8.79[b]	1	0.003	0.22[c]
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, yr	94	25.4	11.1							
Antipsychotic dose[h]	95	1.81	1.4							
Positive symptoms[i]	95	6.39	4.2							
Negative symptoms[j]	95	7.06	4.5							
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

Notes: NA = Not applicable as the groups were matched on gender and race.
[a]Independent samples t tests or Pearson's χ^2 test.
[b]χ^2 value.
[c]Cramer's V.
[d]As rated on the Patient Health Questionnaire-9.
[e]As assessed by the Short Form Health Survey–36 Mental Composite score.
[f]As assessed by the Short Form Health Survey–36 Physical Composite score.
[g]As assessed by the Cumulative Illness Rating total score.
[h]Antipsychotic medication daily dosages were converted to World Health Organization average daily doses based on published standards (WHO: Guidelines for ATC classification and DDD assignment World Health Organization, 2010; WHO: Introduction to Drug Utilization Research, World Health Organization Collaborating Centre for Drug Statistics Methodology, 2009).
[i]As assessed by the Scale for the Assessment of Positive Symptoms total score.
[j]As assessed by the Scale for the Assessment of Negative Symptoms total score.

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 × 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 × 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 comorbidities, with arthritic disease, taking anti-inflammatory medications, and with higher BMI.

TABLE 2. Correlations Between Key Demographic and Clinical Variables and TNF-α and IL-6 Levels in Study Participants with and Without Schizophrenia[a]

	TNF-α				IL-6			
	Schizophrenia		HC		Schizophrenia		HC	
	N	r or t	N	r or t	N	r or t	N	r or t
Sociodemographic factors								
Age, yr	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[b]	95	0.50
Race (Nonwhite vs. white)	95	−0.51	95	−1.26	95	0.74	95	1.44
Education, yr	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 and cognitive factors								
Depressive symptom severity[c]	93	0.23[b]	92	0.28[d]	93	0.40[d]	92	0.22[b]
Mental well-being[e]	94	−0.14	92	0.06	94	−0.26[b]	92	−0.17
Executive function	95	−0.19	95	−0.03	95	−0.19	95	−0.11
Physical factors								
Physical well-being[f]	94	−0.09	92	−0.16	94	−0.30[d]	92	−0.19
Physical comorbidity[g]	95	0.14	95	0.30[d]	95	0.19	95	0.15
Arthritis (no vs. yes)	76	0.42	45	−2.6[b]	76	−1.9	45	−0.11
Taking anti-inflammatory medication (no vs. yes)	95	−0.72	95	−3.5[d]	95	−2.0[b]	95	−0.55
BMI	94	0.16	92	0.25[b]	94	0.45[d]	92	0.38[d]
Schizophrenia-specific factors								
Duration of illness, yr	94	0.14	—	—	94	0.10	—	—
Antipsychotic dose[h]	95	−0.10	—	—	95	−0.11	—	—
Positive symptoms[i]	95	0.10	—	—	95	0.21[b]	—	—
Negative symptoms[j]	95	0.09	—	—	95	0.19	—	—

Notes: [a]Spearman's bivariate correlation or independent samples t tests.
[b]Significant two-tailed correlation coefficients at 0.05 level.
[c]As rated on the Patient Health Questionnaire-9.
[d]Significant two-tailed correlation coefficients at the 0.01 level.
[e]As assessed by the Short Form Health Survey–36 Mental Composite score.
[f]As assessed by the Short Form Health Survey–36 Physical Composite score.
[g]As assessed by the Cumulative Illness Rating total score.
[h]Antipsychotic medication daily dosages were converted to World Health Organization average daily doses based on published standards.
[i]As assessed by the Scale for the Assessment of Positive Symptoms total score.
[j]As assessed by the Scale for the Assessment of Negative Symptoms total score.

Across both groups, IL-6 levels were significantly higher among women and 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 comorbidities, 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 comorbidity, and anti-inflammatory medications, in both cases decreasing to a small, nonsignificant 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 nondepressed people with schizophrenia (N = 63) compared with nondepressed 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.

DISCUSSION

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[14,19–28,34–38,43,46–61] but not others.[19,20,22,25,29–44,62–67,77–80] We did not find a significant difference in IFN-γ levels between schizophrenia and HC groups, similar to several published studies.[37,66,77–80] 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

TABLE 3. General Linear Models Testing Group Effect with Depression, Mental and Physical Health, and BMI as Covariates[a]

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

Notes: [a]Degrees of freedom = 3,186 for the full model and 1,186 for each covariate except when indicated.
[b]Cohen's d.
[c]Significant two-tailed correlation coefficients at the 0.01 level.
[d]Significant two-tailed correlation coefficients at the 0.05 level.
[e]As rated on the Patient Health Questionnaire-9.
[f]As assessed by the Short Form Health Survey–36 Mental Composite score.
[g]As assessed by the Short Form Health Survey–36 Physical Composite score.
[h]As assessed by the Cumulative Illness Rating total score.
[i]Degrees of freedom = 3,182 for full model and 1,182 for each covariate.

limited generalizability because all study participants were men and smoked fewer than five cigarettes per day.[43]

In general, we did not see age effects for TNF-α or IL-6, which was consistent with a number of studies[14,20,29,30,38,43,44,51,54] but not with others.[23,60,82] 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 with those free of mental illness. However, interpretation of this negative finding is limited by the cross-sectional design, potential nonlinear 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, nonsignificant effects. The literature supports findings of increased inflammation in people with major depression.[98,99] Recent studies of cytokines have not differentiated between a depressive component of the schizophrenia pathology and a secondary depressive disorder.[100] Noto et al.[101] found elevated systemic TNF-α and IL-4 levels in patients with first episode psychosis and depressive symptoms compared with nondepressed psychotic patients. Smagula et al.[102] found peripheral inflammatory biomarkers, including TNF-α levels, to be associated with brain structure in patients with late-life depression. 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.[103] Treatment-resistant depressed patients were found to have higher baseline levels of inflammatory markers.[104] 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 comorbidity has been described in the literature, often in the context of aging, when both inflammation and comorbidities increase.[105] 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.[106] 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[107–111] and in vitro,[112–115] our findings are consistent with three studies in schizophrenia that did not find any difference in cytokine levels between the smokers and nonsmokers.[23,38,44] Thus, we postulate that the increased inflammation found in persons with schizophrenia compared with 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-naive, 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 ($t(94) = 0.164$, $p = 0.87$, $d = 0.022$), although the ICC was

not negligible (ICC = 0.124). We did not conduct further analyses on IFN-γ levels because 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.[116,117] We only looked at potential confounds individually, although 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 with an HC group. Within-individual inflammatory changes with aging may differ between the diagnostic groups. Understanding the temporal interplay between cytokine levels, depression, physical comorbidity, 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.[118]

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