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Effects of IL-6/IL-6R axis alterations in serum, plasma and cerebrospinal fluid with the schizophrenia: an updated review and meta-analysis of 58 studies

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Abstract

Studies investigating the association between IL-6/IL-6R axis and schizophrenia (SZ) susceptibility found inconsistent data. To reconcile the results, a systematic review followed by a meta-analysis was performed to assess the associations. This study followed the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines. A comprehensive search of the literature was carried out in July 2022 using electronic databases PubMed, EBSCO, Science Direct, PsychInfo, and Scopus. Study quality was assessed by the Newcastle–Ottawa scale. Pooled standard mean difference (SMD) with 95% confidence interval (CI) was calculated by fixed-effect or random-effect model analysis. Fifty-eight studies were identified, including 4,200 SZ patients and 4,531 controls. Our meta-analysis results showed an increase of IL-6 levels in plasma, serum, or CSF and decreased IL-6R levels in serum in patients under treatment. Further studies are needed to better elucidate the correlation between the IL-6/IL-6R axis and the schizophrenia.

Keywords Interleukin · Cytokine · Receptor · Association · Schizophrenia

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Introduction

Schizophrenia (SZ) is considered a severe psychiatric disorder and one of the top causes of disability. Schizophrenia is a multisystemic disorder associated with several immune dysfunctions, including abnormal levels of cytokines [1, 2]. The manifold interactions between the nervous system and the immune system could underlie the development of SZ. Studies have demonstrated that interactions between the brain and the immune system can lead to changes in cognition, mood, and behavior [3, 4].

Interleukin (IL-6) is the major pro-inflammatory cytokine within the IL-6 family that is released from various cell types in the blood (monocytes, macrophages, T and B cells). For signaling, IL-6 binds to the non-signal-transducing IL-6 receptor (IL-6R), followed by complex formation with the signal-transducing co-receptor glycoprotein 130 (gp130) [5, 6].

Abnormalities of protein levels of pro-inflammatory cytokines and their soluble receptors have been reported in the serum/plasma of SZ patients. In a detail, reports have shown alterations in IL-6 levels in SZ. In this sense, investigations have described a relationship between increased IL-6 levels

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and tissue concentrations with clinical features of the disease, such as the duration of the disorder or treatment resistance [7–9].

As the IL-6/IL-6R axis continues to be implicated in more psychiatric diseases, the need to better understand the dysregulation of the signaling pathways driving the schizophrenia also grows [10]. Ultimately, therapeutics targeting the IL-6/IL-6R axis may require to be further tailored to specific cell types or tissue compartments. Therefore, we performed an updated comprehensive meta-analysis to further evaluate the correlations between IL-6 or IL-6R concentrations and SZ risk covering all currently available data in order to provide evidence for clinical practice.

Materials and methods

Literature search

The Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) statement was used when we performed this study. We searched the electronic databases PubMed, EBSCO, Science Direct, PsychInfo, and Scopus to identify suitable studies published prior to July 2022 using the following search strategies: (1) Interleukin-6 OR "IL-6" OR Interleukin-6 receptor OR "IL-6R"; (2) Plasma OR Serum OR Cerebrospinal fluid; and (3) Schizophrenia. Some articles were identified via manual screening of relevant references from other studies on the subject.

Selection criteria

Studies included in the current meta-analysis met the following criteria: (1) studies using a population-based case–control design; (2) SZ cases were clinically defined; (3) studies must clearly present means and standard deviations (SD) of IL-6 and/or IL-6R levels for both patients and controls; and (4) articles were provided in English language. We excluded studies with duplicate data, studies that reported IL-6 and/or IL-6R using dichotomous data (e.g., negative or positive), or studies without a control group. All literature search and selection processes were cross-checked by two researchers (YHD and TBGC).

Data extraction and study quality

The same two reviewers independently assessed the included studies. Decisions were compared and disagreements were resolved by consensus or by involving a third investigator.

We extracted the following data including first author, publication year, research country, the ethnicity of samples, the number of subjects, gender, mean age, age of SZ onset, psychiatric drugs used, biological sample type, mean, and SD of IL-6/IL-6R levels or available data to calculate these values for patients and controls, source, and detection method used for IL-6/IL-6R analyses.

The Newcastle–Ottawa Scale (NOS) was used to assess the quality of the included studies. The NOS contains three domains (study selection, group comparability, and exposure) covering four, two, and three points. Quality categories were determined by the NOS score of each study. We defined that the score of high quality with 6 or more, medium quality from 3 to 5, and low quality less than 3.

Data analysis

The standard mean differences (SMD) with a 95% confidence interval (CI) were calculated to explore the differences in IL-6 or IL-6R levels between the patient and control groups. The heterogeneity among the included studies was investigated using Q-test statistics and I^2 test; P value less than 0.10 from Cochran's Q-test or more than 50% for I^2 test indicated significant heterogeneity. A fixed-effects model was applied for homogeneous data, and a random-effects model was applied for heterogeneous data. Sensitivity analysis was used to assess the results after removing any of the studies one at a time. The risk of publication bias was assessed using Begg's test and Egger's test. A value of $P < 0.05$ indicated no publication bias. Three meta-analyses were performed for IL-6 according to type of biological sample (serum, plasma, and cerebrospinal fluid (CSF)) and one meta-analysis for IL-6R (serum).

Subgroup analyses stratified by ethnicity (Caucasian or Asian) and medication use (drug-free or under treatment) were also conducted. Drug-free status was defined as a condition of no medical drug intake for at least 2 weeks before admission in the case of SZ patients. All statistical analyses were performed using the Comprehensive Meta-analysis version 2 (Biostat, Englewood, NJ, USA).

Results

Literature identification

The initial search using keywords identified in 462 records that required further screening. After removal of duplicates, 261 articles remained and 178 articles were eligible for abstract review based on title. After, 103 articles were selected for full-text review. Eventually, there were 56 articles that were included. The PRISMA flowchart is shown in Fig. 1.

Study characteristics

A total of 58 case–control studies were retrieved comprising 4,200 SZ patients and 4,531 controls. Specifically, 53 studies

reported only IL-6 levels, 2 studies measure IL-6R levels, and finally 3 studies both IL-6 and IL-6R levels. Some studies analyzed the IL-6/IL-6R protein levels in several biological samples, due to above, separated meta-analyses were performed for each protein and biological sample (serum, plasma and CSF).

First, IL-6 meta-analysis included 35 articles that detected IL-6 levels in serum [1, 8, 11–43] with 2,648 SZ patients and 3,014 controls, 18 articles in plasma [2, 7, 9, 44–58] with 1,410 SZ patients and 1,440 controls, and finally, 3 articles in CSF [25, 49, 59] with 138 SZ patients and 34 controls. Second, IL-6R levels only were quantified in serum samples; therefore, the meta-analysis included five articles [12, 14, 25, 60, 61] with 207 SZ patients and 159 controls.

All studies included in the meta-analysis were case–control studies and published in English language. DSM-IV criteria were the most used for the clinical diagnosis. Data on medicated patients were reported in 34 studies while 32 studies reported separate data on drug-free patients and only 2 studies were conducted in mixed populations with medicated and drug-free patients. Detailed characteristics of individual studies are presented in Table 1 and 2. The overall quality score of studies according to NOS ranged from 7 to 9 (see Table 1 and 2).

Meta-analysis of IL-6 levels

From the 56 association studies of IL-6 levels between patients with schizophrenia and healthy controls that met the criteria selection were analyzed according to the biological sample used (plasma, serum, or CSF). The overall data showed a significant P value in plasma ($P < 0.0001$), serum ($P < 0.0001$), and CSF ($P = 0.001$) analyses.

Moreover, we performed an analyses based on Caucasian and Asian populations; both had a significant P value ($P < 0.001$) in plasma or serum samples. In particularly, Caucasian analyses present four times more increase of IL-6 levels in serum (point estimate 1.11, lower limit 0.80, upper limit 1.42) compared with plasma (point estimate 0.24, lower limit 0.09, upper limit 0.39) samples.

Also, we consider important to analyze the pharmacological treatment of the patients with schizophrenia. Therefore, the studies were grouped in patients with schizophrenia under treatment and drug free; plasma and serum analyses revealed a statistical association ($P < 0.001$) of IL-6 levels in both groups (Fig. 2). Nevertheless, in patients under treatment, a considerable increase of IL-6 levels was observed in plasma (point estimate 1.05, lower limit 0.84, and upper limit 1.26) compared with serum samples (point estimate 0.46, lower limit 0.36, and upper limit 0.56); more details in the Table 3 and Fig. 3.

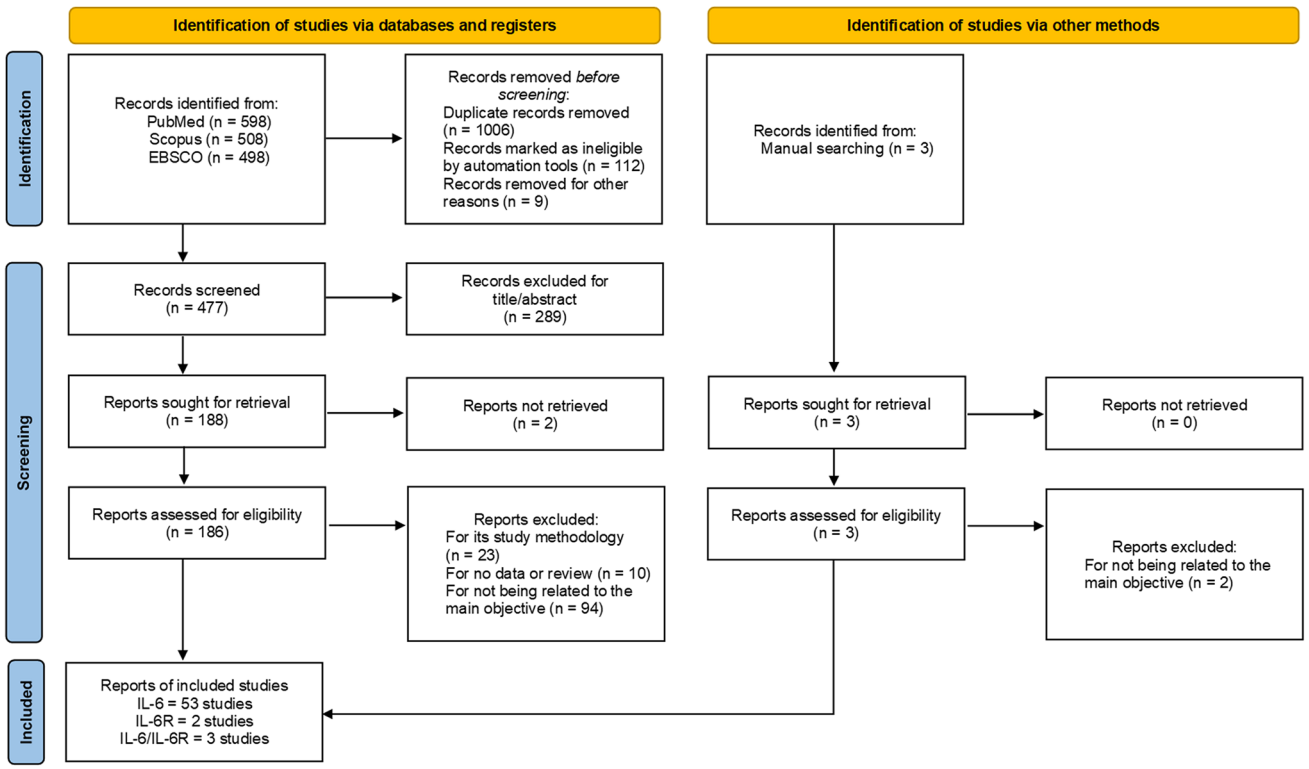


Fig. 1 The flow diagram of the study selection

Table 1 Characteristics of the included studies in the meta-analysis investigating the association between IL-6 protein and risk of schizophrenia

			Patients with SZ										Healthy control			NOS scale
First author	Year	Country	N	Gender (M/F)	Mean age	Diagnostic	Sample			Assay method	Medication			N	Gender (M/F)	Mean age	
							Serum	Plasma	CSF		Drug-free	Under treatment	Mixed				
Ganguli et al. [1]	1994	USA	128	71/57	34.5	–	✓			ELISA	✓			110	61/49	31.7	8
Xu et al. [44]	1994	UK	52	–	–	–		✓		RA	✓	✓		10	7/3	–	7
Maes et al. [45]	1995	USA	14	3/11	27.8	Paranoid, residual, undifferentiated, chronic or subchronic		✓		EIA	✓	✓		21	8/13	33	8
Naudin et al. [11]	1996	France	30	–	–	Chronic	✓			IA		✓		15	–	–	7
Maes et al. [46]	1997	Belgium	17	11/6	38.2	–		✓		ELISA	✓	✓		23	13/10	35.3	8
Frommberger et al. [47]	1997	Germany	32	18/14	33	–		✓		–	✓	✓		12	6/6	31	8
Monteleone et al. [48]	1997	Italy	17	7/10	25.4	Paranoid, disorganized, chronic or subchronic		✓		ELISA	✓	✓		17	7/10	29.6	8
Lin et al. [12]	1998	Italy	27	18/9	47.1	Chronic or subchronic	✓			ELISA		✓		15	8/7	45.1	8
Van Kammen et al. [49]	1999	USA	61	61/0	38.1	Chronic		✓		ELISA			✓	25	25/0	35	8
Akiyama [13]	1999	Japan	14	11/15	34.4	Paranoid or disorganized	✓			ELISA	✓			27	10/17	34.8	8
Maes et al. [14]	2000	Italy	31	–	–	–	✓			ELISA		✓		7	–	–	7
Zhang et al. [15]	2002	China	70	56/14	42.5	Paranoid or disorganized	✓			ELISA	✓			30	22/8	40.4	8
Garver et al. [59]	2003	USA	31	28/3	34.1	–				ELISA	✓			14	10/4	32.9	8
Zhang et al. [16]	2005	China	78	60/18	43.7	–	✓			ELISA	✓			30	22/8	40.4	8
Na and Kim [17]	2007	Korea	43	23/20	32.8	Paranoid, disorganized or undifferentiated	✓			ELISA		✓		50	26/24	31.4	8

Table 1 (continued)

First author	Year	Country	Patients with SZ										Healthy control			NOS scale
			N	Gender (M/F)	Mean age	Diagnostic	Sample			Assay method	Medication			N	Gender (M/F)	Mean age	
							Serum	Plasma	CSF		Drug-free	Under treatment	Mixed				
Singh et al. [18]	2009	India	30	–	–	Paranoid, residual, disorganized or catatonic	✓			ELISA	✓	✓		30	18/12	33.8	7
Singh et al. [18]	2009	India	20	–	–	Paranoid, residual, disorganized or catatonic	✓			ELISA		✓		30	–	–	7
García-Miss et al. [19]	2010	Mexico	70	–	–	Paranoid	✓			ELISA	✓	✓		70	–	–	7
Lin et al. [8]	2011	Taiwan	34	16/18	34.6	Residual	✓			ELISA	✓	✓		30	14/16	27.6	8
Hope et al. [50]	2011	Norway	153	83/60	32.6	–		✓		ELISA			✓	239	105/134	36	8
Krause et al. [2]	2012	Germany	21	18/13	36.7	–		✓		–	✓	✓		31	18/13	37.7	8
Zakharyan et al. [51]	2012	Armenia	10	5/5	26.2	Paranoid		✓		ELISA	✓			105	51/54	37.3	9
Zakharyan et al. [51]	2012	Armenia	103	53/50	46	Paranoid		✓		ELISA		✓		105	51/54	37.3	9
Dennison et al. [52]	2012	Ireland	40	24/16	38.23	–		✓		ELISA		✓		40	13/27	36.2	8
Di Nicola et al. [20]	2013	UK	24	16/8	28.1	Affective psychosis	✓			CLIA		✓		24	15/9	26.6	8
Borovcanin et al. [21]	2013	Serbia	133	53/80	35.7	–	✓			ELISA		✓		36	36/0	36.5	8
Kalmady et al. [53]	2014	India	28	14/14	29.9	–		✓		ELISA	✓			37	20/17	27.4	8
Ding et al. [54]	2014	China	69	37/32	27.4	–		✓		ELISA	✓			60	27/33	26.8	7
Neelamekam et al. [22]	2014	Singapore	20	14/6	38	–	✓			MI		✓		19	11/8	35.6	8
Klemettila et al. [23]	2014	Finland	190	108/82	42.9	–	✓			ELISA		✓		903	500/403	46	8
Luo et al. [24]	2014	China	160	83/77	35.3	Chronic	✓			ELISA		✓		80	65/15	26.7	8
Hayes et al. [25]	2014	Germany	46	10/36	25.8	–	✓			ELISA		✓		35	14/21	26.4	8

Table 1 (continued)

First author	Year	Country	Patients with SZ										Healthy control			NOS scale
			N	Gender (M/F)	Mean age	Diagnostic	Sample			Assay method	Medication			N	Gender (M/F)	Mean age	
							Serum	Plasma	CSF		Drug-free	Under treatment	Mixed				
Song et al. [26]	2014	China	62	33/29	24.7	–	✓			ELISA	✓	✓		60	33/27	26.2	7
Noto et al. [27]	2015	Brazil	55	36/19	24.7	–	✓			CBA		✓		57	30/27	26.6	8
Pandey et al. N. [7]	2015	USA	30	20/10	30.4	–		✓		ELISA		✓		30	17/13	34.6	8
Hope et al. [55]	2015	Norway	121	66/55	36	–		✓		EIA		✓		241	180/61	36	8
Simsek et al. [28]	2016	Turkey	30	13/17	14.7	–	✓			CBA	✓			26	12/14	14.5	7
Zhang et al. [29]	2016	China	92	75/17	47.5	Paranoid, residual, disorganized or undifferentiated	✓			ELISA		✓		60	44/16	47.7	8
Ali et al. [30]	2017	Egypt	44	–	–	–	✓			ELISA	✓			50	–	–	7
Gurung et al. [31]	2018	India	67	51/16	33.8	–	✓			ELISA		✓		72	55/17	34.2	9
Gurung et al. [31]	2018	India	28	17/11	35.2	–	✓			ELISA	✓			72	–	–	9
Dahan et al. [32]	2018	Israel	41	29/12	35.2	–	✓			ELISA		✓		25	11/14	41	8
Ding et al. [33]	2018	China	54	27/27	46	–	✓			CLIA		✓		29	14/15	41.8	8
Kalmady et al. [9]	2018	India	75	41/34	30.69	–		✓		CBA	✓			102	57/45	25.7	8
Fang et al. [56]	2019	China	174	82/92	35.83	–		✓		QA		✓		29	12/17	33.2	8
Luo et al. [34]	2019	China	68	29/39	34.2	Chronic	✓			ELISA		✓		80	65/15	26.7	7
Liu et al. [35]	2019	China	52	31/21	20.7	–	✓			ELISA		✓		41	23/18	22.1	8
Wu et al. [36]	2019	China	44	26/18	31.2	–	✓			ELISA	✓	✓		44	20/24	34.3	8
Azizi et al. [37]	2019	Iran	24	17/7	34.1	–	✓			ELISA		✓		24	17/7	33.82	8
He et al. [38]	2020	China	35	20/15	26.1	–	✓			MI	✓	✓		36	22/14	25.8	8
Borovcanin et al. [39]	2020	Serbia	27	16/11	36.1	–	✓			ELISA		✓		18	12/6	36.6	8
Dai et al. [40]	2020	China	83	45/38	23.7	–	✓			ELISA	✓			60	32/28	24.6	7
Liu et al. [57]	2020	Taiwan	210	142/68	41.6	Chronic	✓			ELISA	✓			122	46/76	41.1	7

Table 1 (continued)

First author	Year	Country	Patients with SZ										Healthy control			NOS scale
			N	Gender (M/F)	Mean age	Diagnostic	Sample			Assay method	Medication			N	Gender (M/F)	Mean age	
							Serum	Plasma	CSF		Drug-free	Under treatment	Mixed				
Wang et al. [58]	2020	China	126	61/65	21.3	–		✓		LA	✓			130	60/70	20.9	7
Di Biase et al. [41]	2021	Australia	497	325/72	40	–	✓	✓		LA	✓			646	257/389	43	8
Mousa et al. [42]	2021	Iraq	115	78/37	36.2	–	✓			ELISA	✓			43	24/19	33.2	8
Ma et al. [43]	2021	China	82	–	30.8	–	✓			ELISA		✓		30	–	20.4	7

CLIA chemiluminescent immunoassay, *CBA* cytometric bead array, *ELISA* enzyme-linked immunosorbent assay, *IA* immunoradiometric assay, *QA* quantibody array, *LA* luminex assay, *MI* multiplex immunoassays, *RA* radioimmunoassay

Table 2 Characteristics of the included studies in the meta-analysis investigating the association between IL-6R protein in serum samples and risk of schizophrenia

First author	Year	Country	Patients with SZ							Healthy control			NOS scale
			N	Gender (M/F)	Mean age	Diagnostic	Assay method	Medication		N	Gender (M/F)	Mean age	
								Drug-free	Antipsychotic				
Müller et al. [61]	1997	Germany	39	22/17	31	–	ELISA	✓	✓	35	14/21	26.4	7
Müller et al. [60]	1997	Germany	25	15/10	34	Paranoid, catatonic or disorganized	ELISA		✓	42	24/18	29	8
Lin et al. [12]	1998	Italy	27	18/9	47.1	Paranoid	ELISA	✓		15	4/3	40.4	8
Maes et al. [14]	2000	Italy	31	–	–	–	ELISA		✓	7	–	–	7
Hayes et al. [25]	2014	Germany	46	10/36	25.8	–	ELISA	✓		25	17/8	30	8

ELISA enzyme-linked immunosorbent assay

Meta-analyses of IL-6R levels

Five association studies of IL-6R levels between patients with schizophrenia and healthy controls were included in the analyses [12, 14, 25, 60, 61], all were performed on biological samples of serum. The overall data analyses did not showed a statistical relationship ($P = 0.533$) of IL-6R in SZ patients compared to healthy controls.

The same outcomes were found when it was analyzed by the studies with Caucasian population ($P = 0.923$) and drug-free schizophrenia patients ($P = 0.457$). On the contrary, patients under treatment present a decrease in IL-6R levels (point estimate -0.753, lower limit − 1.07, upper limit − 0.42, and P value < 0.001); see Table 4.

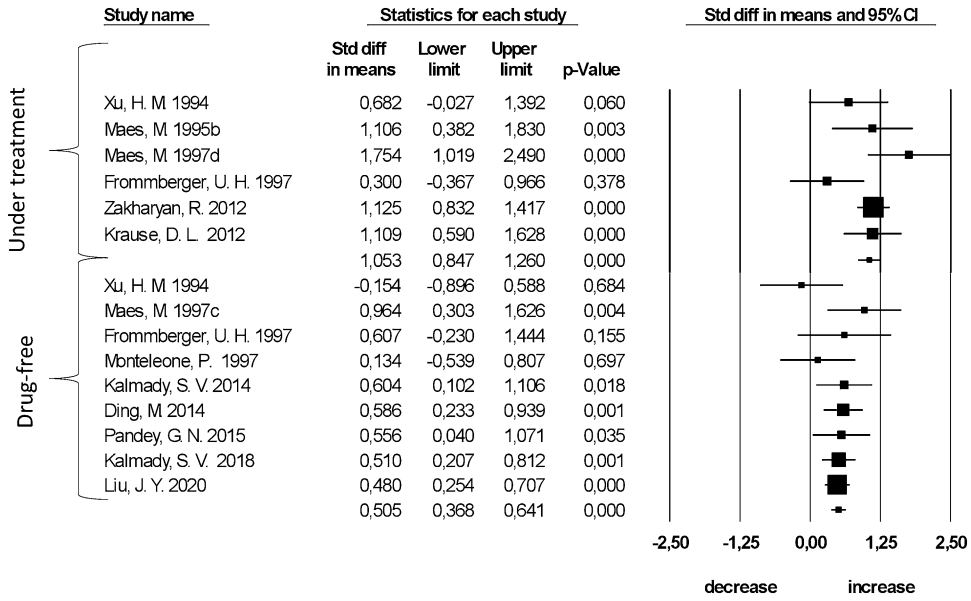
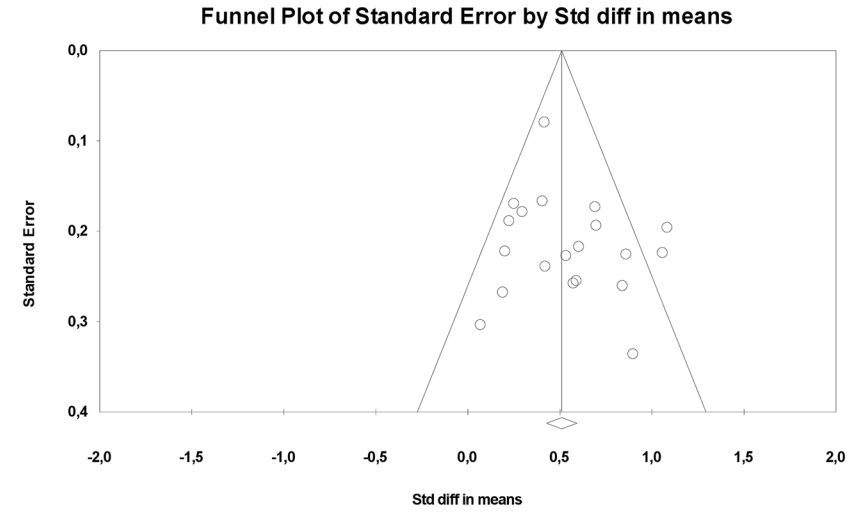


Fig. 2 Meta-analysis of IL-6 plasma levels in patients with schizophrenia under treatment vs drug free

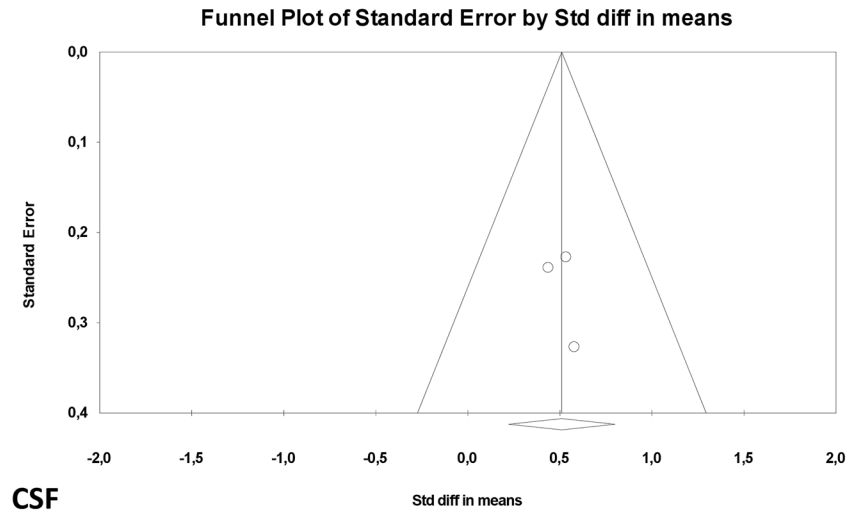
Table 3 Analyses of IL-6 levels between patients with schizophrenia and controls

Biological sample	Test of association				Test of heterogeneity		Test of publication bias
	Point estimate	Lower limit	Upper limit	*P* value	*P* value	I^2%	*P* value
Overall data							
Plasma	0.41	0.32	0.50	0.000	0.104	39.38	0.948
Serum	0.50	0.42	0.59	0.000	0.101	46.33	0.271
CSF	0.51	0.22	0.80	0.001	0.930	0.000	0.638
Caucasian population							
Plasma	0.24	0.09	0.39	0.001	0.105	45.80	0.791
Serum	1.11	0.80	1.42	0.000	0.388	0.000	0.643
Asian population							
Plasma	0.49	0.36	0.62	0.000	0.977	0.000	0.592
Serum	0.67	0.50	0.84	0.000	0.169	32.46	0.542
Schizophrenia patients under treatment							
Plasma	1.05	0.84	1.26	0.000	0.108	48.69	0.716
Serum	0.46	0.36	0.56	0.000	0.106	39.71	0.139
Drug-free schizophrenia patients							
Plasma	0.50	0.36	0.64	0.000	0.586	0.000	0.771
Serum	0.51	0.35	0.67	0.000	0.207	27.73	0.487

Plasma



Serum



CSF

Fig. 3 Funnel plots of IL-6 plasma, serum, and CSF levels in patients with schizophrenia

Discussion

The present meta-analysis synthesized evidence about the association of IL-6 and IL-6R between patients with SZ and healthy controls. The analysis demonstrated that high IL-6 levels and low IL-6R levels are associated with the schizophrenia. However, we want to highlight some factors.

First, even in SZ patients, the primary effect of the IL-6 regulation is in the brain, and the meta-analysis with the overall data did not differ between plasma, serum, or CSF (*P* value < 0.001 in the three groups). This evidences the influence of immune system in the schizophrenia. In this sense, high levels of IL-6 are associated with an altered brain morphology and the severity of the disease [62]. Specifically, increased levels of IL-6 are related with the negative symptoms of the schizophrenia. Because this modulation could allow a neurodegeneration which influence in the cognitive function. In fact, IL-6, IL-1β, and TNF-α play an important role in neuroinflammation which is common related with neurotoxic properties [63]. For example, in animal model, studies observed that IL-6 decreases the survival rate of serotoninergic neurons [64]. Furthermore, there is evidence that pro-inflammatory cytokine, such as IL-6, influences the tryptophan transformation into kynurenine. From this pathway, especially kynurenic acid can induce abnormal behavior by interfering with the glutamate transmissions [65]. Subsequently, these events could allow an alteration in the dopamine pathways leading the symptoms of schizophrenia; Fig. 4 [66].

Another fact to take in consideration is the participation of pharmacological treatment of SZ patients. Notably, treatment with several antipsychotic drugs is associated with adverse cardio-metabolic side effects, such as weight gain and dyslipidemia. These metabolic effects of antipsychotic drugs are associated with increased peripheral inflammation, especially with elevated levels of IL-6 and macrophage infiltration into adipose tissue [63, 67]. Hence, we evaluated for separation of the patients with a current pharmacological treatment and drug-free SZ patients. In agreement with the previous reports, our findings with plasma samples reveal a higher increase of IL-6 levels in SZ patients under treatment than in drug-free patients. Subsequently, this highlights the importance of the inflammation for the development of metabolic syndrome in schizophrenia under pharmacological treatment, such as antipsychotics. Therefore, this evidence once again emphasized the need for secure treatment for patients with SZ in order to avoid possible effect of the drug therapy.

Furthermore, in order to have a more understandable comprehension of the role of IL-6 pathway, we evaluated the role of IL-6R. This pro-inflammatory pathway is used by various cell types within the brain, hence, the importance on the pathogenesis of schizophrenia [68]. Our findings reveal a statistical association in patients with treatment and IL-6R serum levels. This is in agreement with previous report that observed significant decrease of the serum levels after neuroleptic treatment [61]. Evidence showed that increased levels of soluble cytokine receptors are correlated with the severity of illness in patients with SZ [68]. Nevertheless, studies also report that treatment with antipsychotic drugs decreased the IL-6R levels [45]. Hence, we could support the hypothesis that symptoms in schizophrenia are correlated with the regulation/modulation of IL-6R and the IL-6 activity.

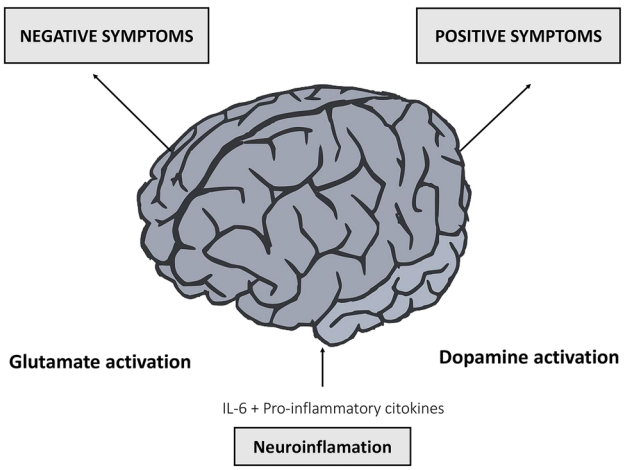


Fig. 4 Implication of pro-inflammatory cytokines, glutamate, and dopamine activation with the subsequent stimulation of positive and negative symptoms in schizophrenia

Table 4 Analyses of IL-6R serum levels between patients with schizophrenia and controls

Groups	Test of association				Test of heterogeneity		Test of publication bias
	Point estimate	Lower limit	Upper limit	*P* value	*P* value	I^2%	*P* value
Overall	− 0.08	− 0.36	0.190	0.533	0.134	46.20	0.305
Caucasian	0.017	− 0–32	0.35	0.923	0.109	49.94	0.549
Under treatment	− 0.753	− 1.07	− 0.42	0.000	0.063	63.80	0.361
Drug-free	− 0.113	− 0–40	− 0.18	0.457	0.069	62.69	0.142

Although the current meta-analysis analyzed the IL-6 and IL-6R levels in SZ patients and could provide clinical evidence of the importance of IL-6/IL-6R pathway, limitations exist. Some included studies did not control the confounding factors that might influence the relationship between IL-6/IL-6R levels and schizophrenia, such as comorbidities (e.g., obesity), time of the sample collection (e.g., morning/evening), among others. However, we tried to control confounding factors such as sample type (plasma, serum, and CSF), use of a pharmacological treatment, and origin of the sample population. But these sub-group analyses could have a statistical limitation because in order to address the confounding factors (sample type, pharmacological treatment, and origin of the sample population), the sample size could be considered small to detect minor effects. Despite these limitations, this meta-analysis provides further evidence of the IL-6/IL-6R activity's importance of the role in the pathophysiology of schizophrenia.

Conclusions

Findings showed an increase of IL-6 levels in plasma, serum, or CSF and decreased IL-6R levels in serum in patients with schizophrenia. These alterations in IL-6/IL-6R levels might facilitate the development of personalized treatment or precision clinical approaches of this disease, by helping stratify patients and interventions using pharmacological strategies aimed at restoring physiological IL-6 pathway.

Author contributions All authors contributed to the study conception and design. Material preparation, data collection, and analysis were performed by TBGC, YHD, CATZ, and MLLN. The first draft of the manuscript was written by IEJR, RFOO, and all authors commented on previous versions of the manuscript. All authors read and approved the final manuscript.

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Declarations

Conflict of interest The authors have no relevant financial or non-financial interests to disclose.

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Consent to participate Not applicable.

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References

1. Ganguli R, Yang Z, Shurin G, Chengappa KN, Brar JS, Gubbi AV, Rabin BS (1994) Serum interleukin-6 concentration in schizophrenia: elevation associated with duration of illness. Psychiatry Res 51:1–10. https://doi.org/10.1016/0165-1781(94)90042-6
2. Krause DL, Wagner JK, Wildenauer A, Matz J, Weidinger E, Riedel M, Obermeier M, Gruber R, Schwarz M, Müller N (2012) Intracellular monocytic cytokine levels in schizophrenia show an alteration of IL-6. Eur Arch Psychiatry Clin Neurosci 262:393–401. https://doi.org/10.1007/s00406-012-0290-2
3. Vidal PM, Pacheco R (2020) The cross-talk between the dopaminergic and the immune system involved in schizophrenia. Front Pharmacol 11:394. https://doi.org/10.3389/fphar.2020.00394
4. Birnbaum R, Weinberger DR (2020) A genetics perspective on the role of the (neuro)immune system in schizophrenia. Schizophr Res 217:105–113. https://doi.org/10.1016/j.schres.2019.02.005
5. Baran P, Hansen S, Waetzig GH, Akbarzadeh M, Lamertz L, Huber HJ, Ahmadian MR, Moll JM, Scheller J (2018) The balance of interleukin (IL)-6, IL-6·soluble IL-6 receptor (sIL-6R), and IL-6·sIL-6R·sgp130 complexes allows simultaneous classic and trans-signaling. J Biol Chem 293:6762–6775. https://doi.org/10.1074/jbc.RA117.001163
6. Rose-John S (2012) IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. Int J Biol Sci 8:1237–1247. https://doi.org/10.7150/ijbs.4989
7. Pandey GN, Ren X, Rizavi HS, Zhang H (2015) Proinflammatory cytokines and their membrane-bound receptors are altered in the lymphocytes of schizophrenia patients. Schizophr Res 164:193–198. https://doi.org/10.1016/j.schres.2015.02.004
8. Lin CC, Chang CM, Chang PY, Huang TL (2011) Increased interleukin-6 level in Taiwanese schizophrenic patients. Chang Gung Med J 34:375–381
9. Kalmady SV, Shivakumar V, Jose D, Ravi V, Keshavan MS, Gangadhar BN, Venkatasubramanian G (2018) Plasma cytokines in minimally treated schizophrenia. Schizophr Res 199:292–296. https://doi.org/10.1016/j.schres.2018.04.022
10. Borovcanin MM, Jovanovic I, Radosavljevic G, Pantic J, Minic Janicijevic S, Arsenijevic N, Lukic ML (2017) Interleukin-6 in schizophrenia-is there a therapeutic relevance? Front Psychiatry 8:221. https://doi.org/10.3389/fpsyt.2017.00221
11. Naudin J, Mège JL, Azorin JM, Dassa D (1996) Elevated circulating levels of IL-6 in schizophrenia. Schizophr Res 20:269–273. https://doi.org/10.1016/0920-9964(96)00014-x
12. Lin A, Kenis G, Bignotti S, Tura GJ, De Jong R, Bosmans E, Pioli R, Altamura C, Scharpé S, Maes M (1998) The inflammatory response system in treatment-resistant schizophrenia: increased serum interleukin-6. Schizophr Res 32:9–15. https://doi.org/10.1016/s0920-9964(98)00034-6
13. Akiyama K (1999) Serum levels of soluble IL-2 receptor alpha, IL-6 and IL-1 receptor antagonist in schizophrenia before and during neuroleptic administration. Schizophr Res 37:97–106. https://doi.org/10.1016/s0920-9964(98)00140-6
14. Maes M, Bocchio Chiavetto L, Bignotti S, Battisa Tura G, Pioli R, Boin F, Kenis G, Bosmans E, de Jongh R, Lin A, Racagni G, Altamura CA (2000) Effects of atypical antipsychotics on the inflammatory response system in schizophrenic patients resistant to treatment with typical neuroleptics. Eur Neuropsychopharmacol 10:119–124. https://doi.org/10.1016/s0924-977x(99)00062-0
15. Zhang XY, Zhou DF, Zhang PY, Wu GY, Cao LY, Shen YC (2002) Elevated interleukin-2, interleukin-6 and interleukin-8 serum levels in neuroleptic-free schizophrenia: association with psychopathology. Schizophr Res 57:247–258. https://doi.org/10.1016/s0920-9964(01)00296-1

16. Zhang XY, Zhou DF, Cao LY, Wu GY, Shen YC (2005) Cortisol and cytokines in chronic and treatment-resistant patients with schizophrenia: association with psychopathology and response to antipsychotics. Neuropsychopharmacology 30:1532–1538. https://doi.org/10.1038/sj.npp.1300756
17. Na KS, Kim YK (2007) Monocytic, Th1 and th2 cytokine alterations in the pathophysiology of schizophrenia. Neuropsychobiology 56:55–63. https://doi.org/10.1159/000111535
18. Singh B, Bera NK, Nayak CR, Chaudhuri TK (2009) Decreased serum levels of interleukin-2 and interleukin-6 in Indian Bengalee schizophrenic patients. Cytokine 47:1–5. https://doi.org/10.1016/j.cyto.2009.05.005
19. García-Miss Mdel R, Pérez-Mutul J, López-Canul B, Solís-Rodríguez F, Puga-Machado L, Oxté-Cabrera A, Gurubel-Maldonado J, Arankowsky-Sandoval G (2010) Folate, homocysteine, interleukin-6, and tumor necrosis factor alfa levels, but not the methylenetetrahydrofolate reductase C677T polymorphism, are risk factors for schizophrenia. J Psychiatr Res 44:441–446. https://doi.org/10.1016/j.jpsychires.2009.10.011
20. Di Nicola M, Cattaneo A, Hepgul N, Di Forti M, Aitchison KJ, Janiri L, Murray RM, Dazzan P, Pariante CM, Mondelli V (2013) Serum and gene expression profile of cytokines in first-episode psychosis. Brain Behav Immun 31:90–95. https://doi.org/10.1016/j.bbi.2012.06.010
21. Borovcanin M, Jovanovic I, Radosavljevic G, Djukic Dejanovic S, Stefanovic V, Arsenijevic N, Lukic ML (2013) Antipsychotics can modulate the cytokine profile in schizophrenia: attenuation of the type-2 inflammatory response. Schizophr Res 147:103–109. https://doi.org/10.1016/j.schres.2013.03.027
22. Neelamekam S, Nurjono M, Lee J (2014) Regulation of interleukin-6 and leptin in schizophrenia patients: a preliminary analysis. Clin Psychopharmacol Neurosci 12:209–214. https://doi.org/10.9758/cpn.2014.12.3.209
23. Klemettilä JP, Kampman O, Seppälä N, Viikki M, Hämäläinen M, Moilanen E, Leinonen E (2014) Cytokine and adipokine alterations in patients with schizophrenia treated with clozapine. Psychiatry Res 218:277–283. https://doi.org/10.1016/j.psychres.2014.04.049
24. Luo Y, He H, Zhang M, Huang X, Zhang J, Zhou Y, Liu X, Fan N (2014) Elevated serum levels of TNF-α, IL-6 and IL-18 in chronic schizophrenic patients. Schizophr Res 159:556–557. https://doi.org/10.1016/j.schres.2014.09.015
25. Hayes LN, Severance EG, Leek JT, Gressitt KL, Rohleder C, Coughlin JM, Leweke FM, Yolken RH, Sawa A (2014) Inflammatory molecular signature associated with infectious agents in psychosis. Schizophr Bull 40:963–972. https://doi.org/10.1093/schbul/sbu052
26. Song X, Fan X, Li X, Zhang W, Gao J, Zhao J, Harrington A, Ziedonis D, Lv L (2014) Changes in pro-inflammatory cytokines and body weight during 6-month risperidone treatment in drug naïve, first-episode schizophrenia. Psychopharmacology 231:319–325. https://doi.org/10.1007/s00213-013-3382-4
27. Noto C, Ota VK, Gouvea ES, Rizzo LB, Spindola LM, Honda PH, Cordeiro Q, Belangero SI, Bressan RA, Gadelha A, Maes M, Brietzke E (2014) Effects of risperidone on cytokine profile in drug-naïve first-episode psychosis. Int J Neuropsychopharmacol. https://doi.org/10.1093/ijnp/pyu042
28. Şimşek Ş, Yıldırım V, Çim A, Kaya S (2016) Serum IL-4 and IL-10 levels correlate with the symptoms of the drug-naive adolescents with first episode, early onset schizophrenia. J Child Adolesc Psychopharmacol 26:721–726. https://doi.org/10.1089/cap.2015.0220
29. Zhang XY, Tan YL, Chen DC, Tan SP, Yang FD, Wu HE, Zunta-Soares GB, Huang XF, Kosten TR, Soares JC (2016) Interaction of BDNF with cytokines in chronic schizophrenia. Brain Behav Immun 51:169–175. https://doi.org/10.1016/j.bbi.2015.09.014
30. Ali FT, Abd El-Azeem EM, Hamed MA, Ali MAM, Abd Al-Kader NM, Hassan EA (2017) Redox dysregulation, immuno-inflammatory alterations and genetic variants of BDNF and MMP-9 in schizophrenia: pathophysiological and phenotypic implications. Schizophr Res 188:98–109. https://doi.org/10.1016/j.schres.2017.01.016
31. Gurung J, Chamlagai D, Bera NK, Chaudhuri TK, Singh B (2018) Elevated levels of C-reactive protein and IL-6 among the antipsychotic medicating schizophrenia patients of Siliguri, West Bengal, India. Nord J Psychiatry 72:311–317. https://doi.org/10.1080/08039488.2018.1441438
32. Dahan S, Bragazzi NL, Yogev A, Bar-Gad M, Barak V, Amital H, Amital D (2018) The relationship between serum cytokine levels and degree of psychosis in patients with schizophrenia. Psychiatry Res 268:467–472. https://doi.org/10.1016/j.psychres.2018.07.041
33. Ding N, Li Z, Liu Z (2018) Escitalopram augmentation improves negative symptoms of treatment resistant schizophrenia patients-a randomized controlled trial. Neurosci Lett 681:68–72. https://doi.org/10.1016/j.neulet.2018.05.030
34. Luo Y, He H, Zhang J, Ou Y, Fan N (2019) Changes in serum TNF-α, IL-18, and IL-6 concentrations in patients with chronic schizophrenia at admission and at discharge. Compr Psychiatry 90:82–87. https://doi.org/10.1016/j.comppsych.2019.01.003
35. Liu Y, Tao H, Yang X, Huang K, Zhang X, Li C (2019) Decreased serum oxytocin and increased homocysteine in first-episode schizophrenia patients. Front Psychiatry 10:217. https://doi.org/10.3389/fpsyt.2019.00217
36. Wu D, Lv P, Li F, Zhang W, Fu G, Dai J, Hu N, Liu J, Xiao Y, Li S, Shah C, Tao B, Zhao Y, Gong Q, Lui S (2019) Association of peripheral cytokine levels with cerebral structural abnormalities in schizophrenia. Brain Res 1724:146463. https://doi.org/10.1016/j.brainres.2019.146463
37. Azizi E, Zavaran Hosseini A, Soudi S, Noorbala AA (2019) Alteration of serum levels of cytokines in schizophrenic patients before and after treatment with risperidone. Iran J Allergy Asthma Immunol 18:262–268. https://doi.org/10.18502/ijaai.v18i3.1119
38. He X, Ma Q, Fan Y, Zhao B, Wang W, Zhu F, Ma X, Zhou L (2020) The role of cytokines in predicting the efficacy of acute stage treatment in patients with schizophrenia. Neuropsychiatr Dis Treat 16:191–199. https://doi.org/10.2147/ndt.S218483
39. Borovcanin MM, Minic Janicijevic S, Jovanovic IP, Gajovic NM, Jurisevic MM, Arsenijevic NN (2020) Type 17 immune response facilitates progression of inflammation and correlates with cognition in stable schizophrenia. Diagnostics (Basel). https://doi.org/10.3390/diagnostics10110926
40. Dai N, Jie H, Duan Y, Xiong P, Xu X, Chen P, Kang M, Li M, Li T, Huang Z, Chen H (2020) Different serum protein factor levels in first-episode drug-naive patients with schizophrenia characterized by positive and negative symptoms. Psychiatry Clin Neurosci 74:472–479. https://doi.org/10.1111/pcn.13078
41. Di Biase MA, Zalesky A, Cetin-Karayumak S, Rathi Y, Lv J, Boerrigter D, North H, Tooney P, Pantelis C, Pasternak O, Shannon Weickert C, Cropley VL (2021) Large-scale evidence for an association between peripheral inflammation and white matter free water in schizophrenia and healthy individuals. Schizophr Bull 47:542–551. https://doi.org/10.1093/schbul/sbaa134
42. Mousa RF, Al-Hakeim HK, Alhaideri A, Maes M (2021) Chronic fatigue syndrome and fibromyalgia-like symptoms are an integral component of the phenome of schizophrenia: neuro-immune and opioid system correlates. Metab Brain Dis 36:169–183. https://doi.org/10.1007/s11011-020-00619-x
43. Ma J, Zhang Y, Huang Z, Liu X, Lv L, Li Y (2021) Relationship between curative effect and serum inflammatory factors level in male patients with first-episode schizophrenia treated with olanzapine. Front Psychiatry 12:782289. https://doi.org/10.3389/fpsyt.2021.782289

44. Xu HM, Wei J, Hemmings GP (1994) Changes of plasma concentrations of interleukin-1 alpha and interleukin-6 with neuroleptic treatment for schizophrenia. Br J Psychiatry 164:251–253. https://doi.org/10.1192/bjp.164.2.251
45. Maes M, Bosmans E, Calabrese J, Smith R, Meltzer HY (1995) Interleukin-2 and interleukin-6 in schizophrenia and mania: effects of neuroleptics and mood stabilizers. J Psychiatr Res 29:141–152. https://doi.org/10.1016/0022-3956(94)00049-w
46. Maes M, Bosmans E, Kenis G, De Jong R, Smith RS, Meltzer HY (1997) In vivo immunomodulatory effects of clozapine in schizophrenia. Schizophr Res 26:221–225. https://doi.org/10.1016/s0920-9964(97)00057-1
47. Frommberger UH, Bauer J, Haselbauer P, Fräulin A, Riemann D, Berger M (1997) Interleukin-6-(IL-6) plasma levels in depression and schizophrenia: comparison between the acute state and after remission. Eur Arch Psychiatry Clin Neurosci 247:228–233. https://doi.org/10.1007/bf02900219
48. Monteleone P, Fabrazzo M, Tortorella A, Maj M (1997) Plasma levels of interleukin-6 and tumor necrosis factor alpha in chronic schizophrenia: effects of clozapine treatment. Psychiatry Res 71:11–17. https://doi.org/10.1016/s0165-1781(97)00036-x
49. van Kammen DP, McAllister-Sistilli CG, Kelley ME, Gurklis JA, Yao JK (1999) Elevated interleukin-6 in schizophrenia. Psychiatry Res 87:129–136. https://doi.org/10.1016/s0165-1781(99)00053-0
50. Hope S, Dieset I, Agartz I, Steen NE, Ueland T, Melle I, Aukrust P, Andreassen OA (2011) Affective symptoms are associated with markers of inflammation and immune activation in bipolar disorders but not in schizophrenia. J Psychiatr Res 45:1608–1616. https://doi.org/10.1016/j.jpsychires.2011.08.003
51. Zakharyan R, Petrek M, Arakelyan A, Mrazek F, Atshemyan S, Boyajyan A (2012) Interleukin-6 promoter polymorphism and plasma levels in patients with schizophrenia. Tissue Antigens 80:136–142. https://doi.org/10.1111/j.1399-0039.2012.01886.x
52. Dennison U, McKernan D, Cryan J, Dinan T (2012) Schizophrenia patients with a history of childhood trauma have a pro-inflammatory phenotype. Psychol Med 42:1865–1871. https://doi.org/10.1017/s0033291712000074
53. Kalmady SV, Venkatasubramanian G, Shivakumar V, Gautham S, Subramaniam A, Jose DA, Maitra A, Ravi V, Gangadhar BN (2014) Relationship between Interleukin-6 gene polymorphism and hippocampal volume in antipsychotic-naïve schizophrenia: evidence for differential susceptibility? PLoS ONE 9:e96021. https://doi.org/10.1371/journal.pone.0096021
54. Ding M, Song X, Zhao J, Gao J, Li X, Yang G, Wang X, Harrington A, Fan X, Lv L (2014) Activation of Th17 cells in drug naïve, first episode schizophrenia. Prog Neuropsychopharmacol Biol Psychiatry 51:78–82. https://doi.org/10.1016/j.pnpbp.2014.01.001
55. Hope S, Hoseth E, Dieset I, Mørch RH, Aas M, Aukrust P, Djurovic S, Melle I, Ueland T, Agartz I, Ueland T, Westlye LT, Andreassen OA (2015) Inflammatory markers are associated with general cognitive abilities in schizophrenia and bipolar disorder patients and healthy controls. Schizophr Res 165:188–194. https://doi.org/10.1016/j.schres.2015.04.004
56. Fang X, Wang Y, Chen Y, Ren J, Zhang C (2019) Association between IL-6 and metabolic syndrome in schizophrenia patients treated with second-generation antipsychotics. Neuropsychiatr Dis Treat 15:2161–2170. https://doi.org/10.2147/ndt.S202159
57. Liu JY, Chen HY, Lin JJ, Lu MK, Tan HP, Jang FL, Lin SH (2020) Alterations of plasma cytokine biomarkers for identifying age at onset of schizophrenia with neurological soft signs. Int J Med Sci 17:255–262. https://doi.org/10.7150/ijms.38891
58. Wang Y, Wei Y, Edmiston EK, Womer FY, Zhang X, Duan J, Zhu Y, Zhang R, Yin Z, Zhang Y, Jiang X, Wei S, Liu Z, Zhang Y, Tang Y, Wang F (2020) Altered structural connectivity and cytokine levels in schizophrenia and genetic high-risk individuals: associations with disease states and vulnerability. Schizophr Res 223:158–165. https://doi.org/10.1016/j.schres.2020.05.044
59. Garver DL, Tamas RL, Holcomb JA (2003) Elevated interleukin-6 in the cerebrospinal fluid of a previously delineated schizophrenia subtype. Neuropsychopharmacology 28:1515–1520. https://doi.org/10.1038/sj.npp.1300217
60. Müller N, Dobmeier P, Empl M, Riedel M, Schwarz M, Ackenheil M (1997) Soluble IL-6 receptors in the serum and cerebrospinal fluid of paranoid schizophrenic patients. Eur Psychiatry 12:294–299. https://doi.org/10.1016/s0924-9338(97)84789-x
61. Müller N, Empl M, Riedel M, Schwarz M, Ackenheil M (1997) Neuroleptic treatment increases soluble IL-2 receptors and decreases soluble IL-6 receptors in schizophrenia. Eur Arch Psychiatry Clin Neurosci 247:308–313. https://doi.org/10.1007/bf02922260
62. Shivakumar V, Debnath M, Venugopal D, Rajasekaran A, Kalmady SV, Subbanna M, Narayanaswamy JC, Amaresha AC, Venkatasubramanian G (2018) Influence of correlation between HLA-G polymorphism and Interleukin-6 (IL6) gene expression on the risk of schizophrenia. Cytokine 107:59–64. https://doi.org/10.1016/j.cyto.2017.11.016
63. Marcinowicz P, Więdłocha M, Zborowska N, Dębowska W, Podwalski P, Misiak B, Tyburski E, Szulc A (2021) A meta-analysis of the influence of antipsychotics on cytokines levels in first episode psychosis. J Clin Med. https://doi.org/10.3390/jcm10112488
64. Jarskog LF, Xiao H, Wilkie MB, Lauder JM, Gilmore JH (1997) Cytokine regulation of embryonic rat dopamine and serotonin neuronal survival in vitro. Int J Dev Neurosci 15:711–716. https://doi.org/10.1016/s0736-5748(97)00029-4
65. Pedraz-Petrozzi B, Elyamany O, Rummel C, Mulert C (2020) Effects of inflammation on the kynurenine pathway in schizophrenia-a systematic review. J Neuroinflammation 17:56. https://doi.org/10.1186/s12974-020-1721-z
66. Büki A, Kekesi G, Horvath G, Vécsei L (2021) A potential interface between the kynurenine pathway and autonomic imbalance in schizophrenia. Int J Mol Sci. https://doi.org/10.3390/ijms221810016
67. Dinesh AA, Islam J, Khan J, Turkheimer F, Vernon AC (2020) Effects of antipsychotic drugs: cross talk between the nervous and innate immune system. CNS Drugs 34:1229–1251. https://doi.org/10.1007/s40263-020-00765-x
68. Potvin S, Stip E, Sepehry AA, Gendron A, Bah R, Kouassi E (2008) Inflammatory cytokine alterations in schizophrenia: a systematic quantitative review. Biol Psychiatry 63:801–808. https://doi.org/10.1016/j.biopsych.2007.09.024