

Supplemental Information

Evidence for Immune System Dysfunction and Inflammation in Schizophrenia

Multiple lines of evidence support an association between immune system dysfunction and schizophrenia. Immune system-related genes, including cytokines (1), cytokine pathways (2), and the major histocompatibility complex (3-5) are all associated with schizophrenia. Prenatal maternal infections (with a variety of agents) are a replicated risk factor for schizophrenia, and cytokines are a plausible common pathway by which infections exert this risk (6). Indeed, in prenatal immune activation animal models of schizophrenia, adult offspring have abnormal blood cytokine levels at an age homologous to the usual age of onset of schizophrenia (7,8). There is also an increased prevalence of autoimmune disease in both patients with schizophrenia and their first-degree relatives (9), suggesting that immune system abnormalities may be an endophenotype of the disorder.

In addition to the above-mentioned risk factors, there is other converging evidence of immune system dysfunction and inflammation in patients with schizophrenia. Abnormal levels of acute phase proteins—plasma proteins synthesized by the liver in response to inflammation—including haptoglobin, α 1-antitrypsin, and c-reactive protein have been reported in patients with schizophrenia (10-14). There is replicated evidence for increased absolute blood monocytes in patients with schizophrenia (15-17). Blood lymphocyte subsets are also abnormal in schizophrenia, with a decreased CD4/CD8 ratio reported in several studies (18-20). Blood levels of neopterin, a marker of increased cell-mediated immunity and oxidative stress, are increased in schizophrenia (21-23). In parallel to these findings, there is also increased measures oxidative and nitrosative stress in schizophrenia (21,24). Both oxidative stress and aberrant cytokine levels may contribute to decreased blood and central nervous system (CNS) membrane levels of polyunsaturated fatty acids observed in schizophrenia (25).

Cytokines in the periphery can cross the blood brain barrier (BBB) and activate astrocytes. A meta-analysis found significantly increased serum levels of S100 β , a marker of astrocyte activation and BBB dysfunction, in patients with schizophrenia (26). Calprotectin, another member of the S100 family and a non-specific marker of inflammation, was up-regulated in frontal cortical microglia in post-mortem brains (27), and positron emission tomography (PET) studies have demonstrated microglial activation in recent-onset schizophrenia (28). CNS levels of neural cell adhesion molecule and soluble inter-cellular adhesion molecule-1, which play important roles in neurodevelopment, neuroplasticity, and immune function, are also abnormal in schizophrenia (29,30). Indoleamine 2,3-dioxygenase

(IDO), the rate-limiting enzyme in tryptophan degradation, is also expressed in astrocytes and microglia, and its activity can be modulated by cytokines. IDO induction results in increased production of kynurenine, which is converted in astrocytes to the NMDA receptor antagonist kynurenic acid (KYN-A). NMDA receptor hypofunction has been implicated in the pathophysiology of schizophrenia (31,32). Previous studies have found increased blood (33), cerebrospinal fluid (CSF) (34), and postmortem brain (35) levels of KYN-A, as well as increased IDO activity (36) in patients with schizophrenia.

Cytokine Profiles of Activated Immune Cells

Activated immune cells have characteristic cytokine profiles. CD4⁺ T-helper (Th) lymphocytes are important regulators of both humoral and cell-mediated immunity (CMI). In response to an antigen and the local cytokine milieu, naïve Th cells can differentiate into a variety of effector cells that direct diverse immune functions. Th1 cells, which secrete IFN- γ , IL-2, and IL-12, stimulate CMI, and thereby promote proliferation of cytotoxic CD8⁺ T-lymphocytes and maximize the killing efficacy of macrophages. By contrast, Th2 cells secrete IL-4, IL-6, and IL-10, which stimulate proliferation of B-lymphocytes, induce B-cell antibody class switching and production of neutralizing antibodies. Th3 cells produce TGF- β and IL-10, and are involved in mucosal immunity and protection. Activated monocytes/macrophages have increased production of IL-1 β , IL-6, IL-8, and TNF- α , which enhance the inflammatory response. Concomitant to the increased production of “pro-inflammatory cytokines”, the “compensatory anti-inflammatory response syndrome” (CARS) is a counter-regulatory mechanism that inhibits the primary inflammatory response and involves an adaptive reprogramming of leukocytes (37). Mediators of the CARS include IL-1RA, sTNF-R, and TGF- β . Table S1 describes characteristic cytokines (or cytokine receptors or antagonists) that have been studied in schizophrenia, including their sources and major functions.

Table S1. Sources and functions of cytokines (or cytokine receptor or antagonists) studied in schizophrenia

Cytokines (or Cytokine Receptor or Antagonists)	Source(s)	Selected Function/Notes
IL-1 β	Macrophages	Pro-inflammatory; Induces acute phase proteins, and IL-6
IL-1RA	Macrophages	CARS; Competitive antagonist for IL-1R
IL-2	Th1 Lymphocytes	T-cell activation; Stimulates CMI
sIL-2R	T-lymphocytes	Shed into serum during T-cell activation; Marker of CMI
IL-4	Th2 Lymphocytes	Inhibits IFN- γ production by Th1 cells; Stimulates B-cell synthesis of IgE
IL-6	Monocytes; Th2 Lymphocytes	Pro-inflammatory; Induces acute phase proteins, and late B-cell differentiation
sIL-6R	Macrophages; Th2 Lymphocytes	Binds and enhances function of IL-6
IL-8	Monocytes	Pro-inflammatory; Induces neutrophil and T-cell chemotaxis
IL-10	Th2 Lymphocytes; Th3 Lymphocytes	CARS; Inhibits IFN- γ production by Th1 cells
IL-12	Macrophages; B-lymphocytes	Pro-inflammatory; Promotes Th1 cell differentiation and IFN- γ production
TNF- α	Macrophages	Pro-inflammatory; Induces acute phase proteins
sTNF-R	Macrophages	CARS; Competitive antagonist for TNF- α
TGF- β	Th3 Lymphocytes	CARS; Inhibits T- and B-cell proliferation, reduces cytokine receptors
IFN- γ	Th1 Lymphocytes	Macrophage activation

CARS, compensatory anti-inflammatory response syndrome; CMI, cell-mediated immunity; IFN, interferon; IL, interleukin; s, soluble; TGF, transforming growth factor; TNF, tumor necrosis factor;

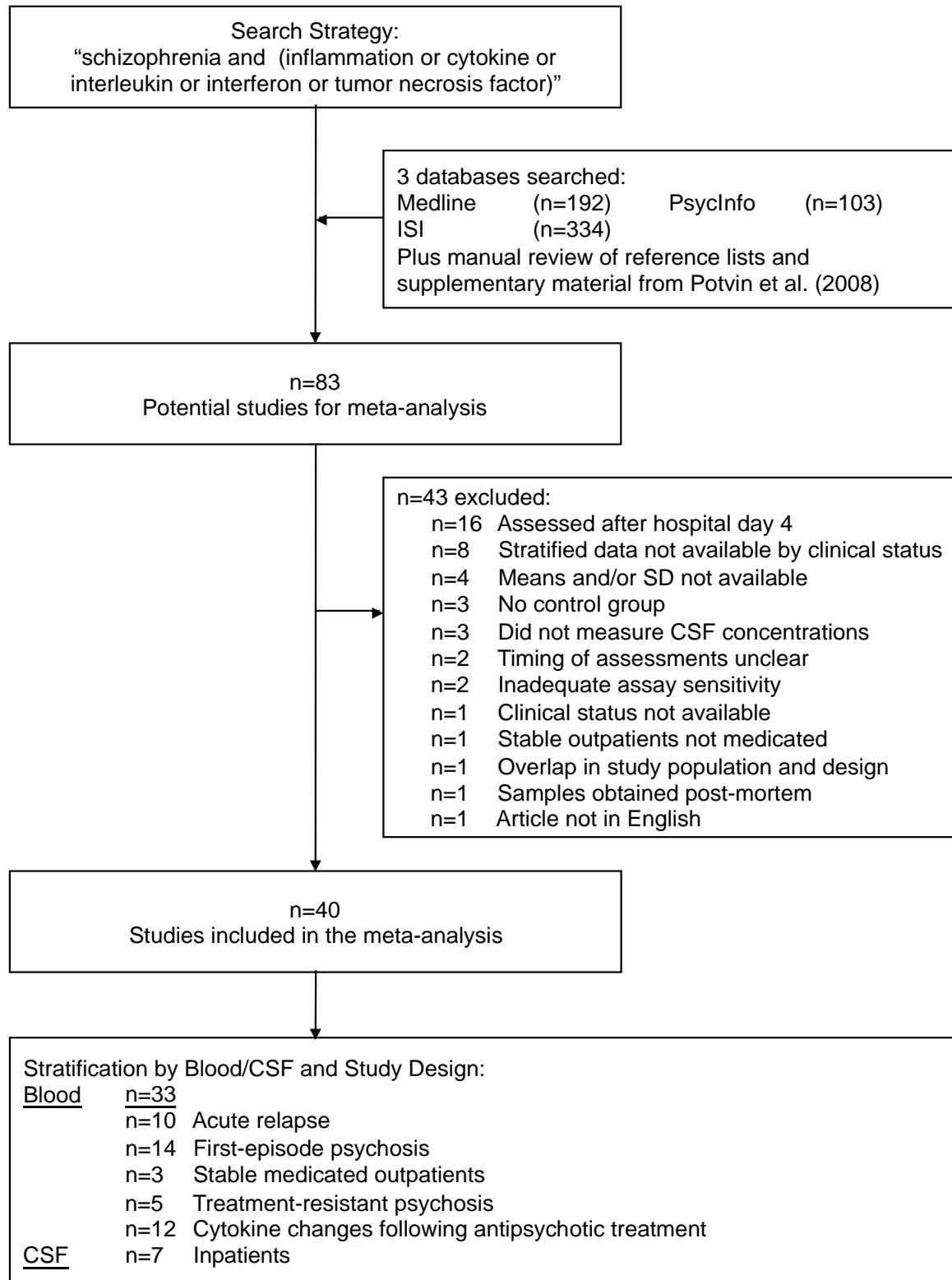


Figure S1. Flow chart of the study selection process

Table S2. Studies of cytokines (or cytokine receptors or antagonists) in schizophrenia

Blood						
Study	Cytokines	Assay	Antipsychotic	Location	Included	Patient Group(s)/Comment
Akiyama 1999 (23)	sIL-2R, IL-6, IL-1RA	Sandwich	No	Japan	Yes	FEP
Baker 1996 (24)	IL-1 β , sIL-2R, IL-6, TNF- α	ELISA	Yes/No	U.S.	Yes	TR
Barak 1995 (25)	IL-1 β , IL-2, sIL-2R, IL-6	RIA	Yes	Israel	No	Timing of assessment unclear
Barry 2009 (22)	IFN- γ	ELISA	Yes	Ireland	Yes	SO
Becker 1990 (27)	IFN	SMA	No	Israel	Yes	FEP
Bresee & Rapaport 2009 (28)	sIL-2R	ELISA	Yes	U.S.	Yes	TR
Cazzullo 2002 (29)	IL-2, IL-4, IL-10, IFN- γ	ELISA	No	Italy	No	Stratified data not available
Cohelo 2008 (30)	TNF- α , sTNF-R1, sTNF-R2	ELISA	Yes	Brazil	No	Assessed at >4 days
Crespo-Facorro 2008 (31)	IL-12	ELISA	No	Spain	Yes	FEP; Treatment
Drexhage 2008 (32)	IL-1 β , IL-6, TNF- α	CBA	Yes	Netherlands	Yes	SO
Ebrinc 2002 (33)	IL-1RA, IL-2	ELISA	No	Turkey	No	Outpatients not medicated
Erbagci 2001 (35)	IL-1 β , sIL-2R, IL-6, IL-8, TNF- α	ELISA	Yes/No	Turkey	No	Assessed at >4 days
Fernandez-Egea 2009 (36)	IL-6; TNF- α	ELISA	No	Spain	Yes	FEP
Frommberger 1997 (37)	IL-6	Bioassay	No	Germany	Yes	AR; Treatment
Ganguli 1989 (38)	sIL-2R	ELISA	Yes/No	U.S.	Yes	FEP
Ganguli 1994 (39)	IL-6	ELISA	Yes/No	U.S.	Yes	AR
Garcia-Miss 2009 (40)	IL-6, TNF- α	RIA	Yes	Mexico	No	Assessed at >4 days
Gattaz 1992 (41)	IL-2, IFN- γ , IFN- α	ELISA	No	Germany	Yes	FEP
Haack 1999 (42)	IL-1RA, sIL-2R, TNF- α	ELISA	Yes/No	Germany	Yes	AR
Hope 2009 (43)	IL-1RA, IL-6, sTNF-R1	ELISA	Yes/No	Norway	No	Stratified data not available
Kaminska 2001 (44)	IL-6, IL-8, IL-10, IFN- γ , IFN- α , TNF- α	ELISA	Yes	Poland	Yes	AR
Katila 1994 (45)	IL-1 β	ELISA	Yes	Finland	No	Stratified data not available
Kim 2000 (46)	IL-1 β , IL-2, IL-6	ELISA	Yes	Korea	Yes	AR; FEP; Treatment
Kim 2001 (47)	IL-1 β , IL-2, IL-6, IL-12, IFN- γ	ELISA			Yes	Treatment
Kim 2002 (48)	IL-12	ELISA	No	Korea	Yes	AR; FEP; Treatment
Kim 2004 (49)	TGF- β	ELISA	No	Korea	Yes	AR; FEP; Treatment
Kim 2009 (50)	IL-2, IL-4, IL-6, TNF- α , TGF- β	ELISA	No	Korea	Yes	AR; FEP; Treatment
Kowalski 2001 (19)	IL-1 β	ELISA	No	Poland	No	Stratified data not available Mean/SD not given
Lin 1998 (52)	IL-6, sIL-6R	ELISA	Yes	Italy	Yes	TR
Maes 1994 (54)	sIL-2R, IL-6, sIL-6R	ELISA	No	U.S.	No	Assessed at >4 days
Maes 1995 (55)	IL-6	ELISA	No	U.S.	No	Assessed at >4 days
Maes 1995b (56)	sIL-2R, IL-6, sIL-6R	ELISA	No	U.S.	No	Assessed at >4 days
Maes 1996 (57)	IL-1RA, sIL-2R	ELISA	Yes/No	U.S.	Yes	AR

Table S2. (continued)

Study	Cytokines	Assay	Antipsychotic	Location	Included	Patient Group(s)/Comment
Maes 1997 (58)	IL-1RA, IL-6, sIL-6R	ELISA	Yes/No	Belgium	No	Assessed at >4 days
Maes 2000 (59)	IL-1RA, IL-6, sIL-6R	ELISA	Yes	Italy	Yes	TR
Maes 2002 (60)	IL-10	ELISA	No	Italy	Yes	TR
Monteleone 1997 (61)	IL-6, TNF- α	ELISA	No	Italy	No	Assessed at >4 days
Muller 1997 (62)	sIL-6R	ELISA	Yes	Germany	No	Assessed at >4 days
Muller 1997b (63)	sIL-2R, sIL-6R	ELISA	No	Germany	Yes	Treatment
Naudin 1996 (64)	IL-6, TNF- α	RIA	Yes	France	No	Timing of assessment unclear
Naudin 1997 (65)	IL-1 β , IL-1RA, sIL-2R	ELISA	Yes	France	No	Stratified data not available
Nimgaonakar 1995 (68)	sIL-2R	ELISA	Unknown	U.S.	No	Stratified data not available
Nunes 2006 (8)	IL-6	CIA	Yes	Brazil	No	Mean/SD not given
O'Brien 2008 (69)	IL-6, sIL-6R IL-8, IL-10, TNF- α	ELISA	Yes	Ireland	Yes	AR
Pae 2006 (70)	IL-2, IL-6, IL-10, IL-1, TNF- α	ELISA	Yes/No	Korea	Yes	Treatment
Rapaport 1989 (72)	sIL-2R	ELISA	Yes	U.S.	No	Assessed at >4 days
Rapaport 1993 (73)	sIL-2R	ELISA	Yes	U.S.	No	Assessed at >4 days
Rapaport 1994 (74)	sIL-2R	ELISA	Yes	U.S., Korea	No	Assessed at >4 days
Rapaport 1994b (75)	sIL-2R	ELISA	No	U.S.	Yes	FEP
Rapaport 1997 (76)	sIL-2R	ELISA	No	U.S.	No	No control group
Sarandol 2007 (79)	TNF- α	ELISA	Yes	Turkey	No	Stratified data not available
Schattner 1996 (80)	TNF- α	Bioassay	No	Israel	No	Stratified data not available
Schwarz 1998 (81)	sIL-2R	ELISA	No	Germany	Yes	Treatment
Shintani 1991 (82)	IL-6	ELISA	Yes	Japan	No	Assessed at >4 days
Singh 2009 (83)	IL-2, IL-6	ELISA	Yes/No	India	Yes	SO
Sirota 2005 (84)	IL-1RA, sIL-2R	ELISA	No	Israel	Yes	Treatment
Song 2009 (86)	IL-1 β , TNF- α	ELISA	No	China	Yes	FEP; Treatment
Theodoropoulou 2001 (87)	IL-1 β , IL-2, TNF- α	ELISA	Yes	Greece	Yes	FEP
van Kammen 1999 (7)	IL-6	ELISA	Yes/No	U.S.	No	Assessed at >4 days
Wilke 1996 (20)	IL-2, IFN- γ	ELISA	Yes	Germany	No	Stratified data not available
Xiu 2008 (90)	IL-3	ELISA	Yes	China	Yes	FEP
Xu 1994 (94)	IL-1 α , IL-1 β , IL-2, IL-6, TNF- α	RIA	Yes/No	UK	No	Inadequate assay sensitivity
Yang 1994 (91)	IL-2	ELISA	Yes/No	U.S.	No	Clinical status not available
Zhang 2002 (93)	IL-2, IL-6	ELISA	No	China	No	Assessed at >4 days
Zhang 2004 (95)	IL-2, IL-6	ELISA	No	China	No	Assessed at >4 days
Zhang 2005 (96)	IL-2, IL-6	ELISA	No	China	No	Population overlap (Zhang 2004)
Zhang 2008 (97)	IL-2, IL-6, IL-8, TNF- α	ELISA	Yes	China	No	No control group
Zhang 2009 (98)	IL-2, IL-6	ELISA	Yes/No	China	No	Assessed at >4 days

Table S2. (continued)

CSF						
Study	Cytokines	Assay	Antipsychotic	Location	Included	Patient Group(s)/Comment
Barak 1995 (25)	IL-1 β , IL-2, sIL-2R, IL-6	RIA	Yes	Israel	Yes	Inpatients
Bechter 2010 (26)	None	N/A	Yes	Germany	No	Did not measure CSF cytokines
el-Mallakh 1993 (34)	IL-2	ELISA	Yes/No	U.S.	Yes	Inpatients
Garver 2003 (6)	IL-6	ELISA	Yes	U.S.	Yes	Inpatients
Katila 199 (45)	IL-1 β	ELISA	Yes	Finland	Yes	Inpatients
Licinio 1993 (51)	IL-1 α , IL-2	ELISA	No	U.S.	Yes	Inpatients
Lu 2003 (53)	sIL-2R, IL-10, TNF- α	ELISA	No	China	No	Article in Chinese
McAllister 1995 (78)	IL-2	ELISA	No	U.S.	No	No control group
Muller 1997 (62)	sIL-6R	ELISA	Yes	Germany	No	No control group
Nikkila 1999 (66)	None	N/A	No	Finland	No	Did not measure CSF cytokines
Nikkila 2002 (67)	None	N/A	No	Finland	No	Did not measure CSF cytokines
Preble & Torrey, 1985 (71)	IFN	Semimicromethod	Yes	Ireland	No	Mean/SD not given
Rapaport 1997 (77)	IL-1 α , IL-2	ELISA	Yes	U.S.	Yes	Inpatients
Soderlund 2009 (85)	IL-1 β , IL-6, IL-8	ELISA	Unknown	Not specified	No	Mean/SD not given
van Kammen 1999 (7)	IL-6	ELISA	Yes/No	U.S.	No	Inadequate assay sensitivity
Vawter 1996 (88)	TGF- β 1, TGF- β 2	ELISA	Unknown	U.S.	No	Samples obtained post-mortem
Vawter 1997 (89)	TGF- β 1, TGF- β 2	ELISA	Unknown	U.S.	Yes	Inpatients
Yao 200 (92)	IL-6, IL-10	ELISA	Yes	U.S.	No	Mean/SD not given

Studies that were included are indicated by bold font.

Reference numbers within the table refer to references in the main text.

AR, acutely relapsed inpatients; CBA, cytometric bead array; CIA, chemiluminescent immunoassay; CSF, cerebrospinal fluid; ELISA, enzyme-linked immunosorbent assay; FEP, first-episode psychosis; IFN, interferon; IL, interleukin; RIA, radioimmunoassay; s, soluble; SMA, semimicroassay; SO, stable medicated outpatients; TGF, transforming growth factor; TNF, tumor necrosis factor; TR, treatment-resistant psychosis.

Table S3. Effect size estimates for individual cytokines (or cytokine receptors or antagonists)

Study	Schizophrenia			Control			Hedges <i>g</i>	95% CI		Cytokine	Notes	Clinical Status
	Mean	<i>N</i>	SD	Mean	<i>N</i>	SD		Lower	Upper			
Frommberger 1997 (37)	1.45	32	0.53	1.01	12	0.18	0.93	0.24	1.62	IL-6	Blood	AR
Ganguli 1994 (39)	-0.88	35	0.93	-1.05	110	1.11	0.16	-0.22	0.54	IL-6	Blood	AR
Haack 1999 (42)	196.50	18	206.10	192.90	64	124.90	0.02	-0.50	0.55	IL-1RA	Blood	AR
Haack 1999 (42)	194.10	18	114.20	189.50	64	90.40	0.05	-0.48	0.57	sIL-2R	Blood	AR
Haack 1999 (42)	9.31	18	5.60	10.92	64	3.64	-0.38	-0.91	0.14	TNF- α	Blood	AR
Kaminska 2001 (44)	0.33	24	1.36	0.87	28	2.91	-0.23	-0.77	0.32	IFN- α	Blood	AR
Kaminska 2001 (44)	8.52	24	8.29	2.35	28	4.62	0.92	0.35	1.50	IFN- γ	Blood	AR
Kaminska 2001 (44)	0.34	24	1.38	11.04	28	14.94	-0.95	-1.53	-0.38	IL-10	Blood	AR
Kaminska 2001 (44)	5.05	24	3.05	2.54	28	2.51	0.89	0.32	1.46	IL-6	Blood	AR
Kaminska 2001 (44)	104.38	24	160.15	6.12	28	16.89	0.88	0.31	1.45	IL-8	Blood	AR
Kaminska 2001 (44)	2.31	24	3.43	5.43	28	7.18	-0.53	-1.09	0.02	TNF- α	Blood	AR
Kim 2000 (46)	1.56	10	0.68	1.30	25	0.30	0.58	-0.17	1.33	IL-1 β	Blood	AR
Kim 2000 (46)	2.97	10	2.22	1.70	25	0.10	1.07	0.29	1.84	IL-2	Blood	AR
Kim 2000 (46)	2.40	10	1.11	2.00	25	0.50	0.54	-0.20	1.29	IL-6	Blood	AR
Kim 2002 (48)	13.00	21	13.80	9.30	85	3.50	0.53	0.05	1.02	IL-12	Blood	AR
Kim 2004 (49)	27.30	45	10.30	18.20	88	11.10	0.83	0.45	1.20	TGF- β	Blood	AR
Kim 2009 (50)	570.70	33	261.50	489.99	174	257.49	0.31	-0.07	0.68	IFN- γ	Blood	AR
Kim 2009 (50)	126.60	33	142.20	255.18	174	231.76	-0.57	-0.95	-0.20	IL-2	Blood	AR
Kim 2009 (50)	110.20	33	111.80	268.72	174	110.01	-1.41	-1.81	-1.02	IL-4	Blood	AR
Kim 2009 (50)	464.70	33	123.00	234.08	174	53.29	3.29	2.80	3.78	IL-6	Blood	AR
Kim 2009 (50)	804.60	33	367.30	717.90	174	375.15	0.23	-0.14	0.60	TGF- β	Blood	AR
Kim 2009 (50)	859.50	33	244.90	577.51	174	171.88	1.50	1.10	1.90	TNF- α	Blood	AR
Maes 1996 (57)	0.34	14	0.23	0.16	30	0.06	1.29	0.60	1.97	IL-1RA	Blood	AR
Maes 1996 (57)	82.00	14	82.00	45.00	30	44.00	0.62	-0.03	1.27	sIL-2R	Blood	AR
O'Brien 2008 (69)	1.59	22	0.80	1.76	24	0.98	-0.19	-0.77	0.39	IL-10	Blood	AR
O'Brien 2008 (69)	0.32	22	0.31	0.36	24	0.29	-0.12	-0.70	0.45	IL-6	Blood	AR
O'Brien 2008 (69)	2.30	22	2.44	1.72	24	1.42	0.29	-0.29	0.87	IL-8	Blood	AR
O'Brien 2008 (69)	20740.00	22	2980.29	19330.00	24	2865.41	0.47	-0.11	1.06	sIL-6R	Blood	AR
O'Brien 2008 (69)	13.49	22	2.02	6.79	24	2.06	3.23	2.35	4.11	TNF- α	Blood	AR
Akiyama 1999 (23)	342.70	14	229.20	242.30	26	82.50	0.65	-0.01	1.32	IL-1RA	Blood	FEP
Akiyama 1999 (23)	2165.00	14	2029.00	999.00	26	495.00	0.91	0.23	1.59	IL-6	Blood	FEP

Table S3. (continued)

Study	Schizophrenia			Control			Hedges <i>g</i>	95% CI		Cytokine	Notes	Clinical Status
	Mean	<i>N</i>	SD	Mean	<i>N</i>	SD		Lower	Upper			
Akiyama 1999 (23)	739.30	14	217.20	520.90	26	12.4	1.67	0.93	2.42	sIL-2R	Blood	FEP
Crespo 2008 (31)	50.20	56	20.30	4.60	28	4.59	2.66	2.06	3.27	IL-12	Blood	FEP
Fernandez-Egea 2008 (36)	3.63	50	6.91	1.02	50	2.10	0.50	0.10	0.90	IL-6	Blood	FEP
Fernandez-Egea 2008 (36)	5.44	26	3.58	4.50	22	2.61	0.29	-0.28	0.86	TNF- α	Blood	FEP
Ganguli 1989 (38)	294.70	4	58.20	343.80	57	138.917	-0.36	-1.37	0.66	sIL-2R	Blood	FEP
Gattaz 1992 (41)	20.80	10	32.40	13.00	15	16.90	0.31	-0.49	1.12	IFN- γ	Blood	FEP
Gattaz 1992 (41)	0.49	10	0.37	0.69	15	11.00	-0.02	-0.82	0.78	IL-2	Blood	FEP
Kim 2000 (46)	1.55	15	0.85	1.30	25	0.30	0.43	-0.22	1.08	IL-1 β	Blood	FEP
Kim 2000 (46)	2.59	15	1.49	1.70	25	0.10	0.96	0.28	1.63	IL-2	Blood	FEP
Kim 2000 (46)	2.85	15	1.83	2.00	25	0.50	0.70	0.04	1.36	IL-6	Blood	FEP
Kim 2002 (48)	9.20	22	4.60	9.30	85	3.50	-0.03	-0.50	0.44	IL-12	Blood	FEP
Kim 2004 (49)	28.40	43	10.20	18.20	88	11.10	0.93	0.55	1.31	TGF- β	Blood	FEP
Kim 2009 (50)	676.00	38	304.00	489.99	174	257.49	0.69	0.33	1.04	IFN- γ	Blood	FEP
Kim 2009 (50)	180.30	38	197.50	255.18	174	231.76	-0.33	-0.68	0.03	IL-2	Blood	FEP
Kim 2009 (50)	83.00	38	80.40	268.72	174	110.01	-1.73	-2.12	-1.34	IL-4	Blood	FEP
Kim 2009 (50)	452.20	38	111.50	234.08	174	53.29	3.19	2.72	3.65	IL-6	Blood	FEP
Kim 2009 (50)	753.40	38	283.90	717.90	174	375.15	0.10	-0.25	0.45	TGF- β	Blood	FEP
Kim 2009 (50)	902.30	38	244.60	577.51	174	171.88	1.71	1.32	2.10	TNF- α	Blood	FEP
Rapaport 1994b (75)	1705.70	12	1124.20	739.80	14	325.5	1.17	0.33	2.00	sIL-2R	Blood	FEP
Song 2009 (86)	25.93	83	13.30	14.19	65	7.86	1.03	0.68	1.37	IL-1 β	Blood	FEP
Song 2009 (86)	31.01	83	13.82	21.33	65	8.90	0.80	0.46	1.14	TNF- α	Blood	FEP
Theodoropoulou 2001 (87)	21.40	53	58.24	12.00	62	47.24	0.18	-0.19	0.54	IL-1 β	Blood	FEP
Theodoropoulou 2001 (87)	220.00	53	182.00	271.00	62	393.70	-0.16	-0.53	0.21	IL-2	Blood	FEP
Theodoropoulou 2001 (87)	24.00	53	8.00	16.00	62	47.24	0.22	-0.14	0.59	TNF- α	Blood	FEP
Xiu 2008 (90)	4.30	24	7.00	15.50	26	10.90	-1.19	-1.79	-0.59	IL-3	Blood	FEP
Barry 2009 (22)	1.22	34	0.29	0.85	36	0.13	1.63	1.09	2.18	IFN- γ	Blood	SO
Drexhage 2008 (32)	12.33	145	11.21	5.50	105	6.64	0.70	0.44	0.96	IL-1 β	Blood	SO
Drexhage 2008 (32)	43.32	145	63.77	21.65	105	31.73	0.40	0.15	0.66	IL-6	Blood	SO
Drexhage 2008 (32)	38.59	145	47.80	15.28	105	22.06	0.59	0.33	0.84	TNF- α	Blood	SO
Singh 2009 (83)	34.54	30	22.09	56.04	30	18.82	-1.03	-1.57	-0.49	IL-2	Blood	SO
Singh 2009 (83)	8.31	30	6.52	33.87	30	13.6	-2.36	-3.02	-1.70	IL-6	Blood	SO

Table S3. (continued)

Study	Schizophrenia			Control			Hedges <i>g</i>	95% CI		Cytokine	Notes	Clinical Status
	Mean	<i>N</i>	SD	Mean	<i>N</i>	SD		Lower	Upper			
Baker 1996 (24)	0.95	32	1.88	1.47	22	1.83	-0.27	-0.82	0.27	IL-1 β	Blood	TR
Baker 1996 (24)	2.35	46	1.61	2.82	30	2.65	-0.22	-0.68	0.24	IL-6	Blood	TR
Baker 1996 (24)	1332.00	42	615.00	1240.00	31	624.00	0.15	-0.32	0.61	sIL-2R	Blood	TR
Baker 1996 (24)	8.12	39	9.13	8.28	28	9.50	-0.02	-0.50	0.47	TNF- α	Blood	TR
Bresee 2009 (28)	304.00	59	212.00	183.00	57	109.00	0.70	0.33	1.08	sIL-2R	Blood	TR
Lin 1998 (52)	6.68	15	7.31	0.38	15	0.65	1.17	0.40	1.95	IL-6	Blood	TR
Maes 2000 (59)	0.31	17	0.20	0.08	7	0.04	1.29	0.34	2.25	IL-1RA	Blood	TR
Maes 2000 (59)	169.00	17	46.00	143.00	7	50.00	0.53	-0.36	1.43	sIL-6R	Blood	TR
Maes 2002 (60)	3.28	17	2.60	0.92	7	0.82	1.01	0.08	1.93	IL-10	Blood	TR
Maes 2002 (60)	163.70	17	125.70	39.50	7	29.60	1.11	0.17	2.04	IL-8	Blood	TR

Study	Post-Treatment			Pre-Treatment			Hedges <i>g</i>	95% CI		Cytokine	Notes	Clinical Status
	Mean	<i>N</i>	SD	Mean	<i>N</i>	SD		Lower	Upper			
Crespo 2008 (31)	62.80	56	30.40	50.20	56	20.30	0.48	0.11	0.86	IL-12	Treatment	FEP
Frommberger 1997 (37)	1.18	32	0.35	1.45	11	0.53	-0.66	-1.36	0.04	IL-6	Treatment	AR
Kim 2000 (46)	1.30	25	0.20	1.60	25	0.70	-0.57	-1.14	-0.01	IL-1 β	Treatment	AR/FEP
Kim 2000 (46)	1.80	25	0.20	2.70	25	1.80	-0.69	-1.26	-0.12	IL-2	Treatment	AR/FEP
Kim 2000 (46)	2.70	25	1.30	2.70	25	1.30	0.00	-0.55	0.55	IL-6	Treatment	AR/FEP
Kim 2001 (47)	3.34	19	2.49	5.04	19	4.63	-0.45	-1.09	0.20	IFN- γ	Treatment	AR
Kim 2001 (47)	175.09	19	108.14	115.99	19	102.20	0.55	-0.10	1.20	IL-12	Treatment	AR
Kim 2001 (47)	0.95	19	0.58	1.18	19	0.75	-0.34	-0.98	0.30	IL-1 β	Treatment	AR
Kim 2001 (47)	0.70	19	2.06	1.29	19	3.92	-0.18	-0.82	0.45	IL-2	Treatment	AR
Kim 2001 (47)	5.32	19	6.34	4.39	19	5.84	0.15	-0.49	0.79	IL-6	Treatment	AR
Kim 2002 (48)	11.50	29	2.90	12.40	29	12.20	-0.10	-0.62	0.41	IL-12	Treatment	AR/FEP
Kim 2004 (49)	20.70	66	9.70	27.70	66	10.20	-0.70	-1.05	-0.35	TGF- β	Treatment	AR/FEP
Kim 2009 (50)	543.97	53	322.22	589.27	53	308.60	-0.14	-0.52	0.24	IFN- γ	Treatment	AR/FEP
Kim 2009 (50)	206.95	53	259.03	140.33	53	176.18	0.30	-0.08	0.68	IL-2	Treatment	AR/FEP
Kim 2009 (50)	38.70	53	25.33	46.91	53	38.37	-0.25	-0.63	0.13	IL-4	Treatment	AR/FEP
Kim 2009 (50)	451.55	53	116.12	487.56	53	100.98	-0.33	-0.71	0.05	IL-6	Treatment	AR/FEP
Kim 2009 (50)	758.73	53	184.11	754.71	53	232.02	0.02	-0.36	0.40	TGF- β	Treatment	AR/FEP

Table S3. (continued)

Study	Post-Treatment			Pre-Treatment			Hedges <i>g</i>	95% CI		Cytokine	Notes	Clinical Status
	Mean	<i>N</i>	SD	Mean	<i>N</i>	SD		Lower	Upper			
Kim 2009 (50)	850.97	53	240.24	923.39	53	289.68	-0.27	-0.65	0.11	TNF- α	Treatment	AR/FEP
Muller 1997b (63)	645.00	30	331.00	530.00	30	260.00	0.38	-0.13	0.89	sIL-2R	Treatment	AR
Muller 1997b (63)	37.60	39	8.90	42.50	39	14.30	-0.41	-0.86	0.04	sIL-6R	Treatment	AR
Pae 2006 (70)	4.90	35	3.80	3.80	35	1.00	0.39	-0.08	0.86	IL-10	Treatment	AR/FEP
Pae 2006 (70)	2.00	35	4.70	1.90	35	3.30	0.02	-0.44	0.49	IL-2	Treatment	AR/FEP
Pae 2006 (70)	16.20	35	10.10	25.70	35	19.40	-0.61	-1.09	-0.13	IL-6	Treatment	AR/FEP
Pae 2006 (70)	13.50	35	8.90	14.80	35	10.80	-0.13	-0.60	0.34	TNF- α	Treatment	AR/FEP
Schwarz 1998 (81)	634.80	28	345.40	473.00	28	220.90	0.55	0.02	1.08	sIL-2R	Treatment	AR/FEP
Sirota 2005 (84)	411.60	32	220.00	252.20	32	184.00	0.78	0.27	1.28	IL-1RA	Treatment	AR/FEP
Sirota 2005 (84)	1702.00	32	516.20	1689.90	32	621.00	0.02	-0.47	0.51	sIL-2R	Treatment	AR/FEP
Song 2009 (86)	20.25	83	12.73	25.93	83	13.30	-0.43	-0.74	-0.13	IL-1 β	Treatment	FEP
Song 2009 (86)	29.77	83	12.64	31.01	83	13.82	-0.09	-0.40	0.21	TNF- α	Treatment	FEP
Barak 1995 (25)	81.20	9	96.70	266.80	10	138.40	-0.8683862	-1.81	0.07	IL-1 β	CSF	Inpatients
Barak 1995 (25)	65.20	9	1.50	69.20	10	24.60	-0.1258765	-1.03	0.78	IL-2	CSF	Inpatients
Barak 1995 (25)	42.50	9	18.70	51.80	10	18.20	-0.2845943	-1.19	0.62	IL-6	CSF	Inpatients
el-Mallakh 1993 (34)	0.46	35	0.22	0.42	16	0.20	0.19759979	-0.40	0.79	IL-2	CSF	Inpatients
Garver 2003 (6)	4.11	31	2.13	3.00	14	1.24	0.57157717	-0.07	1.21	IL-6	CSF	Inpatients
Katila 1994 (45)	17.90	4	1.00	25.90	5	4.60	-1.2756188	-2.72	0.17	IL-1 β	CSF	Inpatients
Licinio 1993 (51)	987.00	10	770.00	447.00	10	244.00	0.5334244	-0.36	1.43	IL-2	CSF	Inpatients
Licinio 1993 (51)	445.00	10	308.00	342.00	10	193.00	0.22610623	-0.65	1.11	IL-1 α	CSF	Inpatients
Rapaport 1997 (77)	1.03	46	0.64	1.25	21	0.76	-0.3184758	-0.84	0.20	IL-2	CSF	Inpatients
Rapaport 1997 (77)	0.96	32	0.64	1.31	21	0.56	-0.5642427	-1.13	0.00	IL-1 α	CSF	Inpatients
vanKammen 1999 (7)	0.53	61	70.00	0.25	25	0.43	0.00465332	-0.46	0.47	IL-6	CSF	Inpatients
Vawter 1997 (89)	7.10	20	5.37	9.40	20	5.37	-0.4181224	-1.04	0.21	TGF- β 1	CSF	Inpatients
Vawter 1997 (89)	267.10	20	72.90	341.80	20	113.59	-0.7636053	-1.41	-0.12	TGF- β 2	CSF	Inpatients

Reference numbers within the table refer to references in the main text.

AR, acutely relapsed inpatients; FEP, first-episode psychosis; SO, stable medicated outpatients; TR, treatment-resistant psychosis.

Table S4. Correlations between cytokine (or cytokine receptor or antagonist) levels and clinical features

Variable	IL-6 (Blood)		IL-6 (CSF)		IL-12 (Blood)	
	Sig/Direction	Study	Sig/Direction	Study	Sig/Direction	Study
Age	Yes, Pos No, Pos No, Pos No No	Ganguli 1994 (39) Lin 1998 (52) Kim 2000 (46) Frommberger 1997 (37) Kaminska 2001 (44)	No, Neg	Garver 2003 (6)	No No	Crespo 2008 (31) Kim 2002 (48)
Age Onset	No No, Pos No No	Akiyama 1999 (23) Kim 2000 (46) Pae 2006 (70) Singh 2009 (83)			No No	Kim 2002 (48) Crespo 2008 (31)
Illness Duration	Yes, Pos Yes, Pos Yes, Pos No	Akiyama 1999 (23) Ganguli 1994 (39) Kim 2000 (46) Lin 1998 (52)			No	Kim 2002 (48)
PANSS Total	Yes, Pos No	Pae 2006 (70) Akiyama 1999 (23)				
PANSS Pos	No No	Akiyama 1999 (23) Kaminska 2001 (44)				
PANSS Neg	No No	Akiyama 1999 (23) Kaminska 2001 (44)				
PANSS Gen	Yes, Pos No	Pae 2006 (70) Kaminska 2001 (44)				
BPRS Total	Yes, Pos No No	Frommberger 1997 (37) Lin 1998 (52) Maes 2000 (59)			No No	Kim 2002 (48) Crespo 2008 (31)
BPRS Pos	No	Maes 2000 (59)				
SAPS			No, Neg	Garver 2003 (6)		
SANS	Yes, Pos	Kim 2000 (46)				
PSAS						

Table S4. (continued)

Variable	TNF- α (Blood)		IL-1 β (Blood)		IL-8 (Blood)	
	Sig/Direction	Study	Sig/Direction	Study	Sig/Direction	Study
Age	No	Kaminska 2001 (44)	No, Neg	Kim 2000 (46)	No	Kaminska 2001 (44)
Age Onset	No	Pae 2006 (70)	No, Pos	Kim 2000 (46)		
Illness Duration	No	Pae 2006 (70)	No, Pos	Kim 2000 (46)		
PANSS Total	No	Song 2009 (86)	No	Song 2009 (86)		
PANSS Pos	No	Kaminska 2001 (44)			No	Kaminska 2001 (44)
PANSS Neg	No	Kaminska 2001 (44)			No, Pos	Kaminska 2001 (44)
PANSS Gen	No	Kaminska 2001 (44)			No	Kaminska 2001 (44)
BPRS Total						
BPRS Pos						
SAPS						
SANS						
PSAS						

Table S4. (continued)

Variable	IL-1RA (Blood)		IFN- γ (Blood)		sIL-2R (Blood)	
	Sig/Direction	Study	Sig/Direction	Study	Sig/Direction	Study
Age			No	Kaminska 2001 (44)		
Age Onset	No	Akiyama 1999 (23)			No	Akiyama 1999 (23)
	No	Sirota 2005 (84)			No	Sirota 2005 (84)
Illness Duration	No	Akiyama 1999 (23)			No	Akiyama 1999 (23)
	No	Sirota 2005 (84)			No	Sirota 2005 (84)
PANSS Total	No	Akiyama 1999 (23)			No	Akiyama 1999 (23)
	No	Sirota 2005 (84)			No	Sirota 2005 (84)
PANSS Pos	No	Akiyama 1999 (23)	No	Kaminska 2001 (44)	No	Akiyama 1999 (23)
	No	Sirota 2005 (84)				
PANSS Neg	No	Akiyama 1999 (23)	No	Kaminska 2001 (44)	No	Akiyama 1999 (23)
					No	Sirota 2005 (84)
PANSS Gen			Yes, Pos	Kaminska 2001 (44)		
BPRS Total	No	Maes 2000 (59)				
BPRS Pos	No	Maes 2000 (59)				
SAPS						
SANS						
PSAS						

Table S4. (continued)

Variable	IL-2 (Blood)		IL-2 (CSF)		IL-10 (Blood)	
	Sig/Direction	Study	Sig/Direction	Study	Sig/Direction	Study
Age	No	Kaminska 2001 (44)	No	Licinio 1993 (51)	No	Kaminska 2001 (44)
Age Onset	No, Pos No No	Kim 2000 (46) Pae 2006 (70) Singh 2009 (83)			No	Pae 2006 (70)
Illness Duration	No, Pos No No	Kim 2000 Pae 2006 (70) Singh 2009 (83)	No, Pos	el-Mallakh 1993 (34)	No	Pae 2006 (70)
PANSS Total						
PANSS Pos	No	Kaminska 2001 (44)			No	Kaminska 2001 (44)
PANSS Neg	No, Pos	Kaminska 2001 (44)			No	Kaminska 2001 (44)
PANSS Gen	No	Kaminska 2001 (44)			No	Kaminska 2001 (44)
BPRS Total	No	Gattaz 1992 (41)				
BPRS Pos						
SAPS						
SANS						
PSAS			No, Pos	el-Mallakh 1993 (34)		

Studies that were included are indicated by bold font.

Reference numbers within the table refer to references in the main text.

BPRS, Brief Psychiatric Rating Scale; CSF, cerebrospinal fluid; Gen, general; IFN, interferon; IL, interleukin; Neg, negative; PANSS, Positive and Negative Syndrome Scale; Pos, positive; PSAS, Psychiatric Symptom Assessment Scale; Sig, signal; sIL, soluble interleukin; SANS, Scale for the Assessment of Negative Symptoms; SAPS, Scale for the Assessment of Positive Symptoms; TNF, tumor necrosis factor.

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